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**Chronic pain in the general
population: Measurement,
burden and associations with
physical activity**

– The HUNT pain study –

Thesis for the degree of Philosophiae Doctor

Trondheim, May 2013

Norwegian University of Science and Technology
Faculty of Medicine
Department of Cancer Research and Molecular Medicine



NTNU – Trondheim
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Kronisk smerte i den generelle folkesetnaden: Kartlegging, bør og assosiasjoner med fysisk aktivitet

Smerte er ei universell oppleving og har som føremål å varsle organismen og beskytta den mot skade. Kronisk smerte har ikkje den same funksjonen, og smerta kan i staden bli ein trussel mot individet i form av liding, redusert funksjon og tap av arbeidsevne. Ulike studiar er usamde om kor mange som er råka av kronisk smerte. Den estimerte førekomsten varierer mellom 11% og 64% hos vaksne. Det er uklårt korleis kronisk smerte best skal definerast og målast, og dette er ei viktig årsak til dei ulike funna.

Fysisk aktivitet kan gi betre helse og førebygga ei rekkje sjukdommar. Det er uklårt om fysisk aktivitet har positiv eller førebyggjande effekt på kronisk smerte i den generelle folkesetnaden.

Hovudmålet med denne avhandlinga var å betre vår kunnskap om førekomsten av kronisk smerte og om samanhengen mellom mosjon og kronisk smerte ved bruk av både tverrsnittss og langsgåande data i frå Helseundersøkinga i Nord-Trøndelag (HUNT).

Eit tilfeldig utval av 6419 deltakarar i HUNT 3 vart invitert til å svara på spørsmål om smerte og mosjon kvar tredje månad gjennom eit år. Rapporteringa av smerte ved bruk av SF-8 var stabil over tid og 26% rapporterte moderat smerte eller sterkare på minst tre av fire målingar. Dette vart definert som kronisk smerte. Moderat smerte eller sterkare siste veka samsvara godt med dette målet, men ei betre semje vart oppnådd i kombinasjon med eit spørsmål om smerte som hadde vara 6 månader eller lengre. Førekomsten av kronisk smerte var høgare blant kvinner, middelaldrande og eldre, og dei med låg utdanning og inntekt. Ein sterk samanheng vart observert mellom kronisk smerte og redusert fysisk, sosial og emosjonell funksjon, samt redusert deltaking i arbeidslivet og høgt forbruk av helsetenester. Både kor ofte, lenge og intenst ein mosjonerte bidrog til å forklare ein lågare førekomst av kronisk smerte. Samanhengen mellom mosjon og kronisk smerte var smålåten hos vaksne i arbeidsfør alder, men sterkare hos eldre, særskilt hos kvinner. Langsgåande analysar stadfesta ein signifikant samanheng mellom intensitet av mosjon og intensitet av smerte innan individa, over tid.

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List of Papers

Paper 1

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Paper 2

Landmark, T., Romundstad, P., Dale, O., Borchgrevink, P.C., Vatten, L and Kaasa, S. Chronic pain: One year prevalence and associated characteristics (the HUNT pain study). Submitted for publication.

Paper 3

Landmark, T., Romundstad, P., Borchgrevink, P.C., Kaasa, S., and Dale, O. (2011). Associations between recreational exercise and chronic pain in the general population: Evidence from the HUNT 3 study. *Pain* 152, 2241-2247.

Paper 4

Landmark, T., Romundstad, P., Borchgrevink, P.C., Kaasa, S., and Dale, O. Longitudinal associations between exercise and pain in the general population (the HUNT pain study). *Plos One*, in press.

Abbreviations

ACR	American College of Rheumatology
BMI	Body Mass Index
CNS	Central Nervous System
CI	Confidence Intervals
GCPS	Grades of Chronic Pain Scale
GDP	Gross Domestic Product
GLM	General linear models
HADS	The Hospital Anxiety and Depression Scale
HUNT	The Nord-Trøndelag Health Study
IASP	International Association for the Study of Pain
ICC	Intraclass Correlation Coefficients
PA	Physical Activity
RPE	Ratings of Perceived Exertion
SES	Socioeconomic Status
VO _{2peak}	Peak oxygen uptake

Summary in English

Pain is a universal experience and serves the primary functions of warning and protecting the organism against injury. When pain becomes chronic, it may cease to serve a protective function and instead becomes a threat to the individual in terms of suffering and impairment of functioning and work capacity. The estimated prevalence of chronic pain ranges from 11% to 64% among adults. A lack of consensus in how chronic pain should be defined and measured is likely to contribute to the wide variability in the findings.

Physical activity may improve health and prevent the development of various diseases. The beneficial effect of physical activity on pain in the general population is uncertain.

The overall aim of this thesis was to improve our knowledge about the prevalence of chronic pain and its relationship with exercise in the general population using both cross sectional and longitudinal data from the Nord Trøndelag Health Study (HUNT).

A random sample of 6419 participants in HUNT 3 was invited to report pain and physical activity every third month over one year. The reporting of pain using the SF-8 Health Survey was stable, and when defined as moderate pain or more on at least three of four measurements, the prevalence of chronic pain was 26%. Moderate pain or more during last week corresponded well with the longitudinal measure, but a better fit was obtained when combined with a recall of pain of at least 6 months duration. The prevalence of chronic pain was higher among women, middle aged and older individuals and those with lower education and income. A strong association was seen between chronic pain and reduced physical, social and mental functioning, as well as work incapacity and health care utilisation. The frequency, duration and intensity of exercise were all independently associated with a lower prevalence of chronic pain. The associations between exercise and chronic pain were modest among those in working age but stronger among older individuals. A significant association between the intensities of exercise and pain were found also within subjects, over time.

1. Background

According to the International Association for the Study of Pain (IASP), pain is an “unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey and Bogduk 1994). Pain is determined by sensory inputs, inputs from the brain, intrinsic neural inhibitory modulation and the body’s stress regulation system and results in an experience comprising sensory-discriminative, cognitive-evaluative and affective-motivational characteristics (Melzack 1999). Thus, pain is produced by the brain when it interprets stimuli as a danger to the body tissue, and it serves a primary function of self-protection.

Bonica (1953) described chronic pain as pain that persists beyond the time one would expect normal healing to occur, a definition that has been used by the IASP (1986) and widely recognised with revisions mainly stressing that chronic pathological processes also may cause continuous or intermittent pain (Manchikanti, Singh et al. 2009). Implicit to the definition is the view that while acute pain has a defensive function of protecting the individual against further harm, the adaptive function of chronic pain is less clear. When pain persists it may cease to serve a protective function and instead degrades health and functioning and contributes to suffering (Chapman and Gavrin 1999).

The distinction between acute and chronic pain may also be seen in their neurobiologic dynamics. In particular central nervous system (CNS) mechanisms are more important in chronic pain. Imaging studies have shown that humans with chronic pain have altered activation in higher centres of the brain such as somatosensory cortices, cingulate cortex and insula and prefrontal cortex (Hunt and Mantyh 2001; Apkarian, Hashmi et al. 2011). Moreover chemical and physiological processes in the spinal chord dorsal horn may be altered by ongoing noxious stimulation from peripheral input leading to increased excitability and synaptic efficacy of neurons in central nociceptive pathways (Siddall and Cousins 2004). This phenomenon is known as central sensitization and may cause pain and chronification of pain even in the absence of noxious stimuli, inflammation or damage to the nervous system (Woolf 2011).

1.1 Chronic pain epidemiology

Epidemiology is the study of the distribution and determinants of illness and disease in populations. Its main application is to guide policy and practice in the prevention of disease and its consequences in populations (Croft, Blyth et al. 2010). Pain has been described as an orphan in the field of epidemiology, in which researchers have mainly been concerned with well defined conditions such as cancer, cardiovascular disease and infectious disease (Von Korff and Le Resche 2005). Traditionally, pain has been viewed as a symptom of an underlying trauma or disease. Accordingly, studies describing the distribution and determinants of the underlying events and the management of the underlying problems were seen as primary to the description and management of pain itself.

1.1.2 Classification of pain in epidemiological research

Previous epidemiologic research has been concerned with identification of individual conditions and the prevention of their causes (Crombie, Davies et al. 1994; Loeser 1994). Standardized diagnostic criteria have been developed for several pain conditions including the American College of Rheumatology's (ACR) criteria for fibromyalgia / chronic widespread pain (Wolfe, Smythe et al. 1990) and the International Headache Society's (2004) criteria for headache disorders, and these have been applied in epidemiological studies. However, the list of separate syndromes is exhaustive and there is no universal consensus on the classification of chronic pain (Merskey 2000). For example, the taxonomy of chronic pain proposed by the IASP (Merskey and Bogduk 1994) includes more than 600 painful disorders. Some conditions have well organised specific criteria (e.g cervical discogenic pain), whereas the categorization of others have been subject to much dispute (e.g. non specific back pain) (Merskey 2000). For epidemiological studies, definitions of back pain therefore need to be simple in their content and language, and complexities which may be crucial in clinical assessments of individuals must be ignored (Dionne, Dunn et al. 2008).

1.1.3 Prevalence of common chronic pain conditions

Numerous epidemiological studies of chronic pain are site specific, i.e. investigating occurrence, causes and consequences of low back pain, neck pain, knee pain,

headache or facial pain etc (Crombie, Croft et al. 1999). The reported annual prevalence of low back pain ranges from 15% to 45% (Andersson 1999) and for neck pain 22% to 65% (Walker 2000; Hogg-Johnson, van der Velde et al. 2008). The estimated prevalence of chronic widespread pain ranges between 7% and 13% (Ospina and Harstall 2002; Neumann and Buskila 2003). Overall, the current global prevalence of headache is 47%; 10% of the adult population suffer from migraine and 38% from tension-type headache and 3% suffer from chronic headache that lasts for more than 15 days per month (Jensen and Stovner 2008).

While there are conflicting evidence for a relation between low back pain and sex, reported risk factors for all conditions are increasing age, female sex, genetics and psychological health. Moreover, each disorder exerts major economic costs to the society (Manchikanti, Singh et al. 2009).

1.1.4 Prevalence of chronic pain

Shared neurobiological and clinical features of the various pain conditions have led several researchers to characterize chronic pain as a disease entity in its own right (Siddall and Cousins 2004; Loeser 2005; Croft, Blyth et al. 2010). A heightened sensitivity of the CNS may create a generalised vulnerability to chronic pain, thus increasing the likelihood of chronic pain to occur simultaneously at different anatomical sites (Croft, Dunn et al. 2007; Woolf 2011) This is exactly what several epidemiological studies now have shown; chronic pain generally presents at multiple anatomical sites (Picavet and Schouten 2003; Schmidt and Baumeister 2007). The number of body sites with pain is linearly associated with reduction in overall health, sleep quality and psychological health (Kamalari, Natvig et al. 2008). Moreover, different types of pain share common characteristics such as duration, frequency and impact on daily activities (van der Windt, Dunn et al. 2008), and a wide range of risk factors are generalized across different pain conditions (Mallen, Peat et al. 2007). Thus, there is a need for establishing an overall prevalence across the diverse types of chronic pain.

The first study directly reporting the prevalence of any pain complaint was conducted among 500 households in the City of Burlington, Canada, and published in 1984

(Crook, Rideout et al. 1984). The authors reported that 16% of the general population reported any “noteworthy pain” within the last two weeks and the majority reported that they were “often troubled by pain”. The prevalence of pain was higher among women, increased with age and was related to functional limitations. In 1998 the first review of the prevalence of chronic pain was published (Verhaak, Kerssens et al. 1998). It included 15 studies published between 1984 and 1994 and reported a median point prevalence of 15% with a range from 2% to 40%. Furthermore, the authors were able to observe some consensus about the characteristics of the subjects who suffered from chronic pain: *“They are relatively often middle-aged women from lower socioeconomic strata. Low back, neck and shoulder are the body areas most frequently affected. Chronic pain is often associated with depression or other kinds of psychological distress”*. The review included heterogeneous studies with different populations, data collection methods and definitions of chronic pain. However, the main aim of the report was to investigate how prevalence of chronic pain had been studied and the authors concluded that neither the method of data collection nor the definition of chronic pain (> 1 month, >3 months or >6 months) could explain the widely varying prevalence estimates. A second review was published in 2002 aiming to present and appraise the published evidence on prevalence of chronic pain (Ospina and Harstall 2002). The review included only studies using the IASP definition of chronic pain (i.e. pain lasting more than 3 months), constituting 5 studies published between 1991 and 2002. They reported a weighted mean prevalence of 35.5%. However, the estimates varied from 10.5% to 55.2% and a lack of consensus about definitions and inconsistencies in measurements made it difficult to quantitatively compare the findings.

Since 2002 there has been published a large amount of studies reporting the overall prevalence of chronic pain. The estimates range between 11% (Ng, Tsui et al. 2002) and 64% (Watkins, Wollan et al. 2008). However, most studies report estimates between 20% to 40% (Catala, Reig et al. 2002; Moulin, Clark et al. 2002; Mantyselka, Turunen et al. 2003; Rustoen, Wahl et al. 2004; Tripp, VanDenKerkhof et al. 2006; Tsang, Von Korff et al. 2008; Miller and Cano 2009; Sjøgren, Ekholm et al. 2009; Johannes, Le et al. 2010; Lee and Tracey 2010; Raftery, Sarma et al. 2011; Toblin, Mack et al. 2011; Wong and Fielding 2011). Several factors may explain the variations in estimates across studies, including year of publication, cultural, socioeconomic and

demographic differences across populations and variations in methodological procedures and case ascertainment. These factors will be addressed in the following paragraphs.

1.1.5 A rising prevalence of chronic pain?

Several studies have shown increases in the prevalence of pain over long periods of time (Harkness, Macfarlane et al. 2005; Freburger, Holmes et al. 2009; Leijon and Mulder 2009; Jiménez-Sánchez, Jiménez-García et al. 2010). The impact of time on the prevalence of pain may be confounded by the age effect in longitudinal studies and cohort effects (shared characteristics of individuals born about the same time) in repeated cross sectional studies. Adjusting for both age and cohort effects, there were no independent time effect on the prevalence of pain in the Swedish population from 1968 to 2002 (Ahacic and Kåreholt 2010). The study reported a significant age effect and a cohort effect for those borne in 1940, however, resulting in an overall increase in the prevalence of pain.

Among the studies reporting prevalence estimates during the last 10 years, there is no obvious indication of an increase with time. This was confirmed by one study investigating the prevalence of chronic pain in Canada in seven cross sectional surveys between 1994 and 2008 (Reitsma, Tranmer et al. 2011) and in two Danish studies conducted in 2000 and 2005 (Eriksen, Jensen et al. 2003; Sjøgren, Ekholm et al. 2009), using similar procedures and showing similar estimates. Monitoring time trends in prevalence is a major objective for epidemiology, however, which may give valuable information regarding new etiological factors or changing importance of etiological factors and it can contribute to the evaluation of interventions (Macfarlane 2010).

1.1.6 Cross-national variation in the prevalence of chronic pain

Two large scale studies have investigated the prevalence of chronic pain in different countries using similar sampling methodology and measurements between the populations. In a pan-European study including 46.394 subjects in 15 European countries and Israel the overall prevalence of chronic pain was 19% (Breivik, Collett et al. 2006). However, large variations between countries were observed, ranging from

12% in Italy to 30% in Norway. The large difference between Norway (30%) and our neighboring country Denmark (16%) is puzzling. However the estimates corresponded fairly well with previous prevalence estimates of 24 % in Norway and 19% in Denmark, although these studies used different sampling and measurements (Eriksen, Jensen et al. 2003; Rustoen, Wahl et al. 2004).

Data from 18 general population surveys using a common survey questionnaire showed aged standardized prevalence rates of 37% in developed countries and 41% in developing countries for chronic pain (Tsang, Von Korff et al. 2008). For developing countries, the estimates ranged from 28% in Lebanon to 58% in Ukraine and for developed countries the estimates ranged from 27% in Japan to 48% in France. Despite the wide variation in the country-specific prevalence rates, several findings were cross-nationally consistent. For example the prevalence was consistently higher among women and increased with age. Moreover, a significant relation between chronic pain and mental disorders were observed across all populations.

Thus, there is evidence that the prevalence of chronic pain may vary substantial between populations. The reason for this is not fully understood but it is likely that many factors are important, including social, cultural and genetic differences across populations. To study the contribution of these factors, standardization of measurements across studies conducted in different populations is necessary. Moreover, measurements must be culturally adapted.

1.1.7 Variations in case ascertainment across studies

Due to the highly subjective component of chronic pain, measures need to rely on self report. Accordingly, cases of chronic pain have generally been identified from retrospective reports of pain duration of more than three or six months. This definition does neither separate mild from moderate or severe pain, nor does it account for temporal aspects such as recurrence. Researchers have therefore used additional criteria of severity and persistence in their case ascertainment. The definitions vary from the broad; including continuous or intermittent pain of any severity, to the constricted; including additional criteria such as pain every day, or pain lasting more than 24 hours and not minor or fleeting, or reports of reduced functioning or health

care use due to the pain, or pain of at least moderate intensity. It seems clear from the recent literature that the use of different additional criteria affects the estimates to a high degree. Studies inquiring about any pain regardless of severity and consistency, but with a duration of more than 3 or 6 months tend to report prevalence in the range of 30% to 50% (Moulin, Clark et al. 2002; Sa, Baptista et al. 2008; Tsang, Von Korff et al. 2008; Jakobsson 2010; Raftery, Sarma et al. 2011; Wong and Fielding 2011), whereas studies that use additional criteria of persistence and / or severity have report estimates between 15% and 31% (Ohayon and Schatzberg 2003; Breivik, Collett et al. 2006; Hardt, Jacobsen et al. 2008; Johannes, Le et al. 2010; Dominick, Blyth et al. 2011; Toblin, Mack et al. 2011). Some studies have not used additional criteria of severity or persistence but still reported prevalence estimates below 25% (Eriksen, Jensen et al. 2003; Meana, Cho et al. 2004; Rustoen, Wahl et al. 2004). However, the phrasing of the question in these studies such as “do you generally have pain” (Rustoen, Wahl et al. 2004) and “are you usually free of pain and discomfort” (Meana, Cho et al. 2004) might have influenced the results.

To summarize, little effort has been given to develop valid measures of chronic pain in population-based research, and the variability in the phrasing of questions and additional criteria has made the literature strikingly chaotic. This makes findings difficult to compare and may be an important cause of the wide variability in prevalence estimates reported. Moreover, to study the effects of cross-national differences in the prevalence of chronic pain and for the surveillance of prevalence across time, measurements need to be standardized, valid and reliable.

1.1.8 Validity of retrospective reporting of pain

Current pain has been shown to affect both the recollection of chronic and acute pain (Redelmeier and Kahneman 1996; Marty, Rozenberg et al. 2009). Moreover, retrospective pain reports may be influenced by other recall biases such as the saliency effect (i.e. episodes of intense pain) and the recency effect (i.e. the intensity of the pain during the last period), although these effects have been subject to little empirical investigation. In a study among subjects undergoing assessment at a treatment centre for chronic pain, the current and retrospective report of average, worst and least pain were all highly correlated with the mean of two weeks of hourly pain reporting

(Salovey, Sieber et al. 1992). We know little about the stability of pain in the general population and the degree to which current and retrospective reports of pain may reflect the dynamic experience of pain over time. Anyways, the recollection of pain over long periods of time would be less biased when it is stable in contrast to when it fluctuates.

An already existing measure of global pain, which is used worldwide, is the bodily pain scale in the SF-36 health survey (Ware, Kosinski et al. 2001) and its shorter form SF-8 (Ware, Kosinski et al. 2001). Also, cultural adaptations have been made so that the various translations may be comparable across countries (Wagner, Gandek et al. 1998). The scale consists of either one (SF-8) or two items (SF-36) and scoring procedures originally gives a scale ranging from 0 (indicates the most severe score) to 100 (indicates no pain). Its validity has been shown amongst others by correlations with other measures of pain, functional disability and unemployment (Ware, Snow et al. 1993, 2000). Several population studies have reported a prevalence of moderate pain or more as indicated by a cutoff at the mid point on the one item scale (Jensen, Sjøgren et al. 2004; Dominick, Blyth et al. 2011). Moreover, this cutoff was shown to be highly related to loss of working days and medical utilization in the Danish population (Jensen, Sjøgren et al. 2004). The literature therefore suggest that this item could be used as a standard measure of pain prevalence in population studies, however, we do not know how good it reflects the prevalence of chronic pain.

1.1.9 Associated characteristics of chronic pain

Most studies report a higher prevalence among women, those with lower socioeconomic status (SES) and among those of higher age. A range of other characteristics associated with chronic pain has been studied, although not as consistently as that of sex, age and SES. One of the most striking findings is the relationship between chronic pain and functional impairments or impaired self reported health. Several researchers have used the Grades of Chronic Pain Scale (GCPS), which has been developed and validated for investigating the level of pain intensity and disability in general population and primary care studies (Von Korff, Ormel et al. 1992). The questionnaire classifies pain into 4 hierarchical grades where higher grades are differentiated by interference with activities. Using the questionnaire in the UK

population, Elliott et al (1999) classified 27% of those with chronic pain as either moderately or severely disabled by pain, whereas the corresponding figures were 37% in Ireland (Raftery, Sarma et al. 2011) and 22% in Hong Kong, respectively (Wong and Fielding 2011).

The SF-36 health survey and its shorter versions consists of 8 subscales: General health, bodily pain, mental health, vitality, physical functioning, social functioning and limitations in work due to physical (role physical) and emotional (role emotional) problems. (Ware, Snow et al. 1993, 2000; Ware, Kosinski et al. 2001). The subscales may also be combined into two summary measures of physical and mental health. Subjects with chronic pain have been shown to report significantly lower functioning and more complaints on each of the subscales compared to non-chronic pain groups in two Danish surveys (Eriksen, Jensen et al. 2003; Sjøgren, Ekholm et al. 2009) and in the New Zealand population (Dominick, Blyth et al. 2011). In a Swedish population study, all subscales discriminated between subjects reporting no chronic pain, chronic regional pain and chronic widespread pain, and changes in SF-36 scores correspondent with changes in pain status at three years follow up (Bergman, Jacobsson et al. 2004). Significantly lower scores on the physical health and mental health composite scores have also been reported in various studies (Raftery, Sarma et al. 2011; Wong and Fielding 2011). Chronic pain has also been shown to relate closely to other measures of self rated overall health and mental health, including anxiety and depression (Blyth, March et al. 2001; Bair, Robinson et al. 2003; Mäntyselkä, Turunen et al. 2003; Ohayon and Schatzberg 2003; Tsang, Von Korff et al. 2008; Toblin, Mack et al. 2011). It has also been shown that mental disorders are both risk factors for developing chronic pain (Magni, Moreschi et al. 1994; Gureje, Simon et al. 2001), and may be consequences of living with chronic painful conditions (Sharpe, Sensky et al. 2001; Wang, Williams et al. 2010).

1.1.10 The economic burden of chronic pain

Chronic pain is not only a burden to the individuals affected, but also to the society at large. Musculoskeletal disorders are major causes of pain and disability across the world and among the most common causes for long term sickness absence (Woolf and Pfleger 2003). By the end of 2010, 299 174 individuals received disability pension in

Norway. Among these 31% were diagnosed with a musculoskeletal condition and 31% with a mental disorder. The same year, musculoskeletal disorders were given as main reason for 42% of all sick leaves, which is about 2.5 million workdays.

(<http://www.nav.no/Om+NAV/Tall+og+analyse/Statistikkportal>).

In addition to the long term sickness absence and disability, pain is a major cause of absence not given by a doctor's certificate, as well as costs due to reduced performance while at work (Stewart, 2003). These data indicates that disability is common among those suffering from chronic pain. However, few studies have investigated the work participation among subjects reporting chronic pain in general population studies.

In addition to the enormous economic consequences caused by reduced ability to work, pain adds major expenses to the health care system. Using information from the register of the National Health Insurance, which includes the use of all medical health care services in primary sector, and the National Inpatient Register, which includes all hospital admissions and discharges in Denmark, Eriksen et al (Eriksen, Sjogren et al. 2004) compared the health care utilisation among the chronic pain group and the control group in the 1994 and 2000 Danish Health and Morbidity surveys. Those with chronic pain had on average 13 contacts per year with the primary care sector compared with 7 in the control group. Hospital admission frequency and number of in hospital days were more than twice as high among those with chronic pain. Female sex, but not age was related to higher utilisation of health care.

In the study conducted in Ireland (Raftery, Ryan et al. 2012), 140 participants with chronic pain were randomly selected from a population based sample and data on direct (health care utilization) and indirect costs (absence from employment) were obtained by interview. The study concluded that the combined cost due to chronic pain was approximately 3% of the Gross Domestic Product (GDP) per year. Moreover 10% of the most expensive patients were responsible for 43% of all costs. In a recent Swedish study, data from national registers were gathered to determine the direct and indirect expenses related to diagnoses commonly associated with chronic pain. The study showed that the average cost per patient per year was € 6500, or a total of € 32 billion in 2007. This was approximately 10% of the GDP (Gustavsson, Bjorkman et al. 2012).

1.1.11 Risk factors - the potential for prevention

The basic idea of prevention is to alter risk factors for a disease at an early point in time to prevent the development of unnecessary individual discomfort and societal costs. It is important to distinguish between primary prevention, which main goal is to prevent the development of a disease and secondary prevention, which main goal is to prevent the consequences or halt further development of the disease. As most people experience pain complaints from time to time, the distinction between primary and secondary prevention may become unclear (Linton and van Tulder 2001). The aim of preventing pain to occur in the first place may be unrealistic and even undesirable. However, preventing pain to become chronic may be viewed as a secondary prevention of pain or a primary prevention of chronic pain.

Apart from the above mentioned risk factors of female sex, middle or older age, low SES and poor mental health, several other risk factors have been identified for chronic pain. These include, genetic predispositions (Hunt 2009), psychological factors such as pain catastrophizing and fear of movement (Picavet, Vlaeyen et al. 2002) and both mechanical and psychosocial occupational factors (Harkness, Macfarlane et al. 2003; McBeth, Harkness et al. 2003).

Lifestyle factors such as diet, smoking and physical activity may be considered broad spectrum risk factors (common causes of multiple diseases), and is of special interest to the field of public health as they may be means of preventing and controlling a wide range of health problems. Several studies have shown a relationship between Body Mass Index (BMI) and smoking and chronic pain (Eriksen, Jensen et al. 2003; Palmer, Syddall et al. 2003; Sa, Baptista et al. 2008; Jakobsson 2010). Regarding physical activity, the picture is complex. First physical activity has variously been considered a risk factor, prognostic factor for relapse and a treatment for pain. Second different types of activities (e.g. activities of daily living, recreational and sports activities and occupational activities) may have specific relations with pain (Abenhaim, Rossignol et al. 2000). In the following, the evidence for a beneficial effect of recreational activity or exercise on pain is discussed.

1.2 Physical activity

Physical activity (PA) is defined as “any bodily movement produced by the skeletal muscles that result in energy expenditure”(Caspersen, Powell et al. 1985). PA may be classified in a variety of ways and includes activities occurring while sleeping, at work or during leisure time. Exercise is a subset of PA that is structured and repetitive and has a final or intermediate objective the improvement of or maintenance of physical fitness (Caspersen, Powell et al. 1985).

The level of the activity may vary according to its frequency, duration and intensity (Pereira, FitzerGerald et al. 1997). What level of activity is necessary to obtain benefits has been a matter of debate. Current public health recommendations are 30 minutes of moderate–intensity activity most days of the week. For sedentary individuals, this provides substantial benefits across a wide range of health outcomes, and increasing the amount may provide further benefits (Blair, LaMonte et al. 2004). However, the frequency, duration and intensity of the activity may be independent and have different associations with different health outcomes. For example the total volume of activity (frequency and duration) is most important for weight reduction (Donnelly, Blair et al. 2009), while intensity of the activity may be more important in preventing cardiovascular disease (Wisloff, Nilsen et al. 2006).

1.2.1 Theoretical models of the relation between physical activity and pain

Physical inactivity has been proposed as a perpetuating factor causing pain to become chronic (Verbunt, Seelen et al. 2003). Mayer and Gatchell (Mayer and Gatchel 1988) used the term “deconditioning syndrome” to describe patients with pain who suffer from physiological loss of fitness such as muscle atrophy, decreased cardiovascular endurance and decreased neuromuscular coordination. They also focused on the psychological distress among chronic pain patients as consequences of both pain and inactivity. The fear-avoidance model describe a sub-group of patients with a strong avoidance of movements due to fear of (re)injury (Vlaeyen and Linton 2000). Pain related fear and avoidance behaviours are described as important factors leading to hypervigilance to illness information, muscular reactivity, physical deconditioning and guarded movements; all of which contributes to chronicity. The avoidance –endurance model describes patients who copes with pain either by avoidance of activity or

endurance of pain. Endurance may lead to chronic pain by overuse and muscular hyperactivity. Moreover, the model describes how the physical activity level of patients with pain may fluctuate substantially over time (Hasenbring, Plaas et al. 2006).

The theoretical models have tended to describe mechanisms linking activity or inactivity to chronic pain in subgroups of patients who are severely impaired, and thus they may not have activity levels representative of the general population. Moreover, the prevalence of inactivity in the population at whole is high (Kruger, Kohl et al. 2007; Haskell, Blair et al. 2009). This leads to the question whether the level of physical activity is lower among subjects with chronic pain than in the general population.

1.2.2 Physical activity and pain in population studies

Several population-based studies have been conducted on the relationship between physical activity and low back and neck pain, and the evidence from these studies has been summarized in several reviews (Hoogendoorn, van Poppel et al. 1999; Hildebrandt, Bongers et al. 2000; Hendrick, Milosavljevic et al. 2011; Heneweer, Staes et al. 2011; Sitthipornvorakul, Janwantanakul et al. 2011). Most studies, both cross sectional and prospective tend to show no relationship between leisure time physical activity, exercise or sports participation and the occurrence of low back and neck pain (Croft, Papageorgiou et al. 1999; Mortimer, Wiktorin et al. 2001; Picavet and Schuit 2003; Pernold, Mortimer et al. 2005; Mortimer, Pernold et al. 2006). The studies are heterogeneous and difficult to compare. However, certain aspects of the relationship have not been studied thoroughly.

Types and dimensions of physical activity have been investigated separately to a very little extent, and few studies have differentiated between acute and chronic pain. In one study, although sports participation was not independently related to the prevalence of low back pain, it was related to the severity of low back pain, once established (Jacob, Baras et al. 2004). In another study, the prevalence of chronic low back pain was higher both among those who engaged in low and high amounts of physical activity (Heneweer, Vanhees et al. 2009). Thus, it seems to be important to account for both the amount of physical activity and the severity and persistence of

pain when investigating the relationship. Investigating the relationship between only dichotomized variables might erroneously conclude that there is no relationship. This was demonstrated in a previous HUNT 2 study. Classifying participants as active / inactive revealed no association with chronic widespread pain, whereas medium but not low and high levels of exercise was related to a lower prevalence of chronic widespread pain (Holth, Werpen et al. 2008).

In studies conducted among older individuals (i.e. 65 year or more) exercise have been shown to prevent an increase in pain with age (Bruce, Fries et al. 2005) and a reduced risk of both short term and long term low back pain episodes (Hartvigsen and Christensen 2007). Thus, associations between chronic pain and leisure time physical activity seem to be stronger among older individuals.

Determining the causal relationship between physical activity and chronic pain is a challenge since lower levels of physical activity may be both a risk factor and a consequence of chronic pain. Prospective studies are therefore needed to investigate the temporal relationship. However, this may also be hard to reveal in prospective studies as both pain and physical activity may vary considerably within individuals across time. Many participants not reporting pain at the baseline of a cohort study may have experienced substantial pain episodes previously, just as their activity levels might have changed prior to the study.

Moreover, chronic pain is determined by multiple causal chains involving a variety of biological, psychological and social risk factors which may interact or be associated with physical activity. A potential relationship may therefore be dependent of, or confounded by, other factors. Such confounding may partly be adjusted for by multivariable statistical analyses. However, these adjustments depend on the inclusion and the precision of other measures in the dataset, and obviously, the inclusion of the correct variables in the statistical model. Residual confounding may therefore occur in multivariable analyses due to measurement error of the confounders and a failure to include relevant confounders. By obtaining longitudinal data with several measurement occasions it is possible to study whether changes in pain and in activity are related within the individual, over time. That is, to study whether individuals report more pain at time points when they report less activity and vice versa. Such analyses are not

subject to confounding of time-invariant factors. Thus, they may give a stronger indication of a direct relationship. Moreover, within-subjects analyses may also be used to investigate whether level of activity at one time point is associated with subsequent changes in pain.

2. Aims of the thesis

The overall aim of this thesis was to improve our knowledge about the prevalence of chronic pain, its associated characteristics and its relationship with exercise in the general population using both cross sectional and longitudinal data.

The following research questions were addressed in this thesis:

How prevalent is chronic pain?

Do recall measures give valid estimates of the prevalence of chronic pain?

To what degree does chronic pain affect self reported functioning, work capacity and health care utilisation in the general population?

Is exercise associated with a lower prevalence of chronic pain?

If so, are the associations similar for frequency, duration and intensity of exercise and do they vary according to sex and age?

Does exercise at baseline predict subsequent level of pain, repeatedly measured over a 12 month period?

Are the levels of exercise and pain related within individuals?

3. Material and methods

3.1 The HUNT study

The Nord-Trøndelag Health Study (“Helseundersøkelsen i Nord-Trøndelag”: HUNT) is the most comprehensive health survey conducted in Norway. It consists of three cross-sectional surveys HUNT 1(1985-1987), HUNT 2 (1995-1997) and HUNT 3 (2006-2008) in which all inhabitants in the county of Nord-Trøndelag 20 years or older were invited to participate. In addition adolescents aged 13-19 years were invited to participate in HUNT 2 and HUNT 3 in terms of the youngHUNT study. Health information was collected by questionnaires, interviews, physical examination and blood samples. The population of Nord-Trøndelag is fairly representative for Norway with respect to geography, economy, industry, sources of income, age and sex distribution and mortality, but the average income and educational level are slightly lower than in Norway as a whole (Holmen, Midthjell et al. 2003). The county is mostly rural and sparsely populated.

The purpose of the HUNT 1 study was to investigate the prevalence of high blood pressure and diabetes, and to evaluate the treatment of patients with high blood pressure, diabetes and tuberculosis. The HUNT 2 and HUNT 3 studies were more comprehensive, including more themes and larger questionnaires. Thus, the scope and content have changed across the three waves and unfortunately the pain questions were only included in HUNT 3. This made longitudinal analyses across two or more of the three waves impossible.

3.1.1 Participants and procedure

In HUNT 3 a total of 94194 individuals received a postal questionnaire together with an invitation to participate in the survey, which also included physical examinations. Participants were asked to bring a questionnaire (Q1) when attending the physical examination. They also received a second questionnaire (Q2) at the examination, which they were asked to return by mail. A total of 50827 (54%) returned Q1 and 41292 returned Q2. The participation rate was higher among women (58%) than men (50%). Demographic characteristics of non-participants were made available from public registers. The youngest age groups had the lowest participation rate; 31% and

42% for the age groups 20-29 years and 30-39 years, respectively, and the age group 60-69 years had the highest participation rate (71%). Participation also increased with higher education and income, and was below average among those who were registered with a social welfare or vocational rehabilitation allowance scheme.

3.1.2 Measurements

Two questions regarding pain were included in HUNT 3: “*Do you have bodily pain which has lasted for more than 6 months?*”, and a verbal pain rating scale including six response categories ranging from no pain to very mild, mild, moderate, severe and very severe pain during the past month. The scale is similar to the bodily pain scale in the SF-36 health survey (Ware, Snow et al. 1993, 2000) which has been recommended as a global measurement of pain severity (Von Korff, Jensen et al. 2000). A division at the mid point of the scale (no to mild vs. moderate to very severe pain) has been shown to be useful in identifying persons with pain of a more complex nature (Jensen, Sjøgren et al. 2004). Case ascertainment of chronic pain was made based on the combination of both reporting pain lasting more than six months and moderate, severe or very severe pain during the past month. Three questions addressed recreational exercise; the average number of times exercising per week (*never, less than once, once a week, 2-3 times per week or almost every day*), the average minutes each time (*less than 15 minutes, 16 – 30 minutes, 30 – 60 minutes or more than 60 minutes*) and average intensity each time (*easy, without breaking a sweat or losing breath, lose breath and brake into sweat or near exhaustion*). The questions were supported with examples of common types of exercise (such as going for a walk, skiing, swimming or other sports). The questions have shown acceptable test-retest reliability with kappa values ranging from 0.52 to 0.77 and significant correlations with VO_{2max} (ranging from 0.31 for duration) to (0.43 for frequency) in adult males (Kurtze, Rangul et al. 2008). In paper 3, participants were categorized in a “non –exercise” category if they reported never exercising or exercising less than once a week on the frequency item, or less than 15 minutes on the duration item. The non exercise category was thereby identical for each dimension of exercise.

In paper 4, the three questions were combined into one variable in the following manner: Those who reported no activity, light intensity activity and activity for less

than 30 minutes were defined as reference group. Those reporting moderate to vigorous physical activity of 30 minutes or more were divided into two groups; those who reported 1-3 times per week, and those who reported nearly every day.

Data on smoking were categorised as non smoker, previous smoker or current smoker, based on self reported smoking habits. Information on organ specific diseases was obtained by self report of the following: myocardial infarction (heart attack), angina pectoris (chest pain), other heart disease, stroke/brain haemorrhage, kidney disease, asthma, chronic bronchitis, emphysema or COPD, diabetes, cancer and epilepsy. Response to these questions were categorized into no, one disease and two or more diseases. The Hospital Anxiety and Depression Scale (HADS) was included in the second questionnaire. HADS is a 14 item self administrated questionnaire measuring depression (7 items) and anxiety (7items) during the previous week. A cut off set at ≥ 8 has demonstrated a sensitivity and specificity at approximately 0.8 for both anxiety disorders and major depression (Bjelland, Dahl et al. 2002).

Statistics Norway provided data on sex, age, education (obtained from the National Education database), income, and unemployment and disability pension (obtained from the Norwegian Labour and Welfare Administration.)

3.2 The HUNT pain study

Two months after baseline of the HUNT 3 study, a random sample of 6419 participants from the municipalities Levanger and Verdal were invited to participate in a longitudinal study on pain and physical activity, the HUNT pain study. The two municipalities included a total of 25255 individuals 16 years and older. The prevalence of higher education (24%) was higher than in Nord-Trøndelag at large (21%), but lower than in the total Norwegian population (27%), whereas the sex and age distributions were similar to the country as a whole.

3.2.1 Participants and procedure

Those who were invited received a questionnaire accompanied by an information letter. For those participating, a mailed questionnaire was mailed every three months

for the following 12 months (five questionnaires in total). The first and the fifth mailings were full length questionnaires, whereas the second, third and fourth were shorter versions. A reminder was mailed to non-responders together with another questionnaire after one month. If the reminder was not returned, but the individuals had not actively withdrawn from the study, another questionnaire was mailed at the end of the 12 month period. The data were scanned using Teleform software. After quality checking, the data was exported into the HUNT databank and each subject was given an identification number. In this way the data for each subject could be linked to all other data in the HUNT databank. The study was planned to go on for five years, and after the first twelve month period, participants received a questionnaire annually.

Among those invited, 4782 (75%) agreed to participate and answered the first questionnaire. Among these 56% were women, 28% were aged 20-44 year, 47% were aged 45 to 64 years and 24% were 65 years or older. One third of the participants had tertiary education, half had secondary education, and 17% had primary education only. Compared to the HUNT 3 population, the sex distribution were equal, whereas the proportion of middle aged and individuals with higher education were higher in the HUNT pain study. Less than 15% (n=642) of the participants were lost to 12 months follow up, and 3555 participants had complete pain recordings on all five occasions. Attrition was neither associated with sex nor education. The proportion of subjects in the youngest age group declined from 28 % at baseline to 26% at one year follow up.

3.2.2 Measurements

Each mailing included the one week recall version of the SF-8 health survey, which consists of the following scales: bodily pain, general health, mental health, vitality, physical functioning, social functioning and limitations in work due to physical (role physical) and emotional (role emotional) problems (Ware, Kosinski et al. 2001). The scoring procedure ensures a mean score close to 50 and a standard deviation close to 10 for each scale, according to the US norm data. The item measuring bodily pain is identical to one of two items in the bodily pain scale of the SF-36 (Ware, Snow et al. 1993, 2000), which was also included in the HUNT 3 study but with a 4 week recall. Health care utilisation during the past 12 months was measured in the full length questionnaire by self report. This included seeing a general practitioner, seeing a

medical specialist in or outside of hospital, being hospitalised, and seeing a physiotherapist, chiropractor, or other therapists giving massage, acupuncture or any alternative treatment.

In the questionnaire, recreational exercise was defined to the responders giving the following examples: *going for a walk, skiing, swimming, exercise or sports*. Responders were asked how often they had engaged in recreational exercise during the last week (*no exercise, 1-3 times, 4-6 times or daily*), and the average duration each time they engaged in recreational exercise (*less than 15 minutes, 15-29 minutes, 30-60minutes or more than one hour*). The Borg ratings of perceived exertion (RPE) scale (Borg 1998) was used as an index of exercise intensity with the following self prepared instruction: “*On a scale from 6 to 20 how hard is the activity that you usually do when you exercise ? (Take an average from the last week)*”. The Borg RPE scale ranges from 6 to 20 with the anchors ranging from “very, very light” to “very, very hard”. It has shown positive correlations with physiological measures of exercise intensity such as heart rate, respiration rate, blood lactate concentration and various measures of oxygen uptake (Chen, Fan et al. 2002). In a recent investigation using the same instruction in another subsample from the HUNT 3 study, the scale corresponded well with Peak oxygen uptake (VO_{2peak}) measured during an exercise test (Nes, Janszky et al. 2012). For the purpose of the current study participants reporting no exercise or who reported exercising for less than 15 minutes were assigned the value 5, given a measure ranging from 5 to 20.

3.3 Statistical analyses

All data computations and statistical analyses were performed using PASW Statistics 18 (SPSS Inc. Chicago, IL, USA) and Stata version 11.0 for Windows (Stata Corporation, College Station, Texas). The following analytical procedures have been employed:

Descriptive statistics includes prevalence of pain with different cutoffs for severity and criteria for persistence. As a measure of stability / tracking, measures of pain at baseline, three month, six month and nine month follow up were cross tabulated against the 12 month follow.

Intraclass correlation coefficients (ICC) were calculated across the five measurements using the entire bodily pain scale in SF-8, also as a measure of tracking.

Sensitivity, specificity and predictive values with their 95% confidence intervals were calculated for recall measures of pain at 12 months follow up, with a longitudinal measure of chronic pain as criterion.

Multiple linear regression analyses with adjustment for sex and age were used to investigate associations between chronic pain as the predictor and seven of the SF-8 subscales (excluding pain) as outcomes.

Logistic regression analysis with predicted probabilities was used to calculate the proportions of disabled and unemployed individuals using age, sex and number of occasions with moderate to severe pain as predictors.

General linear models (GLM) for the binomial families, the binreg function in Stata, were used to calculate adjusted prevalence ratios with 95% CIs of chronic pain for demographic characteristics and all three dimensions of exercise.

Spearman's correlation coefficients were calculated between the three exercise dimensions among those exercising.

The Imputation of Chained Equations (ICE) procedure in STATA was used to evaluate possible selection bias introduced by missing data in the HUNT 3 questionnaire. A large amount of additional information from the HUNT 3 study was used to impute missing data under the assumption of missing at random.

Multilevel mixed effects linear regression analyses were performed using the xtmixed function in STATA to investigate the longitudinal association between exercise and pain.

3.5 Ethics

The HUNT 3 study and the HUNT pain study were approved by the Regional Committee for Medical and Health Research Ethics Central-Norway and the Norwegian Data Inspectorate. Informed consent was obtained by all participants. The use of information from Statistics Norway was not included in the consent. However all data were handled anonymously. Exemption from the duty of confidentiality were obtained from the Ministry of Education and Research to get data on highest level of educational attainment and from the Norwegian Labour and Welfare Administration to get data on income, unemployment, vocational rehabilitation allowance and disability pension.

3.6 Financial support

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4. Results, summary of papers

Paper 1 Estimating the prevalence of chronic pain-Validation of recall against longitudinal reporting (the HUNT pain study)

In this study, pain was measured every three months over a 12 month period and classified longitudinally according to the number of occasions with pain above the cut off points: Mild, moderate and severe. Recall measures of pain (SF-8 bodily pain scale, a question with 6 months recall and the two measures combined) at 12 months follow up were compared with chronic pain defined as at least three of four consecutive measurements of moderate pain or more from baseline to nine month follow up.

Participants with complete longitudinal data on pain as well as complete recall data on pain from the fifth mailing (12 month follow up) were included in the analyses (N=3364). The reporting of pain was stable as shown by mostly no or single point transitions on the pain scale, and an Intraclass Correlation Coefficient (ICC) of 0.66 (95% CI: 0.65 - 0.67). Using different cut off points for pain severity and persistence, the prevalence ranged from 2% consistently reporting severe or very severe pain on all occasions to 71% reporting at least mild pain on one or more occasions. We defined chronic pain as moderate pain or more on at least 3 of 4 consecutive measurements. This gave a prevalence of 26%. Using this definition as criterion, the 6-month recall question had a sensitivity of 0.93 and a specificity of 0.69. A better trade off between sensitivity (0.82) and specificity (0.84) was seen for the SF-8 one week recall item with a cut off at moderate pain. The two measures combined gave the best fit with a sensitivity of 0.80 and a specificity of 0.90.

This study shows that pain reports are stable in the general population and cross sectional measures may adequately reflect the experience of chronic pain. The SF-8 question with a cut off at moderate pain may give valid prevalence estimates of chronic pain, although it may overestimate the problem. Combining the SF-8 question with a recall measure of longer duration may increase the validity; however, questions measuring pain duration have not yet been standardized.

Paper 2 Chronic pain: one year prevalence and associated characteristics (the HUNT pain study)

Demographic and lifestyle characteristics of subjects with chronic pain, as well as associations between chronic pain and self reported health and functioning, health care use and disability were investigated.

Participants with complete longitudinal data on pain were included in the analyses (N=3421). When defined as moderate pain or more on at least 3 of 5 consecutive occasions, the prevalence of chronic pain was 36% (95% CI; 34-38) among women and 25% (95% CI; 22-26) among men. The prevalence was higher among middle aged (35%; 95% CI 32-37) and older adults (36%; 95% CI 32-38), compared to younger adults (20%; 95% CI 17-23) and among those with lower education or low household income. Chronic pain was also more common among smokers (34%; 95% CI 32-37), and former smokers (38%; 95% CI 35-42), compared to non smokers (25%; 95% CI 23-27), and among those with higher body mass index.

Participants with chronic pain had consistently lower scores on the SF-8 health survey subscales. After adjustment for sex and age, the mean differences ranged from 4 points (95% CI 3.7-4.4) for mental health, to 8.3 points (95% CI 8.0-8.7) for physical functioning. They also reported more use of both primary and secondary health care. The proportion of disabled individuals increased linearly with the reporting of pain: from 15% among participants who reported moderate to severe pain at two occasions, to 43% among those with five occasions of moderate to severe chronic pain. The proportion of unemployed individuals increased from 6% among participants with no reports of moderate to severe pain to 20% for participants with five consecutive measurements of moderate to severe pain.

The results show that chronic pain is very common and has a substantial impact on self reported functioning and disability. Therefore chronic pain should be regarded as a major public health problem.

Paper 3 **Associations between recreational exercise and chronic pain in the general population: Evidence from the HUNT 3 study**

The associations between frequency, duration and intensity of recreational exercise and prevalence of chronic pain were investigated. Their independent contributions were investigated by mutual adjustments.

Participants in the HUNT 3 study with complete responses on pain, exercise, smoking and education were included in the main analyses (N=46533). Chronic pain was defined as reporting of pain lasting 6 months or more and moderate pain or more during the last 4 weeks.

The total prevalence of chronic pain was 29%; 33% among women and 26% among men. Compared with those not exercising, the prevalence was lower among those who exercised; 10-12% for participants aged 20-64 years exercising 1-3 times a week, for at least 30 minutes or of moderate duration, and, depending on sex and the load of exercise, 5%-35% lower for those aged 65 years or more. Among those exercising, frequency, duration and intensity were weakly correlated. A multivariable model including all three dimensions revealed similar associations as in the simpler models.

These findings reveal that the prevalence of chronic pain is lower among those who exercise and that the associations are stronger for older subjects, especially for women. Disentangling the role of exercise frequency, duration and intensity is difficult. However, when mutually adjusted all dimensions remained associated with chronic pain, indicating that they may all be important.

Paper 4 Longitudinal associations between exercise and pain (the HUNT pain study)

In this population based study, last week pain and exercise were measure repeatedly over 12 months. We investigated the longitudinal association between exercise and pain with the aim of answering the following research questions:

Is exercise reported at HUNT 3 related to subsequent levels of pain during the 12 month follow up?

Do subjects report less pain at time points when they report higher intensity of exercise?

Does a subject's level of exercise at one time point predict its reporting of pain three months later?

Among those invited to participate in the HUNT pain study (N=6419) 4219 subjects returned at least two questionnaires. Compared to those not reporting regular exercise in HUNT 3, those reporting at least moderate exercise 1-3 times a week on average reported less pain during the follow up in analyses adjusted for sex, age, education and smoking (coefficient: 1.12; 95% CI: 0.60 – 1.63). The difference remained significant, although attenuated when additionally adjusted for baseline level of pain (coefficient: 0.42; 95% CI: 0.23 - 0.82). Within subjects, an increase in exercise was accompanied by a simultaneous reduction in intensity of pain (coefficient: 0.25; 95% CI: 0.21 - 0.28) indicating that individuals reported less pain at times when they reported higher level of exercise. We found, however, no indication that level of exercise at one occasion was followed by changes in pain reporting three months later.

Although weak, these longitudinal associations give a stronger indication of a causal relationship since baseline level of regular exercise predicted a lower level of subsequent pain and since changes within subjects are not confounded by a range of factors that differs between individuals.

5. Discussion

5.1 General discussion

5.1.1 Prevalence of chronic pain

Previously, very high prevalence rates of chronic pain have been reported in Norway (Rustoen, Wahl et al. 2004; Breivik, Collett et al. 2006). However, our knowledge about the severity and persistence of the condition has been limited, and the prevalence has been higher than in other European countries. Thus, there has been a concern that the prevalence was overestimated. The longitudinal design of the HUNT pain study is unique in that a random population sample was followed with measurements at three months intervals. The one year prevalence of chronic pain could thus be estimated with different criteria for persistence and severity, and the estimates were not biased by recall. As one could expect, the estimates ranged widely according to the severity criterion employed. However, contrary to our expectations, the reporting of pain was very stable across time. Thus, the prevalence of chronic pain was 26% using 3 out of 4 consecutive measurements, three months apart, with at least moderate pain as criterion. A single point estimate using the one week SF-8 bodily pain scale gave a prevalence of 33% and a good fit with the longitudinal measure. Combining at least moderate pain on the SF-8 scale with a question of pain lasting six months or more gave a prevalence of 28% and a somewhat better fit with the longitudinal estimate. A similar definition was also used in the HUNT 3 study, giving an estimate of 29%.

The findings therefore confirm previous estimates of chronic pain in Norway (Rustoen, Wahl et al. 2004; Breivik, Collett et al. 2006). The estimates are also in the mid range of what has been reported in previous studies worldwide (Catala, Reig et al. 2002; Moulin, Clark et al. 2002; Mantyselka, Turunen et al. 2003; Tripp, VanDenKerkhof et al. 2006; Tsang, Von Korff et al. 2008; Miller and Cano 2009; Sjøgren, Ekholm et al. 2009; Johannes, Le et al. 2010; Lee and Tracey 2010; Raftery, Sarma et al. 2011; Toblin, Mack et al. 2011; Wong and Fielding 2011). Moreover, chronic pain was related to substantially lower scores on self reported health and functioning as measured by the SF-8 health survey, as well as high rates of disability and health care utilization.

The considerable stability of pain in the repeated measures is at odds with several previous publications, highlighting that pain may be unpredictable in its course (Cedraschi, Robert et al. 1999; Steingrimsdóttir, Vøllestad et al. 2004). However, several other studies have reported considerable stability in the long term course, both in terms of reporting chronic pain (Andersson 2004) pain severity (Smith, Elliott et al. 2004) and numbers of painful bodily sites (Kamalari, Natvig et al. 2009). In a recent review on the course of low back pain in primary care, it was shown that 65% of the patients still reported pain one year after baseline (Itz, Geurts et al. 2013), indicating a much more persistent course than formerly believed.

The significantly lower self reported health and functioning among those classified with chronic pain is in concordance with a large amount of studies conducted in both clinical and population samples (Sprangers, de Regt et al. 2000; Eriksen, Jensen et al. 2003; Mäntyselkä, Turunen et al. 2003; Bergman, Jacobsson et al. 2004; Sjøgren, Ekholm et al. 2009; Raftery, Sarma et al. 2011; Wong and Fielding 2011). The finding supports the clinical significance of the pain reported and thereby the validity of the measurements used to estimate the prevalence. Moreover it underscores the multidimensionality of chronic pain, and the challenges it poses on many levels.

Work incapacity and unemployment were both linearly associated with the number of occasions with reports of moderate pain or more. These data confirms what has been seen from several previous studies using other measures of chronic pain (Woolf and Pfleger 2003; Raftery, Ryan et al. 2012). The findings are also in accordance with figures from the Norwegian National Labour and Welfare Administration (NAV); musculoskeletal complaints are the most common causes of sick leave and disability (Brage, Ihlebaek et al. 2010). However, these are the first figures presenting the relationship between chronic pain and work related disability in an unselected sample from the Norwegian population. The linear association also shows that there are no distinct cut-points indicating when the persistence of pain becomes disabling. This underscores the complexity in predicting work incapacity for those with chronic pain, of which psychological, social, economic and occupational factors contribute to the puzzle (Main and Williams 2002). We also showed that pain is not only related to an increased probability of being granted disability pension, but also for being unemployed. These data highlights the importance of the work aimed at preventing

long term or permanent work absence due to chronic pain, and that this work poses a challenge to social policy makers, health care providers as well as employers.

Work incapacity is related to many non-medical factors such as low level of education, lack of skills and factors at the workplace (Ostby, Orstavik et al. 2011). Securing a good educational system may be one of the most important political priorities for preventing future work incapacity in the younger generations. Moreover, strategies to train or retrain workers with low education or limited skills into meaningful occupations may be appraised as an alternative to permanent disability more often. Moreover temporary or permanent interventions such as job training, workplace adaptations, changes of job content and a gradual increase in working hours are factors that may have beneficial effects on the return to work rate among sick listed (Bloch and Prins 2001). Support for the importance of these factors has recently been obtained from a randomised controlled study investigated the effect of integrated care, directed at patients with chronic pain and their work place (Lambeek, van Mechelen et al. 2010). This study showed that efforts, in the form of enhancing communication and coordination between healthcare professionals, addressing workplace obstacles for return to work as well as planning and completing a graded activity program, indeed may reduce disability due to chronic low back pain.

A large proportion of the population reported some form of health care utilisation. The proportion of individuals with chronic pain having seen a medical specialist or other health professionals including a physiotherapist, chiropractor or any alternative treatment were almost twofold compared to those with no chronic pain. Although these data are quite rough and based on self report, they are similar to findings from a Danish survey based on registry data of health care use (Eriksen, Sjogren et al. 2004), and they clearly indicate the considerable strain chronic pain is on the health care system.

We have little knowledge about how the health care system should be organised to meet this challenge. The management of chronic pain has been described as a chaotic component of contemporary medicine; many medical specialities are involved, and little is known about the cost-effectiveness of various treatments (Loeser 2005; Dagenais, Roffey et al. 2009). Data also suggest increasing health care costs due to pain conditions, without evidence for any corresponding improvement in health and

functioning (Martin, Deyo et al. 2008). This calls for a better integration of the various health care services offered, and more knowledge about what are the most efficacious treatments.

As chronic pain is so common, effective management in primary care could reduce the burden in the whole population. On the other hand, treatments with risks such as long term opioide- use have the potential to negatively affect a large amount of subjects as well (Von Korff and Deyo 2004). Thus, a population health perspective would involve the organisation of health care so that safe and effective treatments are readily available for those in need. An example of this might be cognitive behavioural therapy or exercise treatments delivered to patients in primary care (McBeth, Prescott et al. 2012).

5.1.2 Physical activity and chronic pain

The second main motive of this study was to investigate the relationship between chronic pain and a potential modifiable risk factor, namely physical activity. Various population-based studies have previously reported no relationship between physical activity and various pain conditions (Hoogendoorn, van Poppel et al. 1999; Hildebrandt, Bongers et al. 2000; Hendrick, Milosavljevic et al. 2011; Heneweer, Staes et al. 2011; Sitthipornvorakul, Janwantanakul et al. 2011). There are indications, however, that the association may be dependent on type and load of physical activity. For example work related activity may be a risk factor for low back pain, whereas leisure time activities might be a protective factor (Hoogendoorn, van Poppel et al. 1999; Hildebrandt, Bongers et al. 2000; Heneweer, Staes et al. 2011). Moreover, a significant association between leisure time physical activity and low back pain may be hidden when the measure is dichotomized into active vs. inactive (Heneweer, Vanhees et al. 2009), and few studies have employed criteria for chronic pain and measures of pain severity when investigating the relationship between physical activity and pain.

We investigated the relationship between all three dimensions of recreational exercise (frequency, duration and intensity) and prevalence of chronic pain of at least moderate intensity. All dimensions were important in explaining the prevalence of chronic pain. Among those in working age, the associations were modest. A U-shaped relationship

was seen between exercise frequency and prevalence of chronic pain, whereas indication of a linear relationship was seen for intensity. Among older individuals the associations were substantial and showed linear relationships. Mutual adjustments indicated that all three dimensions contributed to explain the prevalence of chronic pain. The cross sectional nature of these findings precludes any inference about the causality of the associations, however.

Analysing the relationship between exercise and pain longitudinally showed a significant association between baseline level of exercise and subsequent change in pain in repeated measures over 12 months of recording. The longitudinal analyses also confirmed a significant relationship also on an individual level. Although the longitudinal associations were weak, they give a stronger indication of causality. The close relationship in time i.e. individuals reported lower level of activity at times, they reported higher level of pain, but the level of activity during one week did not predict level of pain during one week three months later suggest that the causal pathways may be bidirectional and complex.

To determine the public health significance of these relationships, several factors should be considered (Kraemer 2010). First, the effect sizes of the relationships were modest in most of the analyses for those in working age. For example, compared to those not exercising there was a 10% lower prevalence of chronic pain for adults in working age exercising 1-3 times a week, of at least 30 minutes duration and of moderate intensity. In the longitudinal analyses, an increase from no to moderate exercise was simultaneously accompanied with a 5% reduction in pain intensity. The fact that the causal direction is likely to be bidirectional also reduced the public health significance of the results. That is, we are more interested in the effect physical activity may have on pain than the reversed effect. However, the reversed effect is likely to account for a proportion of our findings. Considering the high prevalence of chronic pain, even low effect sizes could have public health significance. That is, if we could increase the level of physical activity in the population, chronic pain could potentially be prevented in a noticeable number of subjects, although the proportion is modest. Moreover, the analyses indicated a stronger relationship among older subjects. Considering the fact that this is where the burden is most prominent, strategies for increasing the physical activity level in this part of the population could have more

significant public health effects. Finally, physical activity has beneficial effects on a variety of other health outcomes and has low risk of adverse effects.

Even though the prevalence of chronic pain is somewhat lower among those exercising the results tell us that the majority of those with chronic pain are not inactive. Thus, for the majority of individuals in the general population reporting chronic pain, the condition should not be attributed to a deconditioning syndrome (Verbunt, Seelen et al. 2003). This is also in line with longitudinal research showing no decline in physical fitness among patients with sub acute low back pain (Bousema, Verbunt et al. 2007). It is therefore important not to overstate the relationship between exercise and chronic pain. Chronic pain is a complex state, affected by a wide range of factors apart from physical activity.

5.2 Methodological discussion

5.2.1 Sample and participation

One of the main advantages of the HUNT study is its comprehensiveness. The entire population of Nord-Trøndelag County was invited to participate and the measures and objectives were many. This ensured a high number of participants and a large amount of data, so that several factors could be accounted for in the statistical analyses. It also ensured statistical power to detect associations even when they were modest.

Although each participant had an equal opportunity of being selected, only 54% of the invited subjects participated in the HUNT 3 study. Moreover, none-response was related to certain characteristics such as sex, age, socioeconomic status and being on a welfare scheme. Many of the factors which were associated with non-participation were also related to the distribution of pain. Therefore, the prevalence estimates may not be representative of the total population. Since participants in the HUNT pain study were drawn from HUNT 3 and the same factors predicted non-participation, an additional selection bias may have occurred. The pain reported in HUNT 3 was similar for participants and non-participants in the HUNT pain study, however. This may indicate that pain is not an important cause for non-participation. On the other hand, different factors associated with non-participation (male, younger age, low education

etc) may have balanced the differences in pain reported among the participants and non-participants.

Although the distribution of health characteristics is different among participants and non-participants, there may be similar associations between variables among the two groups. This has been shown repeatedly in epidemiological studies and indicates that the variable associations are less likely to be affected by the non-response (Van Loon, Tijhuis et al. 2003; Galea and Tracy 2007).

5.2.2 Confounding

A confounder is a third variable associated with the predictor and causally linked to the dependent variable, and which affects the association between them. Confounding is thus a mixing (confusion) of effects, and can lead to false conclusions. Confounding can be adjusted by study design (e.g. randomised controlled trial) and statistical procedures (e.g. stratification, multivariable analyses or within-subjects analyses).

In paper 2 associations were primarily adjusted for sex, age and education in multivariable analyses. Some confounding may therefore not have been accounted for. In particular, conditions and disorders associated with chronic pain may have accounted for the health care use and work disability, regardless of the pain, in some individuals.

The associations between exercise and chronic pain in paper 3 were analysed in more depth and the many variables included in the HUNT 3 dataset made it possible to consider several potential confounders. Age, female sex, educational level, organ specific disease and depression are established risk factors for chronic pain which where also associated with physical inactivity in the dataset. Associations between smoking and pain have also been shown previously. Whether this association is causal is not well documented, but several causal mechanisms have been suggested (Palmer, Syddall et al. 2003). Also, smoking and physical inactivity may be part of the same lifestyle leading to increased risk for developing chronic pain. Therefore, smoking was treated as a possible confounder. Analyses were stratified by sex and age (20-64 years and 65 years and more). Adjusting for age, education and smoking reduced the

association between exercise and chronic pain to approximately one half of what it was adjusting for age only. Adjusting for comorbidity; either depression alone, organ specific disease alone or both at the same time reduced the association further by approximately 10%. Physical workload has been shown be associated with pain (Hoogendoorn, van Poppel et al. 1999) and might be related to leisure time physical activity. A model including a dichotomized variable (physical strenuous work vs. mostly sedentary work) was carried out and revealed only minor differences in outcomes. However, including this variable caused a substantial loss of participants.

In paper 4, the association between baseline exercise and subsequent level of pain was adjusted for the same confounders that was relevant in paper 3; sex, age, education and smoking. In addition we adjusted for baseline pain. In some cases, when there is considerably measurement error, adjustment for baseline scores of the outcome variable might cause inflation of the association (Glymour, Weuve et al. 2005). Such adjustments should therefore be done with caution. Our adjustments, on the other hand, led to an attenuation of the associations, which was in accordance to what would be expected. The within subjects analyses of the relation between exercise and pain had the advantage of not being subject to confounding of time invariant factors such as sex, socioeconomic status, genetic makeup, etc. This is a major advantage of the within-subjects analyses as confounding of unrecorded variables or measurement error of co-variables could not affect the estimated association. These analyses are therefore less biased and give stronger indication for a causal relationship. Factors that may vary within individuals, such as mood, sleep and anxiety could have confounded the associations. However, these factors may be part of causal chains between physical activity and pain, and including them as time-varying covariates in the analysis would require quite complex theoretical models of the relationships.

5.2.3 Missing responses

Missing responses in the questionnaire may influence associations as these are unlikely to be random. In paper 3 we investigated whether missing responses influenced the associations between exercise and chronic pain by comparing the findings from a complete case dataset and a dataset based on multiple imputations of missing data. No

differences were obtained between the two datasets, indicating a high internal validity of the complete case analyses.

5.2.4 Measurements

Both pain and physical activity are complex phenomena with a high risk of error in the measurements, especially as these are primarily based on self report. Measurement error may be random or systematic (bias). Random error may simply be defined as variability in the data that we can not readily explain. The statistical variation underlying an estimate may be expressed using confidence intervals (CI). A wide CI indicates high variability (low precision) and a narrow CI indicates low variability (high precision). Random error may be reduced with more comprehensive measures (e.g. several items measuring the same underlying construct) or with increasing sample size. In the HUNT studies the large sample size ensured generally narrow CIs. However, the low proportion of older participants reporting hard exercise made the CIs very wide and hence, difference in chronic pain among those exercising hard and those not exercising was not statistically significant.

To reduce the effect of systematic errors (bias), careful attention should be given to the properties of the measurements being used. In the following some of these properties will be discussed.

5.2.4.1 Pain

Pain is a complex, subjective experience and it is not a goal for epidemiological studies to cover the whole range of dimensions of which there are developed measures (Grimmer-Somers, Vipond et al. 2009). We decided to focus on two of the most salient dimension of pain; its intensity and persistence.

A large amount of work has been dedicated to develop reliable and valid measures of pain intensity. Even though findings show that the reporting of pain is dependent on contextual factors (weather, time of day, sex of the observer etc) (Levine and De Simone 1991; Fors and Sexton 2002), subjects may easily quantify pain intensity and may accurately report the average intensity of pain over an extended period of time

(Salovey, Sieber et al. 1992). Recalled pain intensity has been found to be strongly correlated with current pain intensity, however, constituting a potential bias in the recollection of pain (Marty, Rozenberg et al. 2009). Measures of pain intensity are also highly correlated to measures of disability, and they are consistently sensitive to change in treatments known to impact pain (Jensen, Chen et al. 2002; Jensen, Chen et al. 2003).

The verbal rating scale of pain included in the HUNT 3 and the HUNT pain study has been extensively used among others in the various versions of the SF-36 health survey. The scale is strongly correlated with other measures of pain intensity and has shown both high test retest reliability and sensitivity to change (Ware 1993). It is validated as a single item measure as part of the SF-8 health survey (Ware, Kosinski et al. 2001).

In the HUNT pain study, the one week recall of the questionnaire was used, rather than the more common 4 week recall. The one week version is more sensitive to change, which we considered an advantage when investigating the one year course of pain. We would expect a 4 week recall to indicate higher stability than the one week version. The considerable stability in the reporting of pain using the one week version indicates that the two versions may be comparable. The comparability was also supported by the fact that using the one week version or the four week version in combination with a question of pain lasting six months or longer gave a very similar prevalence estimates. The two versions of the single item measure may give different prevalence estimates however, and these differences should be further evaluated.

Clinical significant pain was defined as the mid point on the scale, distinguishing between no to mild pain and moderate to very severe pain. This cut off point has previously been shown to distinguish between subjects from the general population in terms of health care utilisation, loss of working days and self reported health (Jensen 2004). It is also in accordance with other studies showing that the mid point on a pain scale may be used to identify clinically significant pain (Jensen, Chen et al. 2003).

There has been little effort to develop valid measures of pain persistence or to distinguish between chronic and acute pain. The assessment of chronic pain for clinical and epidemiological studies has thus been highly divergent (see introduction).

We used a self prepared question which was based on the IASP (1986) definition of chronic pain. That is, lasting more than 6 months. In the HUNT 3 questionnaire the phrasing was: “*Do you have bodily pain now that has lasted for 6 months or more?*” In the HUNT pain questionnaires the phrasing was “*Do you have bodily pain that has lasted for 6 months or more?*” The subtle difference between these two questions; only one of them including the adverb *now*, made a notable difference in terms of prevalence estimates obtained. In paper 1, the proportion reporting yeas to the HUNT pain question was 47%. In paper 3 the HUNT 3 question was used and the proportion reporting yeas was 39%. This discrepancy reveals that even small differences in the phrasing of a question may have an important impact on the outcome. In both studies, when the questions were combined with at least moderate pain, the prevalence estimates were similar; 28% in paper 1 and 29% in paper 3. The findings of paper 3 also showed that this measure was highly convergent with the longitudinal reporting of pain of at least moderate intensity.

5.2.4.2 Physical activity

Physical activity is a complex behaviour which is difficult to measure by self report. There are several dimensions of physical activity including type, frequency, duration and intensity and questionnaires vary in their complexity regarding these dimensions, and in their time frames for the assessment (Pereira, FitzGerald et al. 1997). Error may occur in terms of social desirability and recall (Adams, Matthews et al. 2004; Taber, Stevens et al. 2009). However, the recollection of activities during last week is fairly accurate (Blair, Haskell et al. 1985).

In the HUNT 3 study a simple measure was included which distinguished between frequency, duration and intensity of recreational exercise on average per week during the past year. The psychometric properties of the three questions have been shown to be adequate for epidemiological purposes (Kurtze, Rangul et al. 2008). In paper 4 we combined the three dimensions into one variable corresponding with the public health recommendations for physical activity; half an hour of moderate activity on most days of the week (Blair, LaMonte et al. 2004), while also accounting for the individual contribution of the three dimensions found in paper 3.

In the HUNT pain study we modified the frequency and duration questions and adopted a one week recall. To measure intensity we used the Borg RPE scale (Borg 1998) with a self prepared instruction. The scale which has 15 response options would give higher variance compared with the three categories used in the HUNT 3 question. We also expected the recall of physical activity during the last week to be more accurate than on average during the past year, and as was the case with pain, we would expect the use of a shorter recall period to be more sensitive to change and give higher within-subject variability. However, when predicting future pain, it is likely that it is the regularity of activity that is important, and not the activity during a specific week. In the longitudinal within subjects analyses, a primary focus should thus be given to the model investigating concurrent associations in exercise and pain over time.

Even though the Borg RPE scale has shown positive correlations with various physiological criterion measures, several factors may influence the validity; including sex of participants, fitness, type of RPE scale used, type of exercise, exercise protocol, RPE mode, psychological factors such as depression and motivation and study quality (Chen, Fan et al. 2002). In the HUNT pain study, the RPE scale was administered as part of a questionnaire and the participants were instructed to report the mean intensity of their exercise during the last week. This diverges from the standard administration, which is during exercise performance tasks. The scale was also included in a questionnaire with an identical instruction in another subsample from the HUNT 3 study, the fitness study, and it showed good concordance with VO_{2peak} (Nes, Janszky et al. 2012).

Pain and fear of movement has also shown to limit the validity of perceived exertion ratings during a bicycle test (Wallbom, Geisser et al. 2002). In another study, pain was reported to affect the validity of exertion reported at low exercise intensity. However, for workloads between 55% and 85% of age-predicted maximum heart rate, RPE had a strong correlation with relative exercise intensity during hydrotherapy among low back pain patients (Barker, Dawes et al. 2003). These studies were conducted among patients referred to pain clinics and may not be generalised to population studies. However, one should be aware of the fact that pain may influence the reporting of

perceived exertion, especially among those affected by the most severe pain exercising at low intensities.

5.2.5 Timing of intervals

In the HUNT pain study, questionnaires were mailed every three months over one year. This included measurements of pain at five occasions for 3364 participants and on several occasions for a considerably larger number of subjects. Including the reminders, more than 25.000 questionnaires were mailed. Substantial resources were also needed for the management of the database, scanning the questionnaires, quality checking and management of the data files. Thus, resource limitations were important considerations when planning the study. A major strength of the actual design was the 12 month follow up which was long enough to ascertain those cases with stable pain for more than six months, i.e. the IASP definition of chronic pain. Moreover the five occasions made it possible to study variations in the pain reported between the baseline and 12 month follow up. However, the recall of the pain reported (one week) did not overlap with the intervals (three months), and large fluctuations in pain may have occurred which was not accounted for by our measurements. Pain may vary considerably during the same day; however the weekly average may be stable across months or years (Fors, Landmark et al. 2012). Thus, the high stability should therefore be considered an indication of the propensity for individuals to report pain, and not an indication that the pain does not vary in intensity.

The longitudinal association between exercise and pain showed that at times individuals report lower intensity of exercise they report higher intensity of pain. However, level of exercise did not predict subsequent level of pain. The three month intervals between measurements may have been too long to capture the true temporal associations. That is, exercise during one week may theoretically predict pain during the next week, although it did not predict pain three months later. A design using different length of time intervals would be needed to study such aspects. However, this would extend our resources or we would have had to reduce the number of participants.

6. Implications and further directions:

6.1 Measuring chronic pain in population studies

The considerable stability of pain indicates that one should be less concerned about fluctuations of pain over time when measuring chronic pain by recall in population studies. Moreover, reports may be less biased by level of pain at the time of recall since pain at the measurement occasion is highly correlated with previous pain. A single point measure of at least moderate pain may correctly exclude those with predominantly mild pain but still capture the majority of those with persistent pain. A major contribution of the HUNT pain study is therefore the suggestion to use the SF bodily pain scale as a measure of the overall burden of pain in the population. This question is validated, translated with cultural adaptations into many languages and extensively used worldwide (Ware, Snow et al. 1993, 2000; Wagner, Gandek et al. 1998). Thus, it may inform us about pain from various large scale population based studies not necessarily devoted to the study of pain. This is not to suggest that more comprehensive measures of pain are redundant. Population based studies should continue to investigate other dimensions of pain such as type, location, number of painful sites, interference with activities etc. However, studies with more comprehensive measures of pain or with a focus on specific pain conditions should also consider using this item as an additional measure of global pain in their questionnaires or interviews.

These findings pave the way for cross national comparisons in the prevalence of pain and its associated characteristics. Since the SF-8 or SF-36 health surveys are included in population studies worldwide, almost on a regular basis, this simple question may be used to gather information on differences in pain between populations and to study factors that may explain these differences; e.g. cultural, economic, political and biological. They may also be used to study and compare associated burden estimates between populations.

The measure may also be used in the surveillance of pain and to study its treatment and costs across time. Monitoring time trends in prevalence may give valuable information regarding etiological factors and it can contribute to the evaluation of interventions

(Macfarlane 2010). Studying the long term effects of risk factors from different stages of life on the onset, persistence and prognosis of pain throughout the life course may add important knowledge and improve our understanding of the problem (Dunn 2010). Our suggestion that a single measure give valuable information about the prevalence of chronic pain may facilitate the study of pain in planned or ongoing life course epidemiological studies.

Future epidemiological studies should aim at identifying targets for the management of pain on both an individual level and population level. This implies identification of clinical characteristics and mechanisms which contributes to explain the chronic pain among cases in population-based studies. Therefore, a study is being planned in which a representative sample of participants from the HUNT pain study will be invited for a clinical examination. This study will give more detailed information about clinical characteristics of the pain reported in the HUNT pain study, such as the prevalence of pain with a neuropathic or inflammatory component and the prevalence of disease related pain. This study may also give information about the need and planning of health care, such as the proportion of patients who need to see a pain specialist.

6.2 Preventing chronic pain with physical activity

Identifying determinants of chronic pain that are modifiable and can be targeted at a population level is another public health concern. A range of factors may be targeted with the aim of preventing pain to develop into chronic pain or to reduce the consequences of chronic pain (Bergman 2007). Promoting a healthy lifestyle such as smoking cessation, obesity reduction and physical activity are targets that may contribute to the reduction of the overall burden of chronic pain in the society.

We have documented a significant relationship between recreational exercise and the prevalence of chronic pain, as well as an association between levels of exercise and pain within subjects in the general population.

The longitudinal analyses indicated that regularity of exercise was important in explaining lower levels of pain. Future studies should investigate the protective effect of regular physical activity on pain in prospective studies with long term follow up. The HUNT pain study has followed participants for four years with annual measures of

exercise and pain. These data provide the opportunity to investigate the association between baseline exercise and the cumulative incidence of chronic pain. The repeated measures also provide the opportunity to investigate the level of exercise before, during and after a new episode of chronic pain, and may therefore provide important information regarding the causal and probable reciprocal relationship.

Randomised controlled trials have shown beneficial effects of exercise treatment on chronic low back pain, chronic widespread pain, neck pain and headache (Hayden, van Tulder et al. 2005; Kay, Gross et al. 2005; Busch, Barber et al. 2007). Most of these studies are conducted in clinical populations in which the effects are likely to be greater than in general populations (Hayden, van Tulder et al. 2005). Moreover, few studies have investigated the role of exercise in preventing pain, and the findings from these are conflicting (Linton and van Tulder 2001; Choi, Verbeek et al. 2010). Thus, in the future, researchers should consider conducting randomised controlled trials in general population samples to study the effect on pain from interventions aiming at increasing the level of recreational physical activity.

7. Conclusions

Chronic pain of at least moderate intensity affects between one fourth and one third of the adult Norwegian population.

Pain is stable in the general population, and recall measures of pain and chronic pain of at least moderate intensity corresponds well with the longitudinal reporting of pain. Thus, they gave valid estimates of the prevalence of chronic pain.

Chronic pain is associated with a substantial loss of self reported functioning and work capacity and an almost doubling of subjects seeking help from a medical specialist or other health care providers. Women, middle aged and older subjects and those at the lower end of the socioeconomic status ladder are most frequently affected.

Exercise is associated with a lower prevalence of chronic pain. The association is stronger for older subjects, particularly for women. Frequency duration and intensity of exercise were all significant in explaining a lower prevalence of chronic pain.

Exercise at baseline is also related to a lower level of pain reported during one year of follow up. Moreover, exercise and pain were significantly associated on an individual level. That is, at times when individuals reported higher level of exercise, they reported lower level of pain.

Although the strength of the associations was modest, increasing the level of exercise in the population may have public health significance on pain as so many individuals are affected.

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Paper I



Research papers

Estimating the prevalence of chronic pain: Validation of recall against longitudinal reporting (the HUNT pain study)

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Methods for classifying chronic pain in population studies are highly variable, and prevalence estimates range from 11% to 64%. Limited knowledge about the persistence of pain and the validity of recall questions defining chronic pain make findings difficult to interpret and compare. The primary aim of the current study was to characterize the persistence of pain in the general population and to validate recall measures against longitudinal reporting of pain. A random sample of 6419 participants from a population study (the HUNT 3 study in Norway) was invited to report pain on the SF-8 verbal pain rating scale every 3 months over a 12-month period and to report pain lasting more than 6 months at 12-month follow-up. Complete data were obtained from 3364 participants. Pain reporting was highly stable (intraclass correlation 0.66, 95% confidence interval 0.65 to 0.67), and the prevalence of chronic pain varied considerably according to level of severity and persistence: 31% reported mild pain or more, whereas 2% reported severe pain on 4 of 4 consecutive measurements. When defined as moderate pain or more on at least 3 of 4 consecutive measurements, the prevalence was 26%. Compared with the longitudinal classification, a cross-sectional measure of moderate pain or more during the last week on the SF-8 scale presented a sensitivity of 82% and a specificity of 84%, and a sensitivity of 80% and a specificity of 90% when combined with a 6-month recall question. Thus pain reporting in the general population is stable and cross-sectional measures may give valid prevalence estimates of chronic pain.

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1. Introduction

Population studies have shown prevalence estimates of chronic pain ranging from 11% to 64% among adults [1–3,5–8,14–17,19,21,23–28,30,32,33,35,37–39,46,47]. Although various studies indicate that chronic pain is a major health problem in every population studied, the large variability leaves uncertainty about the real extent of the problem. The findings are also difficult to compare due to heterogeneity in the measurements of chronic pain. Most studies have used duration of pain for more than 3 or 6 months; however, phrasing of the questions and additional criteria for severity vary. Chronic pain may also vary over time. This may complicate case ascertainment because some researchers

include intermittent pain in their definitions, whereas others do not [3,14,46]. The time-related variability may also bias self reports because current pain or previous salient episodes of pain may influence responses to the questionnaires or interviews [4,34].

There has been no systematic attempt to standardize measurements of chronic pain for population studies. Brief and common measures may facilitate standardization if we had knowledge about their validity. The SF-36 and its variant forms are general health surveys with psychometric properties extensively documented [43–45]. They have been widely used internationally, and cultural adaptations have been made so that the various translations may be comparable across countries [42]. The surveys include an item of pain severity that has previously been shown to adequately distinguish subjects with a complex pain condition from subjects with minor problems in population studies [20]. However, the pain item does not inquire specifically about chronic pain, and we know little about its validity in representing the dynamic experience of pain over time.

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In the present population study, the SF-8 health survey was repeated at 3-month intervals over a 12-month period, and chronic pain could thus be defined by the longitudinal recordings. The primary aim of this report was to validate the estimation of chronic pain from the SF-8 pain scale, a recall measure of longer duration, and the 2 measures combined against the longitudinal recording of pain.

2. Methods

2.1. Participants and procedure

In 2006 to 2008, the total population age 20 years or more in Nord Trøndelag county, Norway (n = 94,194) was invited to participate in a population-based health survey: the HUNT 3 study. A total of 50,827 (54%) people participated. The response rate was higher among women (58%) than men (50%) and lowest among the youngest age groups (31% and 42% for the age groups 20 to 29 and 30 to 39 years, respectively). The study population is fairly representative for Norway with respect to geography, economy, industry, sources of income, age and sex distribution, and mortality, but the average income and educational level are slightly lower than in Norway as a whole.

Two months after participating in the HUNT 3 study, a random sample of 6419 subjects were invited to report pain every 3 months during a 12-month follow-up (in all 5 questionnaires from baseline to 12-month follow-up). A reminder was mailed together with another questionnaire after 1 month. If the reminder was not returned, but the subjects had not actively withdrawn from the study, they received no new questionnaire until the 5th mailing. Of 6419 subjects invited to participate, 3364 (52%) had complete pain ratings on all 5 occasions. The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

2.2. Questionnaire

At each of the five 3-month measurements, participants were asked: "How much bodily pain have you had during the last week? (no, very mild, mild, moderate, severe, very severe)". The item was administered as part of the SF-8 health survey [44], and it is also included in the various versions of the SF-36 health survey [43]. Based on the stability analyses (Tables 1 and 2), chronic pain was defined longitudinally as moderate pain or more on at least 3 of the 4 measurements from baseline to 9-month follow-up.

At the 12-month follow-up, subjects were also asked to report chronic pain by recall: "Do you have bodily pain that has lasted for more than 6 months?" Three recall measures at 12-month follow-up could then be validated against the longitudinal definition of chronic pain: moderate pain or more during last week; pain of at least 6 months duration; and the combination, pain of at least 6 months duration and at least moderate pain during the last week.

At the HUNT 3 study, before entering the present study, participants had answered 2 slightly different questions: "How much bodily pain have you had during the last 4 weeks? (no, very mild, mild, moderate, severe, very severe)", and "Do you have bodily pain now, that has lasted for more than 6 months?"

Information on the highest attained level of education for both responders and nonresponders obtained from the National Education Database (NUDB). NUDB includes individual data on education since 1970. All data are updated annually. For the current analyses, data from 2008 were used. Educational attainments were reclassified into 3 levels: primary education, upper secondary education, and higher level (tertiary) education (<http://www.ssb.no/vis/english/magazine/art-2006-10-13-01-en.html>).

2.3. Statistical analyses

Persistence of pain was calculated by cross-tabulating pain reports at the end of the 12-month follow-up by pain reports at the preceding measures (baseline and 3-month, 6-month, and 9-month follow-up), thereby reporting the proportion of individuals maintaining or varying in their pain, and the degree of the variation across different time intervals. To simplify presentations, the 6-point SF-8 scale was collapsed into a 4-point scale by merging the no pain and the very mild categories and by merging the severe and very severe categories as follows: no/very mild, mild, moderate, or severe/very severe pain. Intraclass correlation coefficients (ICC) were also calculated across the 5 measurements using the entire scale. To calculate the prevalence of pain considering different levels of persistence and severity, the 6-point verbal pain rating scale was dichotomized using 3 different cutoff points: mild pain or more, moderate pain or more, and severe or very severe pain. The dichotomized scores on the measurements from baseline to 9-month follow-up were summed, and the numbers of measurements (0 to 4) above the respective cutoff points were used to calculate prevalence (percentages and cumulative percentages). Four of the 5 measurement occasions were used in the longitudinal classification of pain, and the 5th measurement, the 12-month follow-up, as a cross-sectional recall measure. Sensitivity, specificity, and predictive values with their 95% confidence intervals (CI) were calculated for the recall measures of pain with the longitudinal measure of chronic pain as a criterion. All analyses were computed using PASW Statistics 18 (SPSS Inc. Chicago, IL).

3. Results

A total of 4782 subjects, 75% of those invited, responded to the first questionnaire. These were older and more likely to be female than the nonresponders (Table 3). They were also more likely to have attained a higher level education. However, the responders and nonresponders did not differ in the probability of reporting chronic pain when they entered the study. Similar disparities were seen between those with complete pain data on all follow-up

Table 1

Distribution of pain at baseline and at 3-month, 6-month, and 9-month follow-up according to pain reporting at 12-month follow-up.^a

12 mo	N	Baseline (%)				3 mo (%)				6 mo (%)				9 mo (%)			
		No	Mild	Mod	Sev	No	Mild	Mod	Sev	No	Mild	Mod	Sev	No	Mild	Mod	Sev
No/very mild	1627	77	14	8	1	76	13	9	2	77	13	7	2	79	12	7	2
Mild	613	42	28	25	5	36	33	26	5	33	35	28	4	34	36	26	3
Moderate	823	20	19	48	13	17	17	54	12	15	18	53	14	14	17	55	14
Severe/very severe	301	9	10	39	42	11	5	39	45	9	10	39	42	8	7	37	48

The scale was collapsed into 4 categories by merging no and very mild and by merging severe and very severe pain.

Mod = moderate; Sev = severe.

^a Pain was measured by the question, "How much bodily pain have you had during the last week?" (no, very mild, mild, moderate, severe, very severe).

Table 2

Prevalence (percentages and cumulative percentages) of pain by number of occasions with pain (measured every 3 months from baseline to 9-month follow-up) and according to the use of mild, moderate, and severe as cutpoints for pain (N = 3364).

Number of occasions with pain at or above cutpoints	Cutpoint for pain					
	Mild		Moderate		Severe	
	%	Cum%	%	Cum%	%	Cum%
4 of 4	31	31	17	17	2	2
3 of 4	13	43	9	26	3	5
2 of 4	13	55	11	37	4	9
1 of 4	15	71	17	54	11	20
0 of 4	29	100	44	100	80	100

Table 3

Demographic characteristics and reports of pain among nonresponders, ^{*}responders, and responders with complete follow-up data in the PainHUNT study.

	Nonresponders 1637		Responders 4782		Complete follow-up 3364	
	N	(%)	N	(%)	N	(%)
Sex						
Female	827	(51)	2676	(56)	1897	(56)
Male	800	(49)	2106	(44)	1467	(44)
Age						
20–44 y	758	(46)	1356	(28)	826	(25)
45–64 y	611	(38)	2265	(48)	1678	(50)
65+ y	258	(16)	1161	(24)	860	(25)
Education						
Primary	345	(21)	815	(17)	542	(16)
Secondary	844	(53)	2355	(50)	1662	(50)
Tertiary	415	(26)	1572	(33)	1151	(34)
Primary	345	(21)	815	(17)	542	(16)
Chronic pain [†]	449	(29)	1367	(29)	940	(28)

^{*} Nonresponders participated in the HUNT 3 study and were invited to participate in the PainHUNT study, but did not respond.

[†] Chronic pain was defined in the HUNT 3 study as pain lasting 6 months or more and at least moderate pain in the last month using two questions: “Do you have bodily pain now that has lasted for 6 months or more?” and “How much bodily pain have you had during the past 4 weeks?”

measures and the nonresponders. Approximately 50% of those with complete follow-up responses (N = 3464) were in the age group of 45 to 64 years, whereas about one fourth were age 20 to 44 years and 65 years or above, respectively. About 50% had secondary education and 34% had tertiary education, and 28% reported chronic pain with at least moderate severity during the last month.

The persistence of pain was investigated by calculating the proportion of individuals maintaining or varying in their pain status and the degree of the variations from baseline and 3-month, 6-month, and 9-month follow-up to 12-month follow-up (Table 1). Typically, the pain status was maintained or single-point transitions were made. For example, among those reporting no or very mild pain at 12-month follow-up, 79% also reported no or very mild pain at 9-month follow-up and 12% reported mild pain at 9-month follow-up. Of those reporting moderate pain at the 12-month follow-up, 55% also reported moderate pain at 9-month follow-up, whereas 14% reported severe pain and 17% reported mild pain at the 9-month follow-up. Of those reporting severe pain at the 12-month follow-up, 48% reported severe pain and 37% reported moderate pain at the 9-month follow-up. The stability was only modestly affected by the duration of the interval. That is, from baseline to 12-month follow-up the figures were similar to the intermediate 3-month, 6-month, and 9-month follow-up. Also, the tracking of pain across all 5 intervals given the full range of the pain scale was seen by an intraclass correlation coefficient of 0.66 (95% CI 0.65 to 0.67).

For prevalence of pain according to the cutoff points mild, moderate, and severe, and according to persistence, the proportion of measurements with pain at or above the respective cutoff points are given in Table 2. Although 31% consistently reported mild pain or more on all 4 measurements, 17% consistently reported at least

Table 4

Prevalence of pain using 3 different cross-sectional pain measures (at 12 months) and 1 longitudinal measure of chronic pain estimated from pain reporting at baseline to 9 months.

	Total	Chronic pain	
	N	%	(95% CI)
12-month follow-up			
≥ Moderate [*]	3364	33	(32–35)
≥ 6 mo [†]	3364	47	(45–49)
Combined [‡]	3364	28	(27–30)
Longitudinal			
≥ 3 occasions, ≥ moderate pain [§]	3364	26	(25–28)

^{*} Measure of pain: “How much bodily pain have you had during the last week?”

[†] Measure of pain: “Do you have pain lasting more than 6 months?”

[‡] Measure of pain: pain lasting more than 6 months and moderate, severe, or very severe pain last week.

[§] Measure of pain: moderate, severe, or very severe pain on 3 or more of 4 consecutive measures 3 months apart.

moderate pain, and only 2% consistently reported severe pain on all measurements. The cumulative prevalence was 71% for at least mild pain, 54% for at least moderate pain, and 19% for severe pain across the 9-month period. The proportion of individuals reporting pain only once was lower: 15% for at least mild pain, 17% for at least moderate pain, and 11% for severe pain. Based on these figures, and on the significant tracking of pain described in the previous paragraph, chronic pain was defined as moderate pain or more on at least 3 of the consecutive measurements. This gave a prevalence estimate of 26% and was used as the criterion that the recall estimates were validated against.

Table 5

Sensitivity, specificity, PPV, and NPV of 3 cross-sectional measures of pain at 12-month follow-up, with the longitudinal measure of chronic pain, baseline to 9-month follow-up, as criterion.

Pain, cross-sectional measures	Chronic pain, longitudinal measure [§]							
	Sensitivity	(95% CI)	Specificity	(95% CI)	PPV	(95% CI)	NPV	(95% CI)
≥ Moderate [*]	0.82	(0.80–0.85)	0.84	(0.83–0.86)	0.65	(0.62–0.68)	0.93	(0.92–0.94)
≥ 6 mo [†]	0.93	(0.92–0.95)	0.69	(0.68–0.71)	0.54	(0.52–0.56)	0.96	(0.95–0.97)
Combined [‡]	0.80	(0.79–0.82)	0.90	(0.89–0.92)	0.75	(0.72–0.78)	0.93	(0.91–0.94)

CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value.

^{*} Measure of pain: "How much bodily pain have you had during the last week?"

[†] Measure of pain: "Do you have pain lasting more than 6 months?"

[‡] Measure of pain: pain lasting more than 6 months and moderate, severe, or very severe pain last week.

[§] Measure of pain: moderate, severe, or very severe pain on 3 of 4 consecutive measures 3 months apart.

The prevalence of pain given 3 different cross-sectional classifications and 1 longitudinal classification is presented in Table 4. Defining pain solely by duration of 6 months or longer gave the highest prevalence, i.e., 47% (95% CI 45 to 49), whereas a definition of at least moderate pain on the SF-8 scale gave a prevalence of 33% (95% CI 32 to 35). Combining the 6-month duration criteria and at least moderate pain gave a somewhat more restrictive estimate (28%; 95% CI 27 to 30), which seemed to be most comparable with the longitudinal estimate of 26% (95% CI 25 to 28). The association between each of the prevalence estimates and sex, age, and education were comparable, with higher prevalence among women, among middle-age and older participants, and among those with lower level of education (data not shown).

Table 5 gives the sensitivity, specificity, and predictive values of the recall measures of pain at 12-month follow-up when compared with the longitudinal measure of chronic pain as criterion. For the 6-month recall question, sensitivity was high, correctly identifying 93% (95% CI 92 to 95) of the positive cases from the longitudinal measure. It had lower specificity, however, correctly identifying 69% (95% CI 68 to 71) of the negative cases from the longitudinal measure. A better tradeoff between sensitivity (82%; 95% CI 80 to 85) and specificity (84%; 95% CI 83 to 86) was obtained using the SF-8 one-week recall item with a cutoff point at moderate pain. The 2 measures combined correctly identifying 80% (95% CI 79 to 82) of the positive cases and 90% (95% CI 89 to 92) of the negative cases. The positive predictive values, i.e., proportion of individuals classified with chronic pain from the longitudinal measures that also reported pain from the cross-sectional measures, increased from 54% (95% CI 52 to 56) for the 6-month recall question alone to the 75% (95% CI 72 to 78) for the combined measure. The negative predictive values, i.e., proportion of individuals not classified with chronic pain from the longitudinal measures not reporting pain at the 12-month follow-up measures, were high, ranging between 93% (95% CI 91 to 94) and 96% (95% CI 93 to 97) for all 3 measures.

4. Discussion

In this population study, the pain item from the SF-8 health survey was repeated every 3 months for 1 year, and chronic pain was defined longitudinally as moderate pain or more on at least 3 of 4 consecutive measurements. At least moderate pain on the 12-month follow-up measure corresponded well with the previous longitudinal reporting of pain, with a sensitivity of 0.82 and a specificity of 0.84. When combined with the 6-month recall question of pain, specificity was improved to 0.90. This was only at a minimal expense of sensitivity. The 6-month recall question alone gave the highest overestimation of the problem. This is partly because many of those reporting pain on this question had mild pain or less. Moreover, the question did not inquire specifically about when the pain was experienced. Thus, subjects may report recovered pain.

This longitudinal study confirms high rates of chronic pain in the population and supports the use of simple recall questions in measuring it. The considerable stability of pain indicates that one should be less concerned about fluctuations of pain over time when measuring chronic pain by recall in population studies. Moreover, reports may be less biased by level of pain at the time of recall because current pain is highly correlated with previous pain. A single-point measure of at least moderate pain may correctly exclude those with predominantly mild pain but still capture the majority of those with persistent pain.

The pain scale used in the current study is included in the various versions of the SF-36 and SF-8 health surveys [43,44] and used in epidemiological and clinical studies worldwide. Estimates using this item may thus adequately reflect the prevalence of chronic pain from a variety of populations. Previous estimates ranges from 14% to 27% [20,36,44]. Compared with our estimate of 33%, these figures suggest a substantial variability between populations, and this variability is maintained when samples are stratified by age and sex. Such findings suggest that cultural and social factors may influence the occurrence of chronic pain. These issues have only been investigated to a very little extent, but may give important information in relation to both understanding the phenomenon and planning health care [31]. International comparative studies should therefore be of priority, and the wide use of the SF questions internationally may give means to such investigations.

In the present study, associations with age, sex, and education were similar for the various definitions of pain. However, there are disagreements between studies on a range of factors hypothesized to be associated with pain [9,18,29]. Standardized measurements would therefore be of importance when comparing and summing findings from studies of associated characteristics and risk factors such as demographic variables, mental health, lifestyle factors, disability, and health care use [10].

The stability of pain in this general population study was remarkable. Previously, chronic pain status has shown a stable course across 4 years in the general population [13], and the number of pain sites has been reported to be stable across 14 years [22]. However, the stability of pain in the present study is more pronounced compared with previous studies describing the persistence of pain among patients in primary care [12,41]. Exacerbations or new onset of symptoms are important reasons for seeking care. As a result of the phenomenon called regression toward the mean, primary care studies may include a higher proportion of subjects with symptoms who will recover or have fluctuating symptoms. On the contrary, in the current study subjects were selected at random time points in the pain course. This implies that classification of chronic pain may be simpler in general population studies than in clinical studies or primary care studies.

The present data show that the estimated prevalence of pain varied according to different cutoff points for severity and persistence. To include subjects who may have persistent and clinically

significant pain, we chose a cutoff point of moderate pain on at least 3 of 4 occasions. Choosing a low cutoff point for severity would include many subjects who are not affected to a significant degree, and hence may not be of interest for many epidemiological purposes. The definition also ensured that moderate pain or greater would be reported on most of the measurement occasions, and on at least 2 consecutive occasions 3 months apart. Choosing 4 of 4 occasions would give a substantially lower estimate, hence recall items would produce more false-positive results. However, as illustrated by the stability analyses, the most probable pain response at the time of not reporting moderate pain was mild pain. Finding one unbiased estimate of the prevalence of chronic pain may not be feasible, however. The range of prevalence estimates according to severity and persistence may have different importance based on the purpose. For example, in predicting who will have a long-term course of substantial pain, a consistent pattern of moderate to severe pain may be a suitable cutoff point, whereas in predicting who will seek health care, a less stringent cutoff point would probably be more appropriate.

The prevalence figures given in this report are based on 52% of the invited sample. Although participants did not deviate from nonparticipants in terms of chronic pain prevalence, the prevalence estimates reported may not be representative of the total population and should be interpreted with caution. The response bias has less effect on the main findings of this report, which is the high correspondence of recall measures with the longitudinal measure of chronic pain.

Previously, problems with the classification of chronic pain have been discussed with regard to the uncertain prediction of the prognosis [11,40]. These studies suggest that in primary care, a distinction between acute and chronic pain based on 3-month or 6-month duration may be arbitrary, and that factors other than duration should also be considered when predicting prognoses and hence classifying chronic pain. Whether the estimates of pain investigated in the current study are suitable predictors of the long-term prognosis should be subject to future investigations.

In conclusion, the present study shows that pain reporting is stable and that a cutoff point at moderate pain on the SF pain item may give valid estimates of chronic pain in population studies. The fact that the SF question is translated into a variety of languages and is included in many surveys worldwide makes this measure useful for comparative studies. To increase validity, the item may be combined with a measure of duration of pain for 6 months or more. However, questions measuring pain duration have not yet been standardized.

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Paper II

Chronic pain: one year prevalence and associated characteristics (the HUNT pain study)

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What's already known about this subject?

The prevalence of chronic pain in Norway is high, affecting nearly one third of the adult population.

What does this study add?

Even though it is very common, chronic pain is highly associated with reduced self reported health and functioning, increased health care utilisation and work incapacity.

Keywords: Pain, Epidemiology, Musculoskeletal, Disability, Functioning, Health Care

Chronic pain: prevalence and associated characteristics

Abstract

Background: Chronic pain is a common, but ill-defined condition, and research findings are often difficult to interpret and compare with others. We have repeated measurements of pain in a longitudinal population study to improve validity. In this paper, associations between chronic pain and demographic characteristics, self reported health and functioning, disability and health care use were investigated.

Methods: A random sample of 6419 participants from a population study (the HUNT Study) was invited to report pain every three months during a 12 month period. Chronic pain was defined as reporting of moderate to severe pain (on the SF-8 verbal rating scale) in at least three out of five consecutive measurements.

Results: The total prevalence of chronic pain was 36% (95% CI; 34-38) among women and 25% (95% CI; 22-26) among men. The prevalence increased with age, was higher among people with high BMI, and in people with low income and low educational level. Smoking was also associated with a higher prevalence of chronic pain. People who reported chronic pain had lower self-reported health and functioning, higher use of health care, and were more often outside the work force.

Conclusion: The results show that chronic pain is common, with substantial impact on functioning, disability and use of health care. Therefore chronic pain should be regarded as a major public health problem.

1. Introduction

In epidemiological studies, chronic pain is usually defined as pain lasting for more than three or six months (Manchikanti et al., 2009). However, the phrasing of the questions and the use of additional criteria to indicate severity of pain varies between studies, and among others, these factors may explain the large variation in prevalence, ranging from 11% to 64% (Ng et al., 2002; Ospina and Harstall, 2002; Watkins et al., 2008). The wide variation in case ascertainment is problematic since it makes prevalence and associated burden estimates difficult to compare. Ultimately, this may have political consequences and negatively impact the credibility of the research (Dionne, 2012).

Previous studies have shown both cross sectional and prospective relationships between chronic pain and various physical and mental aspects of self-reported health and functioning in the general population (Bergman et al., 2004; Elliott et al., 2002; Eriksen et al., 2003). Others have reported high direct and indirect economic costs of chronic pain, in terms of health care utilisation and absence from employment (Dagenais et al., 2008; Manchikanti et al., 2009). The estimated costs range between 3% of the GDP in Ireland (Raftery et al., 2012) to 10% of the GDP in Sweden (Gustavsson et al., 2012). However, these estimates are highly influenced by the methodology used, and there are large differences in social welfare policies between countries (Dagenais et al., 2008).

Although the prevalence of chronic pain is high in Norway, we have limited knowledge about its consequences (Breivik et al., 2006; Rustoen et al., 2004). Those with chronic pain utilize large resources of the health care services, but the management of pain is reported to be inadequate (Breivik et al 2006). In the disability statistics, musculoskeletal disorders is given

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as the cause for approximately 35% and 30% of all sick leaves and disability pensions, respectively (Brage et al., 2010). However, the validity of the diagnoses is uncertain; they are often provided by the primary physician and non-medical factors such as social problems, lack of education, and characteristics at work may contribute to the final conclusion (Haukenes et al., 2011; Ostby et al., 2011) Chronic pain may also be an important cause for disability among subjects classified with other conditions than musculoskeletal disorders, such as mental disorders (Overland et al., 2012). It is therefore important to study the relationship between chronic pain and disability in representative samples from the population.

In a previous study, longitudinal data on pain measured every third month over one year was used to estimate the prevalence of chronic pain (Landmark et al., 2012). The study confirmed a high prevalence, with almost one third of the adult Norwegian population being affected by chronic pain of at least moderate intensity. The aim of the current paper is to further investigate the importance of this finding by studying the consequences of chronic pain in terms of self-reported health and functioning, health care utilisation and work incapacity.

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2. Methods

2.1. Participants and procedure

The present study is a component of a large population based health survey; the HUNT 3 Study. Between 2006 and 2008, the total population 20 years of age and older in Nord-Trøndelag county in Norway (n=94194) was invited to participate, and a total of 50827 (54%) individuals attended the study. The study population is fairly representative for Norway with respect to geography, economy, industry, sources of income, age and sex distribution and mortality, but the average income and educational level are slightly lower than in Norway as a whole (Holmen et al., 2003).

Two months after baseline of the HUNT 3 Study, a random sample of 6419 participants was invited to a sub-study of pain (the HUNT pain study). Among them, 4782 (75%) accepted the invitation and received postal questionnaires every three months for the following 12 months (five questionnaires in total). A reminder was mailed to non-responders together with another questionnaire after one month. If the reminder was not returned, but the individuals had not actively withdrawn from the study, another questionnaire was mailed at the end of the 12 month period.

The study was approved by the Regional Committee for Medical and Health Research Ethics Central-Norway and the Norwegian Data Inspectorate.

2.2. Questionnaires

Each mailing included the one week recall version of the SF-8 health survey (Ware et al., 2001). The SF-8 health survey consists of the following scales: bodily pain, general health, mental health, vitality, physical functioning, social functioning and limitations in work due to

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physical (role physical) and emotional (role emotional) problems. The eight subscales may also be combined into two summary measures of physical and mental health. The scoring procedure ensures a mean score close to 50 and a standard deviation close to 10 for each scale, according to the US norm data. In the present study, a mean score across all five measurements was constructed for each scale, to cover the 12 month study period.

The following question measures bodily pain in SF-8: “How much bodily pain have you had in the past week?” with response categories ranging from no pain to very mild, mild, moderate, severe or very severe pain. The question has shown robust psychometric properties and is recommended as a global measure of pain severity (Von Korff et al., 2000). The severe and very severe categories were merged, and chronic pain was defined as a score that indicated moderate or more intensive pain in at least three of the five consecutive measurements. It has previously been shown that moderate pain is adequate to distinguish subjects with a complex pain condition from subjects with minor problems in population based samples (Jensen et al., 2004). At the HUNT 3 Study, the participants had answered the same question, but with a four week recall, before entering the present study, in addition to the following question: “Do you have bodily pain now which has lasted for more than 6 months?” These two questions were combined to a measure of chronic pain of at least moderate intensity during the past month and used to compare those who accepted the invitation to the HUNT pain study and completed all five pain measurements, and those who declined to participate in the HUNT pain study.

Health care utilisation during the past 12 months was measured by self report, and included seeing a general practitioner, seeing a medical specialist in or outside of hospital, being hospitalised, and seeing a physiotherapist, chiropractor, or other therapists giving massage,

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acupuncture or any alternative treatment. Reports covered the same 12 month period as the pain measurements.

Height and weight were measured, and body-mass index (BMI) was calculated as weight divided by height squared.

Information on income, education, disability pension awards and unemployment was obtained from Statistics Norway, which provided data from the National Education database (NUDB) and the Norwegian Labour and Welfare Administration. Level of income is presented as quartiles of the household income divided by the squared number of household members. Information on the highest attained level of education was classified into three levels; as primary, secondary or tertiary education. Any person who was registered with a disability pension of 50% or more during the study period was coded as being work disabled.

2.3. Statistical analyses

Descriptive statistics are given as numbers and percentages with 95% confidence intervals (CIs). Multivariable associations between demographic characteristics and chronic pain were calculated as prevalence ratios with 95% CIs using General linear models (GLM) for the binomial families, the binreg function in STATA. Associations between chronic pain as the predictor and seven of the SF-8 subscales (excluding pain) as outcomes were calculated using multiple linear regression with adjustment for sex and age. The proportion of individuals reporting health care utilisations were calculated with GLM using chronic pain and age as predictors. The proportions of disabled and unemployed individuals were calculated using predicted probabilities from logistic regression analysis with age, sex and number of

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occasions with moderate to severe pain as predictors. All analyses were conducted using Stata version 11.0 for Windows (Stata Corporation, College Station, Texas).

3. Results

3.1. Comparison between participants and non- participants

Figure 1 shows the flow of participants included in the HUNT pain study and the main analyses. Participants with complete pain reporting over the 12 month period (n=3421) were older, more likely to be female and to have higher level of education compared to those who were invited, but declined to participate. The prevalence of chronic pain (29%), as measured in the HUNT 3 survey, was however, similar between groups.

3.2. Prevalence and characteristics of chronic pain

The total one year prevalence of chronic pain was 31% (95% CI 30-33), defined as reporting of moderate to severe pain in at least three of the five measurements (Table 1). Estimates were higher among women (36%; 95% CI 34-38) than men (25%; 95% CI 22-27), and among middle aged (35%; 95% CI 32-37) and older adults (36%; 95% CI 32-38), compared to younger adults (20%; 95% CI 17-23). Educational level and household income were inversely associated with the prevalence of chronic pain, and body mass index was positively associated. The prevalence among never smokers was 25% (95% CI 23-27), as compared to 34% (95% CI 32-37) among former smokers and 38% (95% CI 35-42) among current smokers. In the multivariable analyses, these estimates remained essentially unchanged.

We also considered possible consequences of chronic pain, including health related quality of life, health care utilisation, and work incapacity and unemployment. Table 2 shows that participants with chronic pain score consistently worse than participants without chronic pain for seven of the eight SF-8 health survey subscales (excluding bodily pain). After adjustment for sex and age, the mean differences ranged from 4 points (95% CI 3.7-4.4) for mental health, to 8.3 points (95% CI 8.0-8.7) for physical functioning. The differences were all in the

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range of 1 and 2.5 standard deviations for the non chronic pain group, and 0.6 to 1.2 standard deviations for the chronic pain group, indicating that the differences are likely to be clinically significant.

The proportion of participants seeking health care was substantially higher within the chronic pain group (Table 4). After adjustment for age, 88% (95% CI 86-90) of participants with chronic pain had seen a general practitioner during the 12 month study period, 52% (95% CI 49-55) had seen a medical specialist and 47% (95% CI 44-50) had seen other health professionals. The corresponding proportions for the non chronic pain group were 70% (95% CI 68-72), 31% (95% CI 30-33) and 20% (95% CI 18-21).

Figure 2 illustrates the relation of persistent pain with disability and unemployment. In age and sex adjusted analyses, the proportion of disabled individuals increased linearly with the reporting of pain: from 15% among participants who reported moderate to severe pain at two occasions, to 43% among those with five occasions of moderate to severe chronic pain. In relation to unemployment, there was also a linear increase; from 6% among participants with no reports of moderate to severe pain to 20% for participants with five consecutive measurements of moderate to severe pain.

In a separate analysis, chronic pain was defined as the reporting of moderate to severe pain at all five measurements. Using this definition, the prevalence was 16% (95% CI 15-17) for the total sample; 12% (95%CI 10-14) among men and 19% (95%CI 17-20) among women. The prevalence increased by age, from 9% (95% CI 7-11) in the age group 20-44 years, 18% (95% CI 16-20) in the 45-64 year group, and 19% (95% CI 18-22), among participants 65 years and older.

4. Discussion

In previous studies the definition and measurement of chronic pain have varied widely and so has the findings. Using a longitudinal design and measuring pain every three months over a 12 month period, we found that about one third had chronic pain. This estimate is within the range of what has been reported in previous studies (Ospina and Harstall, 2002). The significance of these figures is shown by a clinically significant association with other measures of self-reported health and functioning, a substantial increase in the use of health care services and high drop out of the work force among those with chronic pain.

Similar to our findings, previous studies suggest that demographic characteristics (sex, age, education) are related to chronic pain, indicated by fairly consistent associations (Blyth et al., 2001; Elliott et al., 1999; Eriksen et al., 2003; Ohayon and Schatzberg, 2003; Rustoen et al., 2004). Thus, the higher prevalence among women, the increasing prevalence with age, and the higher prevalence in people at the lower end of the socioeconomic status ladder, indicates where the burden of chronic pain is most prominent, and where efforts to change the situation should be emphasised. The strong relation with age, for example, begs for particular attention, especially due to the many challenges related to the aging of the population.

The responses to the SF-8 health survey suggest that people with chronic pain have low scores on self-reported functioning, and on general and mental health, and similar findings have been reported by others (Bergman et al., 2004; Eriksen et al., 2003; Sprangers et al., 2000).

Although reduced general functioning may be a consequence of chronic pain, it has also been suggested that poor social and physical functioning may predict the onset of chronic pain (Elliott et al., 2002). In relation to mental health and vitality, associations with chronic pain

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are also likely to be complex (Nijrolder et al., 2010; Ohayon and Schatzberg, 2003). However, the close association with different dimensions of self-reported health and functioning underscores the multidimensionality of chronic pain, and the challenge it poses on many levels.

In our study, disability was far more common among those reporting chronic pain, and reflects the high prevalence of musculoskeletal complaints that is represented in the disability statistics (Brage et al., 2010). That chronic pain have a high impact on work capacity was also shown in a pan European study showing that almost 60% of those with chronic pain reported reduced ability to perform work outside home (Breivik et al., 2006). It has previously also been shown that widespread pain is a strong risk factor for disability pension, and that the risk for disability increases with increasing number of pain sites affected (Kamaleri et al., 2009, Øverland et al., 2011).

We also showed that both disability and unemployment was linearly associated with the number of measurements with moderate to severe pain. This finding suggest that there is no distinct cut-off to indicate when the persistence of pain becomes disabling. Thus, the relation of chronic pain with disability is likely to involve psychological, social, economic and occupational factors (Main and Williams, 2002). The higher proportion of unemployed individuals among those with chronic pain indicates that the sick leave and disability statistics does not capture all those who have lost work capacity due to chronic pain. This is also indicated by findings showing that pain complaints are major causes for reduced performance at work (Stewart et al., 2003).

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The figures clearly tell us that chronic pain is a substantial obstacle to maintain work capacity for a large number of individuals. We need more knowledge about how this problem should be managed. Few studies have investigated the benefits of treatment on return to work.

However, it has been shown that integrated care directed at patients with chronic low back pain and their work place, have beneficial effects that may prevent disability (Lambeek et al., 2010).

A large proportion of participants with chronic pain in our study reported some form of health care utilisation. Although our data are based on self report, the findings show that chronic pain is a considerable strain on the health care system. The findings are also in correspondence with a Danish study using data from national registers and showed that hospital admissions, in hospital days and number of contacts with primary care were about twice as high for the chronic pain group compared with the control group (Eriksen et al., 2004) The management of chronic pain has been described as a chaotic component of contemporary medicine; many medical specialities are involved, and little is known about the cost-effectiveness of various treatments (Dagenais et al., 2009; Loeser, 2005). Data also suggest increasing costs, without evidence for any corresponding improvement in health and functioning (Martin et al., 2008). Simultaneously, it has been shown that a small proportion of patients accounts for a very high proportion of the costs (Engel et al., 1996; Raftery et al., 2012).

We found that obesity and smoking were associated with a higher prevalence of chronic pain We have also reported elsewhere that lower level of exercise was associated with a higher prevalence of chronic pain (Landmark et al., 2011). The results of others have not been consistent, and it has been suggested that patterns of causality for these factors are complex

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(Heneweer et al., 2011; Hildebrandt et al., 2000; Hooten et al., 2011; Janke et al., 2007).

Nonetheless, the findings should increase our awareness that lifestyle factors may influence the occurrence of chronic pain.

In the prevention and treatment of chronic pain, it may be appropriate to target a range of lifestyle factors, including obesity, smoking, and exercise. Although the evidence is not conclusive, several prospective studies have suggested that the prevalence of chronic pain may be reduced by modifying these factors (Heneweer et al., 2011; Hildebrandt et al., 2000; Hooten et al., 2011; Janke et al., 2007). Exercise may improve functioning among patients with chronic low back pain (Hayden et al., 2005), and combined with interventions at the work place, a substantial reduction in disability may be achieved (Lambeek et al., 2010). The complexity of pain suggests that improving the integration of various treatment efforts may be beneficial, possibly reducing the high indirect costs of chronic pain, caused by lost productivity and drop out of the work force (Stewart et al., 2003).

In a previous paper, using the same dataset, we reported the prevalence of pain employing different criteria for persistence and stability. As expected the prevalence estimates varied greatly according to the criteria employed (Landmark et al., 2012). However, a cut off at moderate pain using the SF-8 bodily pain scale on a single time point corresponded well with the longitudinal estimate of chronic pain of at least moderate intensity. Taken together, these two studies show that the prevalence of chronic pain is high, have substantial social and economic consequences, and may be validly estimated in cross sectional studies with a measure that may readily be standardized across studies.

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Our study has some limitations. The average age of the study population was slightly higher than in the general population, and educational level was somewhat higher. The prevalence of chronic pain reported in this study may therefore not be representative of the total population. The external validity of the associations being studied is less likely to be influenced by the non response, however (Galea and Tracy, 2007). In our sample the reporting of chronic pain was remarkably stable over the 12 month period (Landmark et al., 2012). We did not assess large fluctuations in chronic pain over time. It has been suggested that fluctuations in pain are associated with functioning and disability, however, the hypothesis has received little empirical attention (Von Korff et al., 2000). The cut-off at moderate to severe pain reported at three separate measurements to indicate chronic pain may be questionable. For example, it is possible that the pain in some participants may be better characterized as recurrent than persistent pain. In a separate analysis, we used a stricter definition of chronic pain, and required moderate to severe pain to be reported at all five occasions. Although the prevalence estimates were lower, the associations with socio-demographic and lifestyle factors, as well as self reported health and functioning, remained nearly the same as using three out of five occasions.

5. Conclusion

In this population study, almost one third consistently reported clinically significant pain during 12 months of longitudinal reporting. The pain was strongly associated with self reported health status, use of health care resources and loss of employment. This is a major challenge for authorities and health care providers both on a national, regional and local level. No health care system would have the resources to provide treatment for all these individuals, and it is an open question how the problem can best be dealt with. Targeting lifestyle factors should be more strongly considered as part of the solution.

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Contributors: TL, PRR, OD, PCB & SK designed the study and obtained the funding. OD administered the data collection overall. TL had the day to day responsibility of data collection and quality, analyzed the data and wrote the paper, PRR analyzed the data and participated in writing the paper, OD participated in the analysis, commented on the draft and participated in writing the paper, PCB commented on the draft and participated in writing the paper, LJV participated in the analysis and wrote the paper, SK had the original idea, participated in the analysis and wrote the paper. All authors discussed the results and commented on the manuscript.

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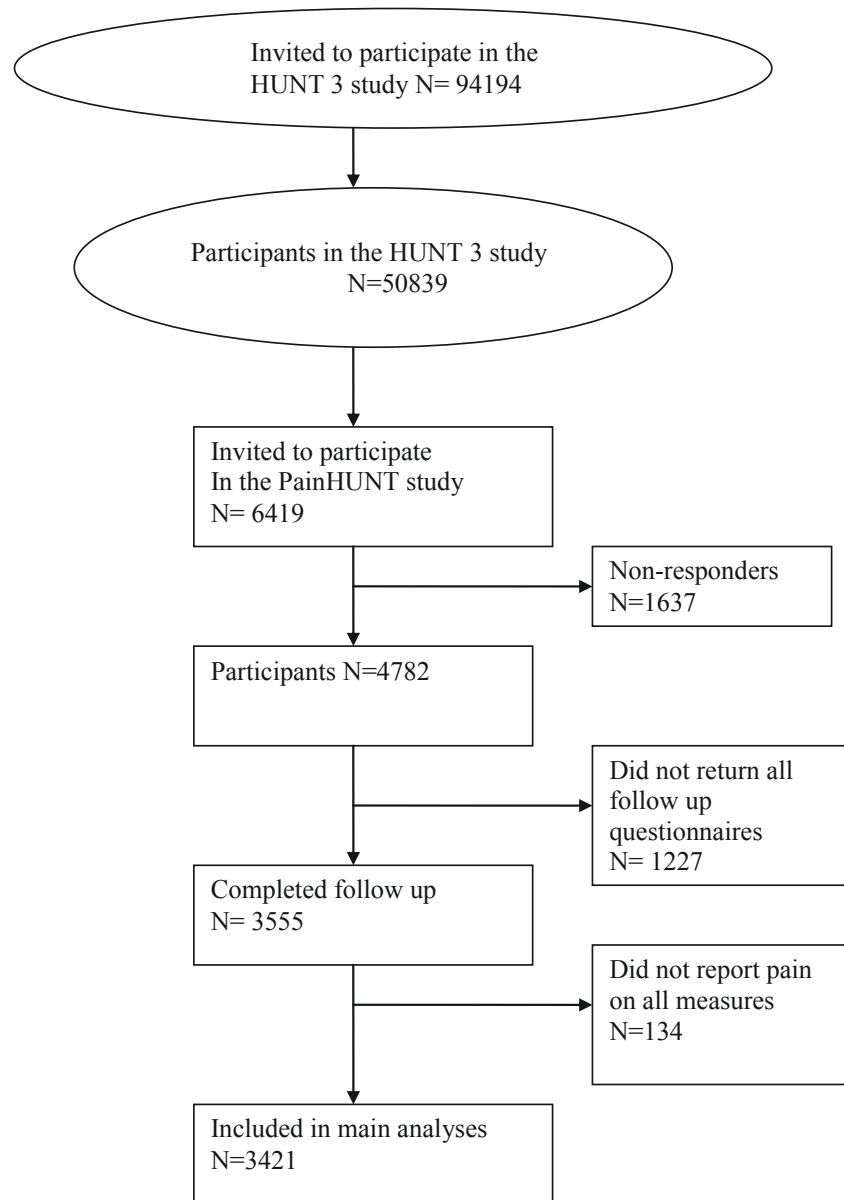
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Figure 1: Flow of the participants included in the current study



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Table 1: Characteristics of the total sample and prevalence of chronic pain^a according to sex, age, BMI, educational level, income and smoking in the HUNT pain study

	Total sample	Chronic pain				
	N	N	%	prevalence (95% CI)	PR	Prevalence Ratios ^b (95% CI)
Overall	3421	1069	31	(30-33)		
Sex						
Female	1931	701	36	(34-38)	1.00	ref
Male	1490	368	25	(23-27)	0.66	(0.60-0.73)
Age						
20-44 yrs	829	166	20	(17-23)	1.00	ref
45-64 yrs	1696	585	34	(32-37)	1.58	(1.37-1.84)
≥65 yrs	896	318	35	(32-39)	1.48	(1.26-1.75)
BMI (kg/m ²)						
< 25	1150	295	26	(23-28)	1.00	ref
25-30	1502	450	30	(28-32)	1.13	(1.01-1.28)
>30	695	301	43	(40-47)	1.46	(1.28-1.65)
Education						
Primary	559	261	46	(42-51)	1.00	ref
Secondary	1691	579	34	(32-36)	0.81	(0.73-0.91)
Tertiary	1162	228	20	(17-22)	0.48	(0.41-0.56)
Income						
Q4 (highest)	888	212	24	(21-27)	1.00	Ref
Q3	904	277	31	(28-33)	1.13	(0.98-1.29)
Q2	833	293	35	(32-38)	1.26	(1.09-1.44)
Q1 (lowest)	796	287	36	(33-39)	1.00	(0.85-1.16)
Smoking						
Never	1482	369	25	(23-27)	1.00	Ref
Previous	1054	363	34	(32-37)	1.30	(1.16-1.46)
current	835	321	38	(35-42)	1.39	(1.24-1.57)

^aChronic pain defined as moderate to severe pain on three or more occasions when measured every third month over a 12 month period.

^bPrevalence ratios adjusted for sex, age (continuous) and education as appropriate

Chronic pain: prevalence and associated characteristics

Table 2 Comparisons between the non chronic pain group and the chronic pain group on the SF-8 subscales (excluding pain).

	No chronic pain		Chronic pain		Mean Difference ^a	(95%CI)
	N	Mean (sd)	N	Mean (sd)		
General health	2335	49.5 (4.9)	1052	41.1 (5.1)	8.0	(7.7-8.4)
Physical functioning	2335	50.8 (3.7)	1059	42.8 (6.0)	7.6	(7.3-7.9)
Role physical	2330	51.7 (3.3)	1051	43.1 (6.7)	8.3	(8.0-8.7)
Vitality	2342	50.1 (6.2)	1065	42.2 (6.4)	7.7	(7.2-8.1)
Mental health	2322	53.0 (4.2)	1058	49.0 (6.4)	4.0	(3.7-4.4)
Role emotional	2314	50.3 (3.1)	1045	45.1 (5.9)	5.1	(4.8-5.4)
Social functioning	2331	52.5 (3.4)	1053	46.7 (5.9)	5.6	(5.3-5.9)

^aMean difference adjusted by age and sex

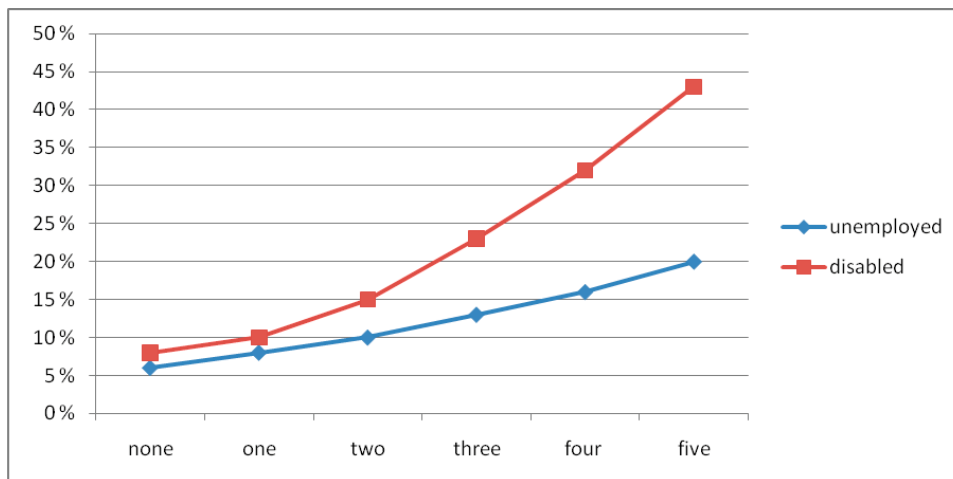
Chronic pain: prevalence and associated characteristics

Table 3 Age and sex adjusted proportions of subjects seeking health care among those without and among those with chronic pain, respectively

	No chronic pain			Chronic pain		
	N	%	(95% CI)	N	%	(95%CI)
General Practitioner	1634	70	(68-72)	959	88	(86-90)
Medical Specialist	736	32	(29-34)	564	52	(49-55)
Other health professional	468	22	(20-25)	495	49	(46-52)

Chronic pain: prevalence and associated characteristics

Figure 2 Age and sex adjusted proportion of individuals in working age (<65 yrs N= 2525) who were registered unemployed or on disability pension according to number of occasions with moderate to severe pain



Paper III

Associations between recreational exercise and chronic pain in the general population: Evidence from the HUNT 3 study

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ABSTRACT

The evidence for an association between leisure-time physical activity and prevalence of pain is insufficient. This study investigated associations between frequency, duration, and intensity of recreational exercise and chronic pain in a cross-sectional survey of the adult population of a Norwegian county (the Nord-Trøndelag Health Study; HUNT 3). Of the 94,194 invited to participate, complete data were obtained from 46,533 participants. Separate analyses were performed for the working-age population (20–64 years) and the older population (65 years or more). When defined as pain lasting longer than 6 months, and of at least moderate intensity during the past month, the overall prevalence of chronic pain was 29%. We found that increased frequency, duration, and intensity of exercise were associated with less chronic pain in analyses adjusted for age, education, and smoking. For those aged 20–64 years, the prevalence of chronic pain was 10–12% lower for those exercising 1–3 times a week for at least 30 minutes duration or of moderate intensity, relative to those not exercising. Dependent on the load of exercise, the prevalence of chronic pain was 21–38% lower among older women who exercised, relative to those not exercising. Similar, but somewhat weaker, associations were seen for older men. This study shows consistent and linear associations between frequency, duration, and intensity of recreational exercise and chronic pain for the older population, and associations without an apparent linear shape for the working-age population.

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1. Introduction

Pain complaints are major health problems accounting for extensive health care utilizations [14,34], work absence [44], and disability [4,15]. Pain may be classified according to a variety of factors [45], and epidemiological studies of pain are highly heterogeneous in ascertaining pain cases [11]. However, prevalence figures tend to be high, with up to 80% of the adult population reporting pain during the past month [27], and 20% of the European adult population reporting moderate to severe chronic pain [6].

Pain is associated with a wide range of risk factors such as gender, age, and socioeconomic status [2,12,13], work characteristics [37,39], and psychological distress [35,50]. It is widely suggested

that physical inactivity is a perpetuating factor causing pain to become chronic [48]. Accordingly, guidelines for the treatment of musculoskeletal pain frequently include recommendations of exercise to prevent development into chronic pain [1,17,29]. However, there is conflicting evidence for the efficacy of exercise treatment in preventing pain [31,33,47] and there is limited evidence for an association between leisure-time physical activity and prevalence of pain in the general population [9,21,25].

Few studies have explicitly differentiated between acute and chronic pain when investigating the relationship with physical activity. In one study, chronic low back pain was not associated with physical inactivity [41]. Considering load of the activity, moderate, but not vigorous activity has been associated with lower prevalence of chronic low back pain [20] and chronic widespread musculoskeletal pain [24]. These studies did not include additional information on pain intensity when ascertaining cases. This might be important because a large proportion of those with chronic pain in the general population report mild pain [8,12].

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Moreover, among older adults, exercise has been shown to prevent an increase in pain with age [7] and a reduced risk of both short-term and long-term low back pain episodes [18]. Thus, associations between chronic pain and leisure-time physical activity may be dependent on age.

In summary, progress in identifying a relationship between physical activity and pain in the general population may have been constrained by a lack of explicit case definitions and limited knowledge of which activity types and loads are important. To expand on previous studies, the current study investigates the associations between frequency, duration, and intensity of recreational exercise and prevalence of chronic pain of at least moderate intensity. Furthermore, previous studies suggest that the association may be dependent on age and gender. Therefore, all analyses were conducted separately for men and women, and for those aged 20–64 years and those aged 65 years or more. Specifically, the following research questions were raised:

- (1) Is recreational exercise associated with a lower prevalence of chronic pain?
- (2) If so, are the associations similar for frequency, duration, and intensity of exercise?

2. Materials and methods

2.1. Study design and subjects

All inhabitants aged 20 years or more in the county of Nord-Trøndelag in Norway have been invited to participate in three population-based health surveys: the Nord-Trøndelag Health Study (HUNT 1–3); <http://www.ntnu.no/hunt/english>. The first HUNT study was carried out in 1985–1987, the second in 1995–1997, and the third (HUNT 3) in 2006–2008. The population of Nord-Trøndelag is stable, with sex and age distributions similar to those of Norway as a whole, but with somewhat lower levels of education and income compared to national averages. The county is mostly rural and sparsely populated [23].

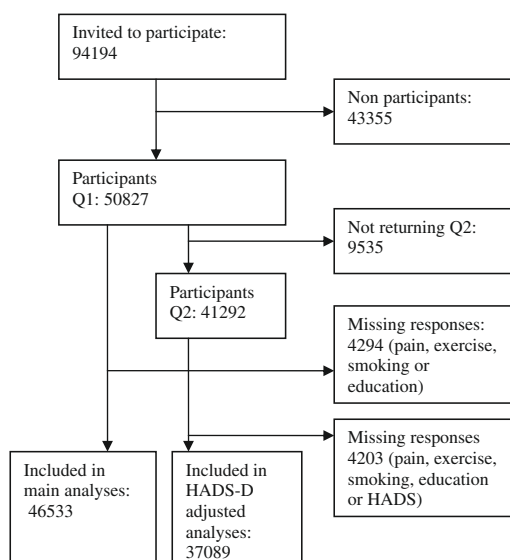


Fig. 1. Flow chart of participants included in analyses. Q1, questionnaire 1; Q2, questionnaire 2; HADS-D, Hospital Anxiety and Depression Scale-Depression.

In HUNT 3, a total of 94,194 individuals received a postal questionnaire together with an invitation to participate in the survey (Fig. 1), which also included physical examinations. Participants were asked to bring a questionnaire (Q1) when attending the physical examination. They also received a second questionnaire (Q2) at the examination, which they were asked to return by mail. A total of 50,827 (54%) returned Q1 and 41,292 returned Q2. Among the total of 50,827 participants, 4294 were excluded from analyses due to missing information on pain, exercise, smoking or education. After omitting these subjects, 46,533 (92%) respondents were included in the main analyses. Among these, 37,089 were included in the analyses adjusting for the Hospital Anxiety and Depression Scale (HADS) (Fig. 1).

The response rate was higher among women (58.5%) than men (49.8%) and lowest in the youngest age groups; 31% and 42% for the age groups 20–29 and 30–39 years, respectively, vs 71% for the age group 60–69 years, which had the highest participation.

HUNT 3 has been approved by the Norwegian Data Inspectorate and the Regional Committee for Ethics in Medical Research.

2.2. Questionnaires

Two questions regarding pain were included: Do you have bodily pain which has lasted for more than 6 months? and How much bodily pain have you had during the past month?, with the following response options: None, very mild, mild, moderate, severe, or very severe. This verbal pain rating scale has been extensively used, among others, in the various versions of the Short Form-36 health survey [52], which has been recommended as a global measurement of pain severity [49]. A division at the midpoint of the scale (no-to-mild vs moderate-to-very-severe pain) has been shown to be useful in identifying persons with pain of a more complex nature [28]. Case ascertainment of chronic pain was made based on the combination of reporting both pain lasting more than 6 months and moderate, severe, or very severe pain during the past month.

Three questions addressed recreational exercise; the average number of times exercising per week (*never, less than once, once a week, 2–3 times per week, or almost every day*), the average minutes each time (*<15 minutes, 16–30 minutes, 30–60 minutes, or more than 60 minutes*), and average intensity each time (*easy, without breaking a sweat or losing breath, lose breath, and break into sweat or near exhaustion*). The questions were supported with examples of common types of exercise (e.g. going for a walk, skiing, swimming, or other sports). The questions have shown acceptable test–retest reliability, with kappa values ranging from 0.52 to 0.77, and significant correlations with VO_2 max (ranging from 0.31 for duration to 0.43 for frequency) in adult males [30]. In the present analyses, participants were categorized in a “non-exercise” category if they reported never exercising or exercising less than once a week on the frequency item, or <15 minutes on the duration item. The non-exercise category was thereby identical for each dimension of exercise. To reflect the average total time spent on exercise per week, the frequency categories were given the following scores; non-exercise = 0, once = 1, 2–3 times = 2.5, and nearly every day = 5. The duration categories were given the following scores: non-exercise = 0, 15–30 minutes = 0.38, 30–60 minutes = 0.75, and more than 60 minutes = 1 [30]. The frequency and duration scores were then multiplied and then divided into 4 categories: non-exercise, <1 hour per week, 1–2 hours per week, and more than 2 hours per week.

The HADS [53] was included in the second questionnaire. HADS is a 14-item self-administered questionnaire measuring depression (7 items) and anxiety (7 items) during the previous week. A cut-off set at ≥ 8 has demonstrated a sensitivity and specificity at approximately 0.8 for both anxiety disorders and major depression [3].

Information on organ-specific diseases was obtained by the self-report of the following: myocardial infarction (heart attack), angina pectoris (chest pain), other heart disease, stroke/brain haemorrhage, kidney disease, asthma, chronic bronchitis, emphysema, or chronic obstructive pulmonary disease, diabetes, cancer, and epilepsy. Responses to these questions were categorized into no disease, 1 disease, and 2 or more diseases. Physical workload was assessed with the question: is your work so physically demanding that you are often physically worn out after a day's work? The response categories *nearly always*, *quite often*, *seldom*, and *almost never* were dichotomized with a cut-off between quite often and seldom.

Data on smoking were categorised as nonsmoker, previous smoker, or current smoker. The highest attained level of education for every participant was obtained from the National Education database, which includes individual data on education since 1970. All data are updated annually. For the current analyses, data from 2008 were used. Educational attainments were re-classified into 3 levels; compulsory education, upper secondary education, and higher level (tertiary) education (<http://www.ssb.no/vis/english/magazine/art-2006-10-13-01-en.html>).

Data on retirement pension, vocational rehabilitation allowance, and disability pension were obtained from Statistics Norway's history of event database, in which data from the Norwegian Labour and Welfare Organisation are provided.

2.3. Statistical analyses

Prevalence ratios adjusted for age, level of education, smoking, and co-morbidity (organ-specific disease and/or depression) for every level of frequency, duration, and intensity of exercise were calculated in separate analyses based on general linear models for the binomial families using the binreg function in Stata version 10.0 for Windows (Stata Corporation, College Station, TX). In these models, the non-exercise category was the reference category for each of the exercise dimensions. To evaluate the independence of each exercise dimensions' association with chronic pain, they were all included in one model. In this model, the reference category was the lowest level of exercise rather than the non-exercise category. Correlations among the 3 exercise dimensions were estimated among those exercising by calculation of Spearman's correlation coefficients.

Age was coded in 15-year categories; level of education as primary, secondary, or tertiary education; co-morbidity as none, 1, or 2 or more organ-specific diseases; depression as cut off ≥ 8 on HADS-Depression (HADS-D); and smoking as never, previous, or current smoker. Analyses were carried out separately for each sex and for those who were between the ages of 20 and 64 years and those aged 65 years or more, respectively. For those aged 20–64 years who were not receiving retirement pension or disability pension, additional analyses were carried out with physical workload as a covariate. Interaction between exercise and gender and exercise and age category (20–64 years or 65 years or more) were carried out using likelihood ratio test.

To evaluate possible selection bias introduced by missing data, we used additional information from the HUNT 3 study to impute missing data under the assumption of "missing at random" [43]. Twenty imputed data sets were obtained using the Imputation by Chained Equations (ICE) procedure in STATA. In the imputation we included all the variables used in the analyses as well as the following variables: self-perceived health (ordinal scale), body mass index (interval scale), hip circumference (interval scale), alcohol consumption (ordinal scale), impairment due to chronic disease (dichotomy), disability pension (dichotomy), income (interval scale), 4 questions on insomnia (ordinal scale), HADS anxiety (ordinal scale), type of physical activity in work (nominal scale),

headache (dichotomy), musculoskeletal complaints (dichotomy), and back operations (dichotomy).

3. Results

3.1. Prevalence of chronic pain and nonexercise

Overall, 39% of the population reported pain that had lasted for 6 months or more. When combining pain for 6 months or more with at least moderate pain during the past month, the prevalence was 29%. As shown in Table 1, chronic pain was more prevalent among women (33%) than men (26%), and the prevalence increased with age. The prevalence of chronic pain was approximately 10 percentage points lower among those who never had smoked compared to current or former smokers. An almost 2-fold increase in the prevalence of chronic pain was seen among those who scored above the cut-off for depression (HADS-D ≥ 8) and those with more than one organ-specific disease. The prevalence of chronic pain was also considerably higher among subjects with low educational attainment. The prevalence of non-exercise increased with age, smoking status, and with having one or more organ-specific diseases as well as depression. The prevalence of non-exercise decreased with level of attained education, and was higher among men (29%) than women (20%).

3.2. Associations between recreational exercise and chronic pain

Among subjects aged 20–64 years who exercised 2–3 times a week, the prevalence of chronic pain was 10% lower for women (prevalence ratio [PR] 0.90; 95% confidence interval [CI] 0.85–0.94) and 12% lower for men (PR 0.88; 95% CI 0.83–0.94) compared to those who did not exercise (Table 2). However, for both women and men exercising 4 times or more, the prevalence of chronic pain was similar to those not exercising. This indicates a U-shaped relation for frequency of exercise with chronic pain in this age group.

For older subjects who exercised 2–3 times a week, the prevalence of chronic pain was 27% lower for both women (PR 0.73; 95% CI 0.67–0.79) and men (PR 0.73; 95% CI 0.65–0.82) compared to those not exercising. In contrast to those aged 20–64 years, exercising 4 times or more was associated with an apparently larger or maintained reduction in chronic pain among the elderly (PR 0.66; 95% CI 0.60–0.72, and 0.79; 95% CI 0.70–0.89 for women and men, respectively).

A gradual reduction in chronic pain was seen with increasing duration and intensity of exercise, regardless of sex and age group. The associations were considerably stronger for those aged 65 years or more compared to those of their younger counterparts (all *P*-values for interactions between age groups and exercise < 0.05). Among the older subjects, the associations were stronger for women than men (all *P*-values for interaction between exercise and gender were < 0.001).

When investigating the association between exercise and chronic pain, several confounders were considered. Adjusting for age, education, and smoking reduced the association between exercise and chronic pain to approximately one half of what it was when adjusting for age only. Additional adjustment for organ-specific disease and depression did not change the associations (data not shown). Physical workload was considered a potential confounder for working participants, however, adjustment for physical workload did not lead to meaningful changes in the associations between exercise and chronic pain (data not shown).

Among those who exercised, we estimated the correlation between frequency and duration of exercise as 0.08, between frequency and intensity 0.34, and between duration and intensity

Table 1
Characteristics of study population, and prevalence of chronic pain^a and non-exercise.^b

	Women			Men		
	n (%)	Chronic pain (%)	Nonexercise (%)	n (%)	Chronic pain (%)	Nonexercise (%)
Age, years						
20–34	4085 (16)	15	18	2835 (13)	11	29
35–49	7443 (30)	28	17	6030 (28)	22	33
50–64	8249 (33)	41	17	7642 (36)	32	28
65–79	4351 (17)	41	22	4145 (19)	28	24
80+	996 (4)	43	42	757 (4)	30	36
Smoke						
Nonsmoker	11,447 (45)	27	16	9029(42)	19	24
Previous smoker	6187(25)	38	16	6468 (30)	30	27
Current smoker	7490 (30)	39	26	5912 (28)	30	39
Education						
Elementary	5214 (21)	45	28	4023 (19)	35	36
Secondary	12,203 (48)	36	19	12,456 (58)	27	31
Higher	7707(31)	21	13	4930 (23)	15	18
Organ disease ^c						
No	18,545 (74)	29	17	14,927 (70)	22	29
One	5030 (20)	40	22	4581 (21)	30	29
Two or more	1549 (6)	58	32	1901 (9)	41	31
HADS-D <8	19,094 (91)	32	17	14,929 (90)	24	26
HADS-D ≥8	2817 (9)	53	30	1728 (10)	43	38
Total	25,124 (100)	33	19	21,409 (100)	26	29

HADS-D, Hospital Anxiety and Depression Scale-Depression.

^c Based on self report of the following: myocardial infarction (heart attack), angina pectoris (chest pain), other heart disease, stroke/brain haemorrhage, kidney disease, diabetes, cancer, epilepsy, chronic bronchitis, emphysema, asthma or COPD (chronic obstructive pulmonary disease).^a Pain lasting more than 6 months and of at least moderate intensity during last month.^b Reports of no exercise or less than once a week or < 15 minutes duration.**Table 2**
Prevalence ratios (PR) for chronic pain with 95% confidence intervals (CI) by frequency, duration, and intensity of exercise in the HUNT 3 study.

	20–64 years						65 years or more					
	Women			Men			Women			Men		
	n	PR ^a	95% CI	n	PR ^a	95% CI	n	PR ^a	95% CI	n	PR ^a	95% CI
Frequency												
Nonexercise ^a	3471	1	Ref	4982	1	Ref	1393	1	Ref	1267	1	Ref
1 time/week	4231	0.92	0.86–0.97	3811	0.90	0.84–0.97	817	0.76	0.69–0.84	748	0.90	0.79–0.95
2–3 times/week	8524	0.90	0.85–0.94	5643	0.88	0.83–0.94	1909	0.73	0.67–0.79	1680	0.73	0.65–0.82
≥4 times/week	3551	1.00	0.94–1.07	2071	1.03	0.95–1.11	1228	0.66	0.60–0.72	1207	0.79	0.70–0.89
Duration												
Nonexercise ^a	3471	1	Ref	4982	1	Ref	1393	1	Ref	1267	1	Ref
15–30 minutes	2213	1.00	0.93–1.07	1618	0.98	0.90–1.07	961	0.79	0.72–0.86	713	0.95	0.83–1.08
30– 60 minutes	10,959	0.92	0.87–0.97	6584	0.90	0.85–0.96	2413	0.70	0.65–0.76	2017	0.75	0.68–0.84
≥60 minutes	3134	0.87	0.81–0.93	3323	0.91	0.84–0.98	580	0.62	0.55–0.71	905	0.72	0.62–0.83
Intensity												
Nonexercise ^a	3471	1	Ref	4982	1	Ref	1393	1	Ref	1267	1	Ref
Light	5491	0.97	0.92–1.02	3031	0.99	0.92–1.06	2797	0.73	0.68–0.78	1882	0.85	0.77–0.94
Moderate	10,228	0.90	0.86–0.95	7529	0.89	0.84–0.94	1069	0.66	0.59–0.73	1691	0.69	0.61–0.78
Hard	473	0.68	0.55–0.84	904	0.77	0.65–0.91	18	0.54	0.25–1.12	29	0.89	0.50–1.60

^a Adjusted for age (15-year categories), smoking (never, past, current), and education (primary, secondary, tertiary).^a Exercising less than once a week or for <15 minutes each time.

0.28. Frequency, duration, and intensity of exercise were all included as covariates in the same model to disentangle their role among those who exercised (Table 3). Similar patterns as those found in the simpler models were seen. For subjects aged 20–64 years, chronic pain was more prevalent among those exercising 4 times or more compared to those exercising once a week (PR 1.10; 95% CI 1.03–1.17 for women, and PR 1.15; 95% CI 1.05–1.25 for men). In general, chronic pain decreased with increasing duration and intensity of exercise. However, for men aged 20–64 years, no clear association was seen between exercise duration and chronic pain.

Frequency and duration were also combined into a measure reflecting the total time spent on exercise during an average week.

For those aged 20–64 years, the total time spent on exercise showed similar but weaker associations with chronic pain as frequency of exercise (data not shown). Adjusting for intensity did not change this. For the older subjects, the associations between total time spent on exercise and prevalence of chronic pain were similar to the associations seen for frequency and duration.

To investigate the effect of the severity of pain on the associations between exercise and chronic pain, the data were reanalysed using different cut-points for pain when ascertaining cases. Selecting 3 (mild) as a cut-point rather than 4 (moderate) resulted in only marginal changes in the associations. Selecting 5 (severe) as a cut-point resulted in lower prevalence ratios but wider confidence intervals. For men aged 20–64 years, the widening of the

Table 3

Multivariable analyses of the association between frequency, duration, and intensity (mutually adjusted) of exercise and chronic pain among those who exercised in the HUNT 3 study.

	20–64 years				65 years and older			
	Women		Men		Women		Men	
	PR ^a	95% CI	PR ^a	95% CI	PR ^a	95% CI	PR ^a	95% CI
Frequency^a								
1 times/week	1	Ref	1	Ref	1	Ref	1	Ref
2–3 times/week	0.99	0.92–1.07	1.00	0.93–1.08	1.00	0.90–1.11	0.87	0.76–1.00
≥4 times/week	1.10	1.03–1.17	1.15	1.05–1.25	0.89	0.79–0.99	0.93	0.81–1.08
Duration^b								
15–30 minutes	1	Ref	1	Ref	1	Ref	1	Ref
30–60 minutes	0.94	0.88–1.00	0.95	0.87–1.04	0.91	0.83–1.00	0.83	0.73–0.95
≥60 minutes	0.89	0.83–0.97	0.97	0.87–1.07	0.83	0.72–0.96	0.81	0.69–0.96
Intensity^c								
Light	1	Ref	1	Ref	1	Ref	1	Ref
Moderate	0.95	0.90–0.99	0.91	0.85–0.98	0.93	0.84–1.02	0.85	0.75–0.95
Hard	0.72	0.59–0.89	0.79	0.66–0.94	0.76	0.36–1.60	1.08	0.60–1.94

PR, prevalence ratio; CI, confidence interval.

^a Adjusted for age (15-year categories), smoking (never, past, current), and education (primary, secondary, tertiary).

^b Additional adjustment for exercise duration and intensity.

^c Additional adjustment for exercise frequency and intensity.

^d Additional adjustment for exercise frequency and duration.

confidence intervals made most of the associations nonsignificant (data not shown).

To check for loss of precision or bias due to incomplete responses, a multiple imputation procedure was performed. Comparing the associations obtained from the multiple imputations procedure and complete case analyses revealed similar results, indicating high reliability of the complete case analyses.

4. Discussion

This study documents a consistent association between frequency, duration, and intensity of recreational exercise and prevalence of chronic pain in the general population. For participants aged 65 years or more, a linear association was seen for every dimension of exercise, and the association was considerable also for the lowest loads. For those aged 20–64 years, the exercise frequency showed a U-shaped relationship with chronic pain, while exercise bouts of more than 30 minutes duration or moderate intensity were needed to show a lower prevalence of chronic pain.

Overall, 29% of the population reported moderate to severe chronic pain. These figures are in accordance with previous studies. The prevalence of chronic pain estimated in seven studies following the International Association for the Study of Pain definition of chronic pain [36] ranged from 11.5% to 55.2%, with a weighted mean of 35.5% [38], and in a pan-European survey, 19% of all adult Europeans, and 30% of the Norwegians reported moderate-to-severe chronic pain [6]. Furthermore, associations with previously well-known risk factors such as gender, age, education, and depression were confirmed.

To our knowledge, this is the first study that investigates the association between frequency, duration, and intensity of recreational exercise and chronic pain of at least moderate intensity in the general population. The findings raise new awareness of the potential benefits of exercise on chronic pain. Several mechanisms may explain a higher prevalence of chronic pain among those not exercising. Physical deconditioning, including reduced cardiovascular capacity, muscular endurance, strength, and motor control may create excessive strain, increased fatigue, and development of micro-injuries [48]. However, there is little evidence that these factors explain chronic pain [5,16,42]. Other mechanisms by which physical activity may operate, such as increased mood, reduced hypervigilance, and anxiety, have received little attention. How-

ever, recreational exercise has shown positive effects on both pain and psychological distress, suggesting a common pathway between recreational exercise and positive mood and pain relief [22,26].

In the working-age population, the prevalence of chronic pain was similar for those not exercising and for those exercising almost every day, whereas it was lower for those exercising 1 to 3 times a week. The reason for this U-shaped relationship is not completely understood. Exercise is generally regarded as a protective factor for health and functioning. However, it has been supposed that both inactivity and excessive activity exerts deleterious effects on general health and compromises musculoskeletal function [1]. A similar U-shaped association between total amount of physical activity and chronic low back pain has been reported previously [20]. The authors noted that individuals engage in a whole range of different activities, some of which may be risk activities and some protective activities of pain. We know little about how exercise may interact with other activities in terms of increasing or reducing the risk for developing chronic pain. However, exercising almost every day may add to the total amount of activity in such a way that the total load of activities increases the risk of chronic pain. On the other hand, we should also bear in mind that many subjects use exercise as a strategy to manage their pain [46]. Accordingly, the U-shape may reflect that a large proportion of those with chronic pain exercise frequently because it eases their pain.

The U-shaped relationship between exercise frequency and chronic pain was not observed for older participants. This difference between the age groups may be attributed to a lower total amount of physical activity among older individuals compared to those of working age [32]. Older individuals generally have lower levels of physical work activities and daily routine activities, and daily exercise may not exceed the total load of physical activity, increasing the risk for chronic pain. To gain insight into this potential interaction between exercise and other types of physical activity, further studies are needed.

Another interesting difference between the age groups was the more distinct association between exercise and chronic pain among the older individuals. Older age is associated with decreasing reserve capacity of musculoskeletal fitness due to physiological ageing and general declines in total activity levels [10,51]. Therefore, the effect of exercise on pain may increase. Also, those who exercise in old age may have done so for a long time, and the payback with reference to chronic pain may require many years

of regular exercise. On the other hand, those who are more likely to maintain exercising in older age may also be more likely to have an innate high pain threshold and therefore report less pain.

Interestingly, among the older adults, the associations were consistently stronger among women than men. This has also been shown previously [7]. The mechanisms underlying this gender difference are not known but should be addressed in future studies.

The analysis including all 3 dimensions of exercise in the same multivariable model showed essentially similar associations as the univariable analyses. This indicates that all 3 dimensions of exercise are of importance for chronic pain, and that mutual adjustment does not change this impression. However, as the 3 dimensions of exercise are correlated and may suffer from different degrees of measurement error, their “independent” associations with chronic pain should be interpreted with some caution [40].

Some limitations of the study need to be addressed. First, the response rate of 54% may reduce the external validity of the results. However, in the previous HUNT surveys, nonparticipation was only minimally dependent on health status [23]. Furthermore, analyses based on the complete response dataset and the multiple imputation dataset were practically identical, indicating high reliability of the analyses based on complete responses. Second, the time frame of the questions measuring exercise was a normal week during the past year. This measure is potentially affected by both a recall bias and a social desirability bias. Interpretation of the responses as the actual extent of exercise should therefore be done with caution. Third, data on comorbidity were obtained by self-report. An underestimation of the prevalence of comorbid conditions would have caused some residual confounding. Moreover, the statistical model failed to converge when entering age, comorbidity, education, and smoking together with exercise. This was solved by including age as a rather broad categorical variable (15-year categories). This could cause residual confounding in the model. However, including age as either a continuous or a 15-year categorical variable in the partly adjusted models revealed minimal differences in the associations. Finally, the cross-sectional nature of the presented data does not allow for any inference about causality between exercise and chronic pain. The causal pathways are likely to be complex and bidirectional. That is, activity level might influence and might be influenced by pain in several ways. The study serves as an exploration of associations, and should indicate which factors are important when investigating the causal links between leisure-time physical activity and pain.

The current study has several major strengths. The use of data from a large population-based health survey made it possible to detect associations even when they were small, and to stratify analyses according to both age and gender without losing statistical power. Furthermore, we were able to control for the effect of a wide range of confounders with extensive data on a variety of health measures and socioeconomic factors. Finally, we used clear case definitions, sensitive to both the duration and severity aspects of chronic pain.

4.1. Conclusion

This study shows that frequency, duration, and intensity of recreational exercise are all associated with a lower prevalence of chronic pain, and that the associations are stronger for older subjects, especially for women. Communicating a potential positive effect of recreational exercise on chronic pain in older age may be of importance as an aging population brings about increasing strain on health care resources. Even though one cannot conclude that exercise may prevent chronic pain based on the current cross-sectional data, benefits of exercise on several disease outcomes have been documented in a large amount of prospective observational studies [19]. As exercise also has shown an effect on the treatment

of chronic pain from randomised controlled trials [1], one may argue that the current results should have implications for the recommendation of physical activity to the general public.

Conflict of interest statement

The authors declare no conflict of interest.

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Paper IV

Longitudinal associations between exercise and pain in the general population - The HUNT pain study

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Abstract

Background: The relationship between physical activity and pain is complex and both cross sectional and prospective population-based studies have difficulties in establishing causal relationships. The aim of the current study was to investigate longitudinal associations between exercise and pain in the general population using both prospective and within-subjects analyses.

Methods: In the population-based HUNT 3 study, participants reported both pain and level of exercise. A random sample of 6419 participants was in addition invited to report their last week pain and exercise every three months over a 12 month period (five measurements in total). We used multilevel mixed effects linear regression analyses to estimate the association between regular levels of exercise (measured in HUNT 3) and subsequent longitudinal reporting of pain. We also used the repeated measurements to calculate within-subjects associations (i.e. the variation in pain as a function of variation in exercise, over time, within individuals).

Results: Among those invited to participate (N=6419), 4219 subjects returned at least two questionnaires. Compared with subjects who reported no or light exercise, those who reported moderate levels of exercise or more at baseline, reported less pain in repeated measures over a 12 month period in analyses adjusted for age, sex, education and smoking. Adjusting for baseline level of pain distinctly attenuated the findings, although they remained significant. Within subjects, an increase in exercise was accompanied by a concurrent reduction in intensity of pain. However, we found no indication that exercise level at one occasion was related to pain reporting three months later.

Conclusion: Regular exercise is associated with a slightly lower level of subsequently reported pain. Exercise and pain are also related within subjects, over time. These data give evidence to a causal relationship between exercise and pain since they are not subject to confounding of time-invariant factors. However, the associations were weak and the mechanisms are likely to be complex and bidirectional.

Introduction:

Pain complaints are common and costly. The prevalence of current pain ranges from 27 % to 49% [1,2], and the prevalence of chronic pain ranges from 11% to 64% in population studies [3-5]. Common pain conditions are major reasons for work related disability and for lost productivity in the work force [6,7]. The health care expenditures among subjects with common pain complaints have been estimated to be more than twice as high as for those without pain complaints, and they seem to continue to escalate [8-10]. Moreover, pain is associated with a substantial reduction in self reported health and functioning [11,12]. These expenses suggest that more attention should be given to potentially effective self management and preventive strategies [13].

Clinical studies have shown that exercise may relieve pain among patients with fibromyalgia and chronic low back pain [14,15] and prevent the recurrence of low back pain after treatment [16]. However, there are conflicting evidence whether exercise may prevent the occurrence of pain among non-patients or not [17-20]. Results are difficult to compare due to high variability in the definitions and measurements of both activity and pain and differences in study design and population. It has been suggested that significant associations may be hidden when measures are dichotomized into active vs. inactive [21]. Physical activity may also be related to the severity of pain once established [22]. In a recent study, we showed that both frequency, duration and the intensity of recreational exercise were independently associated with a lower prevalence of chronic pain of at least moderate intensity in the general Norwegian population [23]. The cross-sectional nature of these findings limits their use in determining causal relationships since low levels of exercise may be both a risk and a consequence of pain. However, in one previous study it was documented that physical activity was associated with less pain measured repeatedly during three years of follow up among midlife women not reporting moderate or severe pain at baseline [24].

Chronic pain is determined by multiple causal chains involving biological, psychological and social risk factors which may interact or be associated with physical activity. A potential relationship may therefore be confounded by other factors. Although such confounding may be adjusted for by multivariable statistical analyses, adjustments depend on the inclusion and the precision of other measures in the dataset, and obviously, the inclusion of the correct

variables in the statistical model. Rest-confounding may therefore occur in multivariable analyses due to measurement error and a failure to include relevant confounders. By employing a longitudinal design it is possible to study whether level of exercise may precede changes in pain. Longitudinal data also makes it possible to study whether changes in pain and in activity are related within the individual. Such analyses are not subject to confounding of factors that doesn't vary within individuals. Thus, the estimates will be less biased.

In the current study, a random sample of subjects from a population-based study reported pain and exercise repeatedly over 12 months. We investigated the longitudinal association between exercise and pain with the aim of answering the following research questions:

Is exercise reported at baseline related to subsequent levels of pain?

Do subjects report less pain at time points when they report higher intensity of exercise?

Does a subject's level of exercise at one time point predict its reporting of pain three months later?

Material and methods:*Study population*

The basis for the present study is the Nord-Trøndelag Health Study (the HUNT study) conducted in the county of Nord-Trøndelag in Norway. The HUNT study consists of three cross-sectional surveys (HUNT 1, 1985-1987, HUNT 2, 1995-1997 and HUNT 3, 2006–2008). All inhabitants in Nord-Trøndelag aged 20 or more (N=94194) was invited to participate in the HUNT 3 study. A total of 50839 (54%) participated. The response rate was higher among women (58%) than men (50%) and lowest among the youngest age groups (31% and 42% for the age groups 20-29 and 30-39 years, respectively). The study population is stable with sex and age distributions similar to the average of Norway, but with somewhat lower levels of education and income compared to national averages. The county is mostly rural and sparsely populated [25].

Participants and procedure

A random sample of 6419 HUNT 3 participants in two municipalities (Levanger and Verdal) was mailed a questionnaire and invited to participation in the current project, which main focus is on physical activity and pain. Questionnaires were mailed every three months for the following 12 months (totally five questionnaires) to those agreeing to participate (n = 4782). Reminders were mailed to non-responders together with a copy of the questionnaire after one month. If the reminder was not returned, but the subjects had not actively withdrawn from the study, no new questionnaires were mailed until the fifth mailing at 12 months follow up.

The study was approved by the Regional Committee for Medical and Health Research Ethics Central-Norway and the Norwegian Data Inspectorate.

Questionnaire

The HUNT 3 questionnaire included three questions regarding exercise during the past year; the average number of times exercising per week (*never, less than once, once a week, 2-3 times per week or almost every day*), the average minutes each time (*less than 15 minutes, 16 – 30 minutes, 30 – 60 minutes or more than 60 minutes*) and average intensity each time (*easy, without breaking a sweat or losing breath, lose breath and brake into sweat or near exhaustion*). The questions have shown acceptable test-retest reliability with kappa values ranging from 0.52 to 0.77 and significant correlations with VO_{2max} (ranging from 0.31 for duration) to (0.43 for frequency) in adult males [26]. In a previous HUNT 3 study [23], we showed that association between frequency of exercise and prevalence of chronic pain was u-shaped among participants in working age, whereas the association between intensity of exercise and chronic pain was linear. The associations were stronger among those above working age (65 years or more) and linear in shape. To account for the unique contribution of all three dimensions (frequency, duration and intensity) of exercise, and the divergence from linearity in the association with chronic pain, we constructed a variable as follows: Those who reported no activity, light intensity activity and activity for less than 30 minutes were defined as reference group. Those reporting moderate to vigorous physical activity of 30 minutes or more were divided into two groups; those who reported 1-3 times per week, and those who reported nearly every day.

The HUNT 3 questionnaire included one question regarding pain intensity: “How much bodily pain have you had during the past four weeks?” This is a six point verbal rating scale including the response options: None, very mild, mild, moderate, severe or very severe. It has been extensively used, among others in the various versions of the SF-36 health survey [27] and is validated as a single item measure as part of the SF-8 health surveys [28].

In the one year follow up study, each of the five mailings included the one week version of the SF-8 bodily pain scale [28]. The scale was transformed according to the scoring procedures by assigning a new value to each response category based on the US SF-36 norm data [28]. This ensured a mean score close to 50 and a standard deviation close 10 in the US normative data. Recreational exercise was defined by giving the following examples: going for a walk, skiing, swimming, exercise or sports. The Borg ratings of perceived exertion (RPE) scale [29] was used as an index of exercise intensity with the following instruction: “On a scale from 6 to 20, how hard is the activity that you usually do when you exercise?”

(Take an average from the last week). The Borg RPE scale has been shown to be a valid measure of exercise intensity in various populations [30]. In a recent investigation using the same instruction in another subsample from the HUNT 3 study, the scale corresponded well with Peak oxygen uptake (VO_{2peak}) measured during an exercise test [31]. Responders were also asked how often they had engaged in recreational exercise during the last week, and the average duration each time. For the purpose of the current study, participants reporting no exercise or exercise of less than 15 minutes were assigned the value 5 and included in the Borg scale. This gave a variable ranging from 5 (no exercise) to 20 (very, very hard).

Information on the highest attained level of education was obtained from the National Education database (NUDB). Educational attainment was classified into three levels; primary, secondary and tertiary.

Statistical analyses:

To investigate longitudinal associations between exercise and pain, multilevel mixed effects linear regression analyses were performed using the `xtmixed` function in Stata version 11.0 for Windows (Stata Corporation, College Station, Texas). In the first analyses the reporting of exercise in the HUNT 3 study (baseline) was used to predict the reporting of pain using information from all five subsequent measurements. That is, we calculated the average difference in pain during the 12 month follow up period between subjects reporting different levels of exercise at baseline. The analyses were adjusted for sex, age, education, smoking and baseline level of pain. In longitudinal studies, mixed models accounts for the dependency of observations within subjects by inducing subject specific (random) effects into the model. This also makes it possible to disentangle the within subjects effects (i.e. the variation in pain as a function of variation in exercise, over time, within individuals) from the between subjects effects (i.e. the variation in pain between individuals as a function of variation in exercise between individuals). In the second analyses we used the repeated measurements in the 12 month follow up to investigate within subjects associations. To do so, predictors (level of exercise at all measurement occasions) were centred around the mean for each person. Each participant's mean score were then subtracted from their scores at each measurement occasion giving deviation scores. In the analyses, the deviation scores were used as predictors to calculate the within subjects associations. Within subjects associations have the advantage of not being subject to confounding by factors that remain constant over time, such as sex,

socioeconomic status, genetic makeup and presence of chronic disease. In the primary model we studied whether change in exercise was associated with a simultaneous change in pain. We then investigated whether level of exercise at one occasion was associated with pain reporting three months later. Mixed models handle missing data at the level of repeated observations by using all available data for each person. Analyses were also carried out separately for each sex, and for those in working age or those above (65 years or more).

Results:

Characteristics of the participants

Of the 6419 subjects invited to participate in the HUNT pain study, 75% (n= 4782) responded to the baseline questionnaire (table1). Among these, 56% were women, 28% were aged 20-44 year, 47% were 45 to 64 years and 24% were 65 years or older. One third of the participants had tertiary education, 50 %had secondary education, and 17 % had only primary education. Compared to the HUNT 3 population, the sex distribution were similar, whereas the proportion of middle aged and individuals with higher education were higher in the HUNT pain study. Less than 15% of the participants were lost to 12 months follow up, and attrition was neither associated with sex nor education. The proportion of subjects in the youngest age group declined somewhat throughout the follow up period, but the mean pain (49.4; sd=9.6) and mean exercise (11.4; sd=3.9) scores were similar throughout the five occasions, indicating no attrition due to the primary study variables. Intraclass correlation coefficients (ICC) for exercise was 0.55 (95% CI 0.54-0.57) and for pain it was 0.66 (95% CI =.65-0.67). Thus, 45% of the variance in exercise and 34% of the variance in pain was accounted for by within-subject variation, respectively. This implies that the measures were quite stable, something that reduces the power to detect significant within subject associations.

Longitudinal associations between exercise and pain

In the HUNT 3 study, subjects reported their level of exercise on an average week during the past year. Compared to those not reporting regular exercise in HUNT 3, those reporting at least moderate exercise 1-3 times a week on average reported less pain during the 12 month of follow up in analyses adjusted for sex, age, education and smoking (coefficient: 1.12; 95% CI: 0.60 – 1.63). The coefficient is positive as higher scores on the SF-8 scale indicate less pain. The difference remained significant, although attenuated when additionally adjusted for baseline level of pain (coefficient: 0.42; 95% CI: 0.23 - 0.82). A similar although weaker association was seen between reports of moderate or hard exercises almost every day and subsequent level of pain (table 2).

Within subjects associations were considered in two different temporal models (table 3). In the first model we investigated whether exercise intensity were associated with concurrently reported pain intensity (during the past week). A significant association was seen (coefficient: 0.25; 95% CI: 0.21 - 0.28), indicating that individuals reported less pain at times when they

reported higher level of exercise. Thus a change from no exercise to moderate exercise was associated with a simultaneous 1.75 points reduction in pain on the SF-8 scale.

Investigating the relation between exercise intensity as predictor and pain intensity three months later, no association was seen (Table 3).

All analyses were also conducted separately for each sex and for those below and above 65 years of age. However, these analyses did not reveal substantial differences in the associations between the sexes and age groups.

Discussion

In this longitudinal population-based study, regular exercise reported at baseline predicted less pain in repeated measures over a subsequent 12 month period. The within subjects analyses revealed no association between exercise at one occasion and pain measured three months later. However, a significant concurrent association between exercise and pain was seen within individuals. That is, subjects reported less pain at times when they reported more exercise and vice versa.

In a recent cross sectional study we found that recreational exercise was associated with a lower prevalence of chronic pain of at least moderate intensity, especially among older subjects [23]. In a previous HUNT study, lower level of physical activity at baseline was associated with higher prevalence of widespread chronic pain 11 years later [32]. However, this study failed to account for baseline pain. It is difficult to infer any temporal relationship between activity and pain from these studies, since pain might have caused reduced physical activity. One previous longitudinal study showed that physical activity was associated with less pain on the SF-36 scale measured repeatedly during three years of follow up among midlife women not reporting moderate or severe pain at baseline [24].

In the present longitudinal study we investigated different temporal relationships between exercise and pain. First, the course of pain over a 12 month period was predicted by baseline level of exercise. Adjustments for covariates notably attenuated the estimate. However, the analyses indicated a significant association that was independent of baseline pain. In the within subjects analyses, level of exercise did not predict pain three months later. There may be several reasons for these seemingly conflicting results. The analyses are distinct in their measurements of activity and pain, in particular their time frames. In the first analyses, the regular level of exercise during the preceding year was used to predict pain measured repeatedly over the following year. This might be a more relevant time frame than the one week used to measure pain and exercise in the within subjects analyses. That is, the regular level of exercise might be associated with the course of pain over one year even though level of exercise during one week was not associated with pain during one week three months later. On the other hand, the within subjects analyses were not confounding by time invariant factors. Thus, the different findings may have occurred due to rest-confounding of the significant results. However, we found a significant within subject association between exercise and pain measured at the same occasion. This finding indicate a direct relationship

between exercise and pain that is not confounded by factors varying between individuals such as sex, socioeconomic status, type of work, genetic makeup, presence of chronic disease etc. However, the close relation in time indicates that the causal mechanisms are reciprocal.

It is difficult to draw firm conclusions about the importance of these findings. Even though we found statistically significant associations, the effect sizes were small and far from what can be regarded as clinically significant [33]. However, considering the high prevalence of chronic pain [5], even low effect sizes could have public health significance. That is, if we could increase the level of physical activity in the population, clinically significant chronic pain could potentially be prevented in a noticeable number of subjects. Future studies should use long term follow up with the aim at identifying the proportion of cases with significant chronic pain that might be prevented by regular exercise. Moreover, the relationship is likely to be stronger in certain clinical populations than in the population at large [14,15]. Identifying subgroups that may benefit more from exercise interventions on a population level should therefore be an objective for future investigations.

Some considerations regarding the statistical analyses need to be mentioned. When modelling within subjects associations, the factors of interest must vary within individuals. In the current study both pain and exercise was relatively stable. This may have reduced our power to study longitudinal associations as only those individuals with time related variations contributed to the within subject estimates. Still, the number of participants was substantial and the model was able to detect significant relations. Although these analyses removed the confounding of time invariant factors, factors that may vary within individuals, such as mood, sleep and anxiety could have confounded the associations. However, these factors may be part of causal chains between physical activity and pain, and including them as time-varying covariates in the analysis would require quite complex theoretical models of the relationships [34]. In the prospective analyses we adjusted for baseline pain. In some cases, when there is considerably measurement error, adjustment for baseline scores of the outcome variable might cause inflation of the association [35]. Such adjustments should therefore be done with caution. Our adjustments, on the other hand, led to an attenuation of the associations, which was in accordance to what would be expected.

We had to rely on self report measures. In terms of pain there is no alternative as pain per definition is a subjective experience. Even though the verbal rating scale we used to assess

pain is well validated [28] , it is unlikely to possess ratio qualities, i.e. equal intervals between the categories. Nevertheless, it has been increasingly recognised that parametric statistics, such as regression analyses, are valid for ordinal pain scales, at least those containing 5 categories or more [36]. Objective measures of physical fitness are likely to give more valid results than self reports of physical activity [37,38]. However, the repetition of measurements at five occasions during one year in a large population-based sample would require extensive financial resources and even though the activity may change, measures of fitness would not change in the same degree. We therefore used the Borg Scale of perceived exertion which gives detailed information on exercise intensity. The scale is well validated and, self-reports of usual exercise intensity is independently associated with VO_{2peak} in the general population [31].

Conclusion:

This longitudinal population-based study shows that baseline exercise predicted the course of pain over a 12 month period and that exercise and pain were related within subjects, over time. These data give evidence to a causal relationship between exercise and pain. However, the associations were weak and the mechanisms are likely to be complex and reciprocal.

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Table 1: Characteristics of the study sample at each follow up (T1-T5) and compared to the entire HUNT 3 population.

	Study sample					Hunt 3
	T1	T2	T3	T4	T5	
	n=4782 %	n=4219 %	n=3926 %	n=3791 %	n=4140 %	n=50827 %
Sex						
female	56.0	56.1	56.3	56.4	56.1	54.6
male	44.0	43.9	43.7	43.6	43.9	45.4
Age						
20 -44 yrs	28.4	26.2	25.1	24.5	26.0	29.6
45-64 yrs	47.4	48.4	48.9	49.1	49.1	43.6
65 yrs or more	24.3	25.4	26.0	26.5	24.9	26.8
Education						
Primary	17.2	16.9	16.7	16.8	16.7	21.2
Secondary	49.7	49.5	49.7	49.6	49.7	52.7
Tertiary	33.2	33.6	33.7	33.7	33.6	26.1

Table 2: Association between exercise* reported in the HUNT 3 study and subsequent reporting of pain† measured every third month during a 12 month follow up period of the HUNT pain study.

	Crude		Adjustment for sex, age, education and smoking		Further adjustment for baseline pain	
	Coefficient	95% CI	Coefficient	95% CI	Coefficient	95% CI
None exercise	0	Ref	0	Ref	0	Ref
1-3 times/week	2.15	1.63 – 2.67	1.12	0.60 - 1.63	0.42	0.23 - 0.82
≥4 times/week	1.53	0.69 – 2.37	0.78	0.03 - 1.60	0.32	-0.32 - 0.96

* Average number of times per week during the last year of at least 30 minutes and either lose breath and brake into sweat or near exhaustion.

† SF-8 Bodily pain scale

Longitudinal associations between exercise and pain

Table 3: Within subjects associations using exercise* to predict pain† at the same time points (concurrent) and after three months (subsequent).

	Coefficient	SE	95% CI	P value
Concurrent	0.25	0.017	0.21 - 0.28	<0.001
Subsequent	0.00	0.02	-0.05: 0.04	0.78

* Perceived exertion; how hard is the activity that you usually do when you exercise?
(Take an average from the last week) 5 = no exercise; 20 = very, very hard.

† SF-8 Bodily pain scale