

Doctoral thesis

Less pain – better sleep and mood? Interrelatedness of pain, sleep and mood in total hip arthroplasty patients

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Scientific environment

I have been employed and funded as a PhD research fellow at the Department of Clinical Psychology, Faculty of Psychology, University of Bergen from 2012 to 2017. Further, I have been a member of the Graduate School of Clinical and Developmental Psychology at the Faculty of Psychology. Also I have been a member of the Bergen Group for Treatment Research, and affiliated with the research environment of the Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital, Bergen, and the Kavli Research Centre for Ageing and Dementia, Haraldsplass Hospital, Bergen from which I also received a research grant.

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Abstract

Sleep and mood disturbances are highly prevalent in chronic pain patients, still sleep parameters have only to a limited degree been included in the studies of patients undergoing total hip arthroplasty (THA). Even less focus has been given to the eventual interrelatedness between pain, sleep and mood beyond studies on the co-occurrence of self-reported symptoms. Therefore, the aim of this doctoral thesis is to examine: 1) How pain relieving THA affects the patients' self-reported sleep or mood disturbance, 2) how THA patients attribute changes in symptoms between pain, sleep and mood, and 3) trajectories of corresponding medication use before and after THA.

This thesis consists of three independent research articles exploring the relationships between pain, sleep and mood through three different perspectives. Paper I is based on a prospective questionnaire-based study. Here, patients from four hospitals across Norway participated by filling out a multi dimensional questionnaire before surgery and 12 months after surgery, containing validated questionnaires on hip related pain and function, sleep, anxiety and depression. Primary findings demonstrated that pain, sleep and mood disturbance were significantly and positively correlated preoperatively. Furthermore, in addition to considerable improvements in functional status and pain after surgery, sleep was also substantially improved. That study also identified a cohort of patients with suboptimal outcomes after the surgery, where persistent insomniacs showed more pain, worse mood disturbance and hip related function the year after THA compared to patients whose insomnia resolved after surgery. Paper II utilized data from the preoperative point of the prospective study forming the basis of Paper I, and explored the patients' perceptions about how their pain, sleep and mood affect each other. An attribution questionnaire was developed specifically for this study, exploring more closely how pain, sleep and mood changed when one of the symptoms worsened, and how pain, sleep and mood changed when one of the symptoms improved. Here, results showed that a large majority of patients perceived worsening of pain to worsen sleep and mood, and conversely, improvements in pain to also improve sleep and mood. Sleep was also perceived to influence pain and mood, but had a lesser impact on other symptoms than pain. Mood was perceived to be the least influential symptom in either direction. Paper III is based on a large register-based study on medication use before and after THA. Here, data from the Norwegian Prescription Database (NorPD) was merged with data from the Norwegian Arthroplasty Registry (NAR), gaining

access to complete data on redeemed analgetics, hypnotics, anxiolytics and antidepressants for a near complete population of hip arthroplasties between 2005 and 2012 (N=49399). Prescription prevalence and total defined daily doses (DDD) was summerized 4 quarters before and 4 quarters after surgery to explore trajectories of medication use the year before and the year after THA. We found that use of medications within all medication classes increased the year before surgery and that analgesics and hypnotic use increased in the postoperative phase. Analgesics and hypnotics showed a significant decrease one year after the surgery.

To conclude, pain, sleep and mood seems to be interrelated in THA-patients, illustrated by reductions in insomnia rates after THA, in perceptions about attributions between pain, sleep and mood both when symptoms worsen and when symptoms improve, and through trajectories of corresponding medication use. Overall, the relationship between pain and sleep appeared more robust than between pain and mood.

List of publications

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List of abbreviations

ADL Activities of Daily Living

BIS Bergen Insomnia Scale

BZD Benzodiazepines

DDD Defined daily doses

DSM Diagnostic and Statistical Manual of Mental Disorders

EEG Electroencephalogram

HADS Hospital Anxiety and Depression Scale

HOOS Hip Osteoarthritis Outcome Scale

IC Informed consent

NAR Norwegian Arthroplasty Register

NorPD Norwegian Prescription Register

NSAID Nonsteroidal anti-inflammatory drug

NSD Norwegian Social Science Data Service

OA Osteoarthritis

OTC Over the counter

PSG Polysomnography

RA Rheumatoid Arthritis

REK The Regional Ethics Committee

QoL Quality of life

VAS Visual Analogue Scale

1. Introduction

Sleep- and mood disturbance are commonly found comorbidities of chronic pain, and scientific and clinical interest in these constructs have surged in recent years. All three disturbances have increased incidence in late life and thus can be expected to increase in prevalence the next decades as a consequence of an ageing population (Neogi, 2013; Sharp & Lipsky, 2002; M. T. Smith & Haythornthwaite, 2004). Also, sleep, mood and pain have substantial impacts on health and disability, representing tremendous health care burdens both at the individual, societal and economic level (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006; Morin & Benca, 2012; Neogi, 2013; Wittchen et al., 2011). Moreover, when these disturbances occur together in a cluster of symptoms, a synergistic interaction effect on pain tolerance is seen (Sivertsen et al., 2015) and in turn their combined impact in terms of personal suffering and lost productivity is likely magnified (Wilson, Eriksson, D'Eon, Mikail, & Emery, 2002). The presence of sleep and mood disorders complicates the treatment and rehabilitation of patients with chronic pain (Gureje, 2007), and consequently there is a lot to gain in understanding how pain, sleep and mood influence each other.

Taken together, epidemiological, cross-sectional, and prospective studies suggest that chronic pain, sleep- and mood disturbance are mutually interrelated, each increasing the risk for the emergence and/or exacerbation of the other (Finan & Smith, 2013). However, there is a paucity of treatment studies on chronic pain reporting sleep as an outcome, and furthermore sleep is not adequately evaluated in existing treatment studies of pain (M. T. Smith & Haythornthwaite, 2004). Secondly, few studies have systematically conceptualized and investigated all three disturbances as an interacting symptom constellation or cluster (Finan & Smith, 2013). Thirdly, the trajectories of chronic pain is modulated by how we *think* of it and how we *deal* with it. For example, causal attributions are a core component of the thinking of the chronic pain patient. These attributions enable a person to predict and hence influence future events, and are, accordingly, found to predict thoughts and behavior aimed at getting well, and motivation to perform preventive health behavior such as symptom management (Michela & Wood, 1986). In chronic pain specifically, such attributions are found to be central cognitive facilitators or impediments to the recovery process (Dean, 1986; DeGood & Kiernan, 1996; Michela & Wood, 1986; Roesch & Weiner, 2001). Symptom management on the other hand, such as pharmacological treatment may alter the trajectory of chronic pain by disrupting the vicious cycles that are often in play.

Elaborating on the pain-sleep-mood interrelationships to include attributions and symptom management will therefore potentially enhance our understanding of this symptom cluster.

In the following sections, the background highlights the theoretical and empirical foundation of the thesis. The first section culminates into the research questions and hypotheses of the present thesis. Further, I then describe the methods used, and present the main results. Later I conclude the thesis by discussing the findings in relation to previous research in the field, the methodological challenges that arise, and the possible implications from the results presented.

1.1 Chronic pain and pharmacological symptom management

Pain is most often defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (The IASP Taxonomy Working Group, 2013) and is associated with a state of vigilance (G. J. Lavigne, Nashed, Manzini, & Carra, 2011). Its expression is influenced by mood (depression, anxiety, catastrophizing), context (beliefs, expectations, placebo), and cognitive sets (hypervigilance, attention) (Tracey, 2010; Tracey & Mantyh, 2007). Acute and chronic pain are different clinical entities. Acute pain is a necessary defence mechanism, related directly to the degrees of existing or imminent tissue damage, and is essential for survival. Chronic pain, defined as pain lasting more than 3 to 6 months, serves no defensive or helpful function, since neither the intensity nor the quality of chronic pain are related to the degree of tissue damage (Dray & Read, 2007). Chronic pain has been ranked the top cause of quality-adjusted life-year loss in primary care, ahead of recognized sources of burden of disease such as depression, anxiety disorders, diabetes, respiratory conditions, high blood pressure and chronic heart disease (Fernandez et al., 2010). Chronification of pain severely increases risks for adverse trajectories and vicious cycles with other comorbidities.

Osteoarthritis (OA) refers to a heterogenic group of painful conditions involving alterations in the structure of the joint (Felson, 2000; Hunter & Felson, 2006) and is the number one cause of chronic pain in European countries (Breivik et al., 2006). As opposed

to other chronic pain conditions which reaches a prevalence plateau in adulthood, prevalence of OA continues to increase well into old age, afflicting 33 % of persons over 65 years (Neogi, 2013). Pain is the most protruding symptom of OA, but also stiffness in and around the joint, limited moveability, and signs of mild inflammation is common (Creamer, 2000). Changes in the joint may in many instances be seen on radiological images, but radiological findings and pain does not necessarily correspond (P. A. Dieppe & Lohmander, 2005). Pain is usually mild and stable early in the course of the disease but some patients experience rapid increase in pain and reduction in function, until it reaches disabling levels whereby a THA is normally recommended (Flugsrud et al., 2010). A high number of patients also experience nightly pain that negatively affects sleep (Allen, Renner, Devellis, Helmick, & Jordan, 2008a; Hawker et al., 2008; Woolhead, Gooberman-Hill, Dieppe, & Hawker, 2010), and a majority states that the onset of the night pain debuts as their OA progressively worsen (Demierre, Castelao, & Piot-Ziegler, 2011). Both the pain from moving and finding a comfortable position, and pain from stiffening of the joint are key elements to nocturnal pain (Woolhead et al., 2010).

1.1.1 Measurement of pain and pain related symptoms

Pain can be assessed through self-report, observational (behavioral) or physiological measures, but because pain by definition is a subjective experience, patients' self-reports provide the most valid measure. Subjective pain measurements help determine characteristics of the pain such as its severity, type and frequency. Pain scales for patients with joint disorders are available that considers pain in relation to activities and movement in the hip joint, and they efficiently track changes in function, symptoms and pain. In the present thesis, both general pain and hip related pain is assessed through self-report. The presence of pain is also indirectly indicated by being prescribed analgesics.

1.1.2 Pharmacological pain management

Pharmacological treatments (also referred to in the present thesis as medication use) with analgesics is the predominant pain management (Hochberg et al., 2012). Persons with joint pain often use multiple analgesics simultaneously, either from the same (Kovac, Saag, Curtis, & Allison, 2008) or different medication classes (Albert, Musa, Kwoh, Hanlon, & Silverman, 2008; Sawyer, Bodner, Ritchie, & Allman, 2006). The use of oral analgesics like paracetamol (Non-opioids), nonsteroid anti-inflammatory drugs (NSAIDs) and opioids are common (Zhang et al., 2008; Zhang et al., 2010), both as prescribed or as over the counter (OTC) medications (Driban et al., 2012). When pain is mild, paracetamol sold OTC is often sufficient to manage the pain. In Norway, some NSAIDs are also sold OTC, but is often prescribed by the doctor when the analgesic effect of paracetamol is inadequate (Zhang et al., 2008). Opioids are powerful, prescription analgesics which can be prescribed when other analgesics insufficiently reduce pain or is not tolerated by the patient (Zhang et al., 2008). Use of analgesics is associated with side-effects, and older persons are especially vulnerable because of a number of age-related changes that affect how medications are absorbed, work and are metabolized in the body (Avouac, Gossec, & Dougados, 2007; Folkehelseinstituttet, 2013; Gallagher, Barry, & O'Mahony, 2007).

1.2 Sleep disturbance and pharmacological symptom management

Sleep is central in terms of maintenance and restitution of bodily and mental functions (Flaherty, 2008) and can be defined as a reversible behavioural state of perceptual disengagement from and unresponsiveness to the environment. It represents a complex amalgam of physiological and behavioural processes (Carskadon & Dement, 2011). As opposed to the high vigilance state of pain, sleep is a state of low vigilance that allows the sleeping brain to preserve sleep continuity. However sleep is characterized also by its readiness to react instantly to potentially harmful inputs (major arousal to full awakenings)

(G. Lavigne et al., 2004; G. J. Lavigne, Smith, Denis, & Zucconi, 2011). The inherent property of pain as a threat to survival makes it a particularly potent disrupter of sleep.

Sleep disturbance describes subjectively perceived sleep problems that are bothersome to the individual. It is the form, severity and duration of the symptoms that differentiate transient sleep disturbances from complaints that warrants clinical attention. Sleep disorders are divided into six main clinical divisions; insomnia, central disorders of hypersomnolence, parasomnias, sleep-related movement disorders, circadian rhythm sleep-wake disorders and sleep-related breathing disorders (American Academy of Sleep Medicine, 2014). Insomnia is the most prevalent sleep disorder and represents an ongoing difficulty of initiating sleep, maintaining sleep, early morning awakening up earlier or experiencing chronically non-restorative sleep, despite adequate opportunity to sleep (Edinger et al., 2004). Insomnia can be a situational, recurrent, or persistent problem (Morin & Benca, 2012) and can occur as a primary or comorbid condition.

Insomnia rates increase with age, from about 4 % in healthy young adults to 25% in older adults (Sivertsen, Krokstad, Overland, & Mykletun, 2009). Rates increase to as much as 53-93% when co-occurring with chronic pain (Brennan & Lieberman, 2009; N. K. Tang, Wright, & Salkovskis, 2007). The presence of insomnia has been linked to many negative consequences, including poorer daytime functioning (eg, tiredness, poorer concentration, memory, and alertness) and increased mood disturbance (eg, irritability, lethargy) physical and mental health complaints, increased health care utilization, work disability and mortality (Ohayon, 2005; Sivertsen, Krokstad, Mykletun, & Overland, 2009; Sivertsen, Krokstad, Overland, et al., 2009; Sivertsen, Overland, et al., 2009; Sivertsen et al., 2014; N. K. Tang et al., 2007). Together, these factors likely interact to deplete the resources of the person and make it even more difficult to manage the pain (N. K. Tang, 2009). Furthermore, the presence of sleep disturbance increases the risk of developing new onset chronic pain (Gupta et al., 2007). Detecting and treating insomnia are therefore important aims in chronic pain patients.

1.2.1 Measurement of sleep

The gold standard of sleep assessment is polysomnography (PSG), where EEG (Electroencephalogram) electrodes are used to measure the brainwave-patterns that are altered as a person moves from a waking state to sleep, and through the different stages of sleep. Despite the clear benefits of this method to monitor sleep quantity and quality, it suffers from practical limitations for the use in large-scale research settings. Furthermore, a diagnosis of insomnia does not require that sleep disturbance be documented objectively (Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006). Single-item assessment of sleep quality or a visual analogue scale (VAS) to index the severity of the sleep complaints have been used in previous research, but their ability to detect symptoms of specific sleep disorders are limited. Several insomnia-specific self-report questionnaires exist that assess cases of insomnia, which are validated against objective measures such as PSG and the sleep latency test. In the present thesis, general sleep and the presence of insomnia is assessed through self-report. Cases of insomnia are also indirectly indicated by being prescribed hypnotics.

1.2.2 Pharmacological management of sleep disturbance

Milder forms of sleep disturbance and insomnia may respond well to nonpharmacological treatment such as sleep hygiene approaches and cognitive behavioral therapy for insomnia. Sedatives and hypnotics are recommended for the short-term management of insomnia (Folkehelseinstituttet, 2016; NICE, 2004) and are used by approximately 1.4% percent of home dwelling persons and 17.3% of persons with insomnia (Sivertsen, Krokstad, Mykletun, et al., 2009). In patients with osteoarthritis, the prevalence of hypnotic use increases to 31% (Allen, Renner, DeVellis, Helmick, & Jordan, 2008b). Sleep medications consist of benzodiazepines (BNZ), z-hypnotics (zopiclone, zolpidem, eszopiclone), melatonin, antidepressants with sedative effects, antihistamines and hypocretine-antagonists. Although proper use of these drugs effectively relieves insomnia symptoms short term, benzodiazepine hypnotics as well as z-hypnotics are considered addictive by the Norwegian Medicines Agency due to side effects such as development of tolerance, risk of misuse, and dependence (Folkehelseinstituttet, 2013; Hajak, Muller, Wittchen, Pittrow, & Kirch, 2003). Treatment guidelines recommend short-term use only, i.e., 2–4 weeks, however, studies indicate that

drug use for longer periods or in higher doses than recommended is prevalent, and is associated with patient characteristics such as old age and multiple drug use (Neutel, 2005). Hypnotic BZD should not be used in the elderly at all, still, substantial numbers of Norwegian older persons receive prescriptions for BZD (Neutel, Skurtveit, & Berg, 2012).

1.3 Mood disturbance and pharmacological symptom management

Mood, a temporary state of mind or temper is a basic psychological state that can be described as having either a positive or negative valence, but it is the negative mood (for example depressive or anxious moods) that has received the greatest attention as comorbid to chronic pain and sleep disturbance. When several symptoms of negative moods are present for a prolonged period of time it can warrant a clinical diagnosis of depression or anxiety. In the present thesis, the term mood disturbance is used to refer to both symptoms of anxiety and depression, when not otherwise specified. Depression is the most commonly studied mental disorder in the context of chronic pain (Gureje, 2007) and manifests as a combination of feelings of sadness, loneliness, irritability, worthlessness, hopelessness, agitation, and guilt, accompanied by an array of physical symptoms and sleep disturbances (Sharp & Lipsky, 2002). The association of pain with anxiety disorders is much less studied despite the close comorbidity between anxiety and depression in chronic pain (Gureje, 2007). Anxiety typically entails feelings of anxiousness, uneasiness, fear or panic, also accompanied with physical symptoms and disturbed sleep. Chronic pain is known to increase the risk of developing depression and anxiety disorders (McWilliams, Goodwin, & Cox, 2004; Tsang et al., 2008), and prevalence of the two latter disorders in populations with joint disorders vary from 19% to 40% (Axford et al., 2010; Gleicher, Croxford, Hochman, & Hawker, 2011; Hawker et al., 2008; Patten, Williams, & Wang, 2006), depending on the measure used and the specificity of the measure.

1.3.1 Measurement of mood disturbance

Assessments of mood disturbance should differentiate between mood, symptoms of depression and anxiety and a clinical diagnosis of depression and anxiety. The latter entails fulfilling diagnostic criteria, for example from the Diagnostic and Statistical Manual of Mental Disorders, version 5 (DSM-5; American Psychiatric Association, 2013), and

warrants a clinical interview with the patient. The presence of symptoms of anxiety and depression can be assessed through self-report measures and is frequently used in research to detect possible cases of the disorders in question. On the other end of the spectrum is mood, which is more transient states of positive or negative feelings, also assessed through self-report. In the present thesis self-report is used to indicate symptoms of anxiety and depression (hereby referred to as anxiety and depression) and positive or negative mood. Cases of anxiety and depression are also indirectly indicated by being prescribed anxiolytics and antidepressants, respectively.

1.3.2 Pharmacological management of mood disturbance

Management of mood disturbance may involve a number of different therapies: medications, behavior therapy, and medical devices. Antidepressants is a group of medications first and foremost known for the ability to normalize depressive symptoms (Lingjærde, 2006). Approximately 4% of the general population use antidepressants (Alonso et al., 2004), increasing to between 23% and 43% in persons suffering from depression (Alonso et al., 2004; Colman, Wadsworth, Croudace, & Jones, 2006). It is assumed that the prescription rates (percent of persons prescribed) are higher in chronic pain populations than in the average population, both because the prevalence of depression is higher in the former population (Bair, Robinson, Katon, & Kroenke, 2003), and because antidepressants are sometimes prescribed for pain (Kroenke, Krebs, & Bair, 2009). Although considered relatively safe to use, antidepressants also can give side-effects, especially in older persons (Bakken et al., 2013; de Abajo, Rodriguez, & Montero, 1999)

Anxiolytics consists mainly of benzodiazepines, and are now recommended primarily for the short-term treatment of anxiety disorders (Bandelow et al., 2008; Mitte, Noack, Steil, & Hautzinger, 2005). In the general population, approximately 10% use anxiolytics, while approximately 23% of persons with anxiety disorders use them (Alonso et al., 2004). Anxiolytic benzodiazepines are recommended only to be prescribed/used by the lowest effective doses in older persons (Neutel et al., 2012).

1.4 Interrelatedness between pain, sleep and mood

As described in the previous sections, sleep- and mood disturbances are common comorbidities to chronic pain (Brennan & Lieberman, 2009; Fielden et al., 2003; Gureje, 2007; N. K. Tang et al., 2007). The next section will present the basis for considering these symptom constellations as interrelated, that is reciprocally or mutually related. This entails that changes in pain levels such as worsening or improvement in pain affects sleep and mood, and vice versa. Furthermore, these interrelationships are expected to be mirrored in both how patients perceive these symptoms to affect each other as well as in the corresponding pharmacological symptom management.

1.4.1 Interrelationships in symptoms

The relationship between pain and sleep is best described as bidirectional where one symptom adversely impacts the other (Finan, Goodin, & Smith, 2013). Pain is perceived during sleep (G. Lavigne et al., 2004) and leads to alterations in sleep architecture such as impairments in the restorative effect of sleep (Blagestad et al., 2012). The risk of nonrestorative sleep and development of pain associated insomnia increase with more severe pain (Moldofsky, 2001). Conversely, disturbed sleep also has a negative effect on pain perception the following day (G. J. Lavigne, Smith, et al., 2011; Schrimpf et al., 2015), and furthermore, has been associated with a lowered pain threshold (Chiu et al., 2005; Onen, Alloui, Gross, Eschallier, & Dubray, 2001). Additionally, a synergistic interaction effect on pain tolerance is seen when combining insomnia and chronic pain (Sivertsen et al., 2015).

Mood disturbance also affects, and is affected by pain. Patients with pain, especially in multiple locations and particularly involving pain of the joints, are more prone toward developing a first onset, and a chronic course of depressive and anxiety disorders compared to subjects without such pain (Gerrits, van Oppen, van Marwijk, Penninx, & van der Horst, 2014; Gerrits et al., 2012). Conversely, anxiety is also associated with an increased risk of developing subsequent pain and is shown to modulate pain thresholds and amplify pain (Feeney, 2004; Hubbard et al., 2011). Disturbed sleep is in turn closely related to mood disturbances, which also works in a vicious dysfunctional circle (Camillo, Thompson, Goodman, & Jiang, 2013) exacerbating all symptoms.

These abovementioned findings reflect the negative, vicious exacerbating cycle between pain, sleep and mood. Conversely, there is also recent research highlighting the amplifying effect of improvements of sleep and mood involved in the recovery from chronic pain (Ashworth, Davidson, & Espie, 2010; Davies et al., 2008; Zautra, Johnson, & Davis, 2005). Improvements in pain also improve sleep and mood (Berge, Dolin, Williams, & Harman, 2004). Conversely, restorative sleep is involved in the resolution of chronic pain (Davies et al., 2008), and chronic pain patients that are “good sleepers” report less pain at night, less negative consequences from their pain and less depression and anxiety (Ashworth et al., 2010). In fact, sleep rebound consecutive to sleep deprivation produces an analgesic effect similar to that observed with acetaminophen or NSAIDs) in healthy volunteers (Onen et al., 2001). Restorative sleep is also shown to affect daily functioning, where it increases positive feelings and facilitates coping with the challenges the next day (Vandekerckhove & Cluydts, 2010) possibly through buffering the relationship between pain and negative affect (Hamilton, Nelson, Stevens, & Kitzman, 2007).

1.4.2 Perceived interrelationships.

The need to find an explanation for suffering is an overriding theme in chronic pain patients (Toye et al., 2013). Thinking about the interaction between pain and sleep is an integral part of chronic pain patients’ insomnia experience (Afolalu, Moore, Ramlee, Goodchild, & Tang, 2016) and they often attribute specific causal relationships in terms of how these conditions influence each other (Hawker et al., 2008; Theadom & Cropley, 2010). For example, it is common for chronic pain patients to attribute their sleep problems to their pain, and believe that their sleep will not improve unless their pain is relieved. Examples of such cognitions are “I can never get comfortable in bed because of the pain,” “The pain will wake me up predictably,” and “I won’t be able to cope with my pain if I don’t sleep well (Theadom & Cropley, 2010). Moreover, Afolalu and colleagues (2016) showed that chronic pain patients often considered their current pain when judging sleep quality. For example, increases in pain were perceived as an indicator of poor night’s sleep and emphasize the self-perpetuating cycle of pain and poor sleep. Considering the association between pain and sleep upon worsening of these symptoms, causal attributions between them are not unsubstantiated considering that poor sleep is usually a marker for worsened physiological and psychological pain-related outcomes (Finan et al., 2013). Importantly, as mentioned in

the previous sections, recent findings illuminate the positive effect of improved sleep on pain and mood, and it is possible that chronic pain patients also hold corresponding beliefs about how improvement in one parameter causes improvement in the other parameter.

1.4.3 Interrelatedness in pharmacological symptom management

Given the close relationship between chronic pain, sleep- and mood disturbance, high levels of comorbidity would be expected to be mirrored in medication use. There is however a paucity in studies on chronic pain patients' reporting on medication use beyond the use of analgesics, but the few that do, report antidepressants and anxiolytics to be frequently prescribed alongside analgesics (Fishbain, 2005). Comorbid hypnotic use is reported by approximately 30% (Allen et al., 2008b). Interrelatedness between pain, sleep and mood would also be indicated if prescription rates related to one comorbid medication class was affected by the reduction of symptoms corresponding to another medication class. For example, one could expect the use of hypnotics, antidepressants and anxiolytics to decrease in addition to decreased analgesics if pain was improved.

1.5 The total hip arthroplasty

As opposed to many other chronic pain conditions, which by definition are intractable, there is a treatment option for patients suffering from osteoarthritis or other chronic pain conditions affecting the joints. In a THA, the patient's degenerated hip joint is replaced with an artificial hip joint. Coined the surgery of the century, THA is one of the most frequent surgeries in the orthopaedic field (Learmonth, Young, & Rorabeck, 2007). It has been shown to be an effective procedure for people with severe hip osteoarthritis, unresponsive to conservative therapy with substantial improvements in pain and function (Hamel, Toth, Legedza, & Rosen, 2008; Learmonth et al., 2007) and is cost effective in improving quality-adjusted years of life (Jenkins et al., 2013). The rates of THAs have

steadily increased the last decades, and in Norway, 8402 primary hip replacements was done in 2015 (Norwegian Arthroplasty Register, 2016). The most frequent cause of eligibility of THA (69%-79%) is OA (Bolland et al., 2011; McHugh, Campbell, & Luker, 2011; Norwegian Arthroplasty Register, 2016). The patient being eligible for THR differ in some respects from those with OA not receiving the operation, including higher level of pain and disability (McHugh et al., 2011) and more stable levels of pain (Kapstad et al., 2007). Therefore, studies on OA-patients cannot automatically be generalized to THA patients. However, they display similar rates of medical comorbidities (Bolland et al., 2011; McHugh et al., 2011) and the presence of comorbid joint pain in addition to the index joint (P. Dieppe et al., 2009; Hoogbeem, den Broeder, Swierstra, de Bie, & van den Ende, 2012). Comorbid joint pain affects over 50% of OA patients, and is associated with unfavourable outcomes on pain, functioning, fatigue, distress and health-related quality of life and higher use of analgesics (NSAIDs and opioids) compared to OA patients without comorbid joint pain (Hoogbeem et al., 2012). Nocturnal pain is present in 4 out of 5 OA patients, and is associated with perceptions of sleep disturbance, affecting both sleep onset and sleep maintenance (Woolhead et al., 2010) and the presence of intrusive night pain is widely used by surgeons as a criterion for recommending THA (Naylor & Williams, 1996). Still, sleep has to a very limited degree been included as an outcome measure after this well established surgery. THA is the treatment design forming the basis of the present thesis.

1.5.1 Pain, sleep, mood and medication use before and after total hip arthroplasty

1.5.1.1 Pain

In addition to the well-documented improvements in function after THA (Hamel et al., 2008; Jones, Voaklander, Johnston, & Suarez-Almazor, 2001), pain is the most investigated outcome measure of THA with significant improvements found already 8 weeks after surgery (Riediger, Doering, & Krismer, 2010) and pain reduction is sustained long-term (up to 7 years) (Nilsson & Isaksson, 2010). The greatest improvements in pain seem to take place within the first 3 to 6 months after surgery (Ethgen, Bruyere, Richy, Dardennes, & Reginster, 2004; Naal et al., 2015), with large effect sizes (Busija, Osborne, Nilsson, Buchbinder, & Roos, 2008) and improvements are found regardless of age (Hamel et al.,

2008; Jones et al., 2001). At 12 months, more than 90% of the patients were satisfied or very satisfied with the achieved result of the surgery (Naal et al., 2015). THA caused pain scores to return to normative population values, and when improvement were found to be modest this seems to be caused by different comorbidities (Ethgen et al., 2004). A review recently reported that between 9% and 24% of patients report long-term unfavourable pain after surgery (Beswick, Wylde, Gooberman-Hill, Blom, & Dieppe, 2012), but whether these reports are affected by the presence of comorbidities or comorbid joint pain are not established.

1.5.1.2 *Sleep disturbances*

Despite decades of research on the pain-sleep relationship, sleep has only to a limited degree been included in THA research, and even less as an outcome measure after surgery. The studies to date both confirm the high rate of sleep problems in this population (Fielden et al., 2003; McHugh et al., 2011), and the improvement of sleep problems found after surgery (Bogoch, Olschewski, Zangger, Henke, & Smythe, 2010; Fielden et al., 2003). Most of these studies, however, used poorly validated measures of sleep such as VAS rating scales of sleep quality. One study measured sleep with a self-made questionnaire in addition to validated subjective and objective measures before and 3 months after THA (Fielden et al., 2003). Here, the participants reported that their usual sleep averaged 20 minutes longer, with fewer awakenings after surgery. In all, 75 % improved in terms of how hip pain disturbed sleep, and between 30% and 44% reported improvements in how comorbid pain disturbed sleep, in difficulty falling asleep, with waking up refreshed and getting enough sleep. Using objective sleep measures, a significant reduction was seen in the amount of time spent in bed after surgery, with trends for a reduction in the amount of activity during sleep and more efficient and less fragmented sleep. That study however, only investigated sleep 3 months post-surgery in a relatively small sample (48 patients). Preoperative sleep has also been found to be the best predictor for postoperative sleep and pain in THA-patients (Bogoch et al., 2010) and sleep disruptions 1 month after total knee arthroplasty predicted in another study greater disability at 3 months postoperative (Cremeans-Smith, Millington, Sledjeski, Greene, & Delahanty, 2006). Collectively, these findings support that sleep is a central condition in

THA patients and underscore the need to include validated measures of sleep in THA studies.

1.5.1.3 *Mood disturbances*

The presence of mood disturbances (both general mental health and disease specific symptoms of anxiety and depression) is negatively associated with pain, function, activity and quality of life (Hossain et al., 2011; Riediger et al., 2010). Preoperative mood disturbance is also found to predict postoperative functional outcome and mobility, postoperative pain, pain relief, use of pain medication, activity, use of walking aids and quality of life (QoL) (Hinrichs-Rocker et al., 2009; Montin et al., 2007; Pinto, McIntyre, Ferrero, Almeida, & Araujo-Soares, 2013; Quintana, Escobar, Aguirre, Lafuente, & Arenaza, 2009; Riediger et al., 2010; Rolfson, Dahlberg, Nilsson, Malchau, & Garellick, 2009; Singh & Lewallen, 2010; Wylde, Hewlett, Learmonth, & Dieppe, 2011). Regarding mood disturbance as outcome after surgery, results are more mixed, and depend partly on the specificity of the measure. Reviews consequently find increased global QoL after surgery (Ethgen et al., 2004). On the global measure of mental health statistical moderate improvements are consistently found after surgery (Badura-Brzoza et al., 2008; Jones et al., 2001; Vogl, Leidl, Plotz, & Gutacker, 2015) with small to medium effect sizes (Busija et al., 2008; Jones et al., 2001) often reaching normative values for the age-matched general population (Jones et al., 2001; Shan, Shan, Graham, & Saxena, 2014). The improvements are also long-lasting and remains improved 7 years later (Nilsson & Isaksson, 2010). However, measures of mental health in the QoL scales used in the aforementioned studies are general and less specific when it comes to more defined mood disturbance such as anxiety and depression. This is illustrated by a study conducted by Salmon and colleagues (2001) where they found an overall improvement in QoL mental health 6 months after surgery. Specifically, anxiety improved and depression did not. These results illustrates well the mixed results on the outcome of mood disruptions after THA. Other studies find no changes in anxiety or depression scores (Riediger et al., 2010) or trait anxiety (Montin et al., 2007). Two studies find that at 12 weeks postoperatively, and sustained at 12 months, significant improvements were found in both anxiety and depression subscales (Badura-Brzoza et al., 2008; Duivenvoorden et al., 2013). However it is worth noticing that the

preoperative anxiety and depression prevalences found in these studies (22% and 24%, respectively) were higher than comparable studies (5%-8% for anxiety and 5%-14% for depression) (Berger et al., 2011; McHugh et al., 2011; Singh & Lewallen, 2010).

Collectively these results show that the effect of THA on mood disturbance is still unknown and probably depends on a number of factors such as sample characteristics in addition to ways of measuring the constructs. More importantly, it illustrates that one cannot generalize findings of mental health generic measures without missing important distinctions between anxiety and depression, and validated, disease-specific measures of anxiety and depression needs to be used in order to establish whether THA improves mood disturbance beyond QoL.

1.5.1.4 *Pharmacological symptom management*

Patients awaiting THA are high consumers of medications such as analgesics to manage pain (Berger et al., 2011; McHugh et al., 2011; Nilsson & Isaksson, 2010; Thomazeau et al., 2014), and medication use increases over time as surgery approaches (Berger et al., 2011). Because of the pain-reducing effect of THA, a natural consequence of the surgery would be reduced need for analgesics. Despite of this, to date only one study have investigated medication use before and after THA, exclusively investigating one class of analgesics. A considerable reduction in NSAID use was found after surgery, from 21% preoperatively to 8% postoperatively (adjusted for age, gender and number of comorbidities) (Bolland et al., 2011). However, NSAID use only constitutes a fraction/part (42%) of prescribed medication for these patients (McHugh et al., 2011). Opioids for example, carry with them higher risks of adverse side-effects, tolerance and addiction (Avouac et al., 2007) and reductions of such drugs would therefore be of high clinical relevance. In addition to analgesics, THA-patients are often prescribed psychotropic drugs to control sleep problems and mental health problems (McHugh et al., 2011), and a further potential benefit of THA would be a reduction in these drugs as well as symptoms of sleep- and mood disturbances. In accordance with this, one study reports a decrease in the use of antidepressants after THA (Duivenvoorden et al., 2013). However, that study also reports higher rates of preoperative depression than comparable studies, and these results therefore needs to be replicated. Hypnotic use have been investigated prior to and after total knee arthroplasty (Fuzier et al.,

2014). Here, Fuzier and colleagues found an increase from 18% to 29% in terms of patients who dispensed at least one prescription the whole year after surgery compared to the whole year before. One potential limitation of summarizing the whole postoperative year as a measure of the effect of the surgery is increased pain and possibly sleep problems in the immediate postoperative phase which could explain an increase in medication use. To obtain a more reliable picture of actual prescription use, it is therefore important to investigate shorter prescription windows.

2. The aims of the study

As described, patients with pain in the joints eligible for THA make up a substantial portion of chronic pain patients. Despite the high prevalence of sleep disturbances in this population, and the assumed interrelatedness between pain, sleep and mood illustrated in the introductory part of this thesis, very limited efforts have been made to illuminate these relationships in THA patients. Due to the high cost of the illness cluster, combined with the large potential for synergetic improvements in symptoms after THA, it is important to characterize the role of sleep- and mood disturbance in these patients. The main aim of this thesis is therefore to explore the interrelatedness between pain, sleep and mood in 1) symptoms, 2) perceived attributions and 3) pharmacological symptom management before and after THA.

2.1 Research Questions and Hypothesis for Paper I

In paper I the following questions are addressed: 1) how symptoms of pain, insomnia and anxiety and depression are correlated preoperatively, 2) the effect of THA on insomnia, anxiety and depression, in addition to pain and hip related outcomes such as stiffness, function and QoL and 3) how levels of pain, anxiety and depression differ between patients with persistent insomnia after THA compared to patients whose insomnia resolved after THA.

It is hypothesized that pain, sleep and mood are correlated before surgery (H1). I also expect insomnia rates to improve after THA (H2). Lastly, I expect persistent insomnia patients to report higher postoperative levels of comorbid pain, anxiety and depression rates and worse functional status than patients with transient insomnia (H3).

2.2 Research Question and Hypothesis for Paper II

In paper II I ask how patients waiting to undergo THA attribute symptoms to affect each other. More specifically, do they perceive worsening in one symptom to affect another symptom? And secondly, do they perceive improvements in one symptom to affect the other symptoms?

My hypothesis is that patients will perceive relationships between pain, sleep and mood, where worsening in one symptom is perceived to worsen the other symptoms and improvements in one symptom is perceived to improve the other symptoms (H1), and that the relationship between pain and sleep is perceived to be more robust than the pain-mood or sleep-mood relationship (H2).

2.3 Research Questions and Hypothesis for Paper III

In Paper III I aim to describe medication use before and after THA, both for analgesics, but also for hypnotics and mood stabilizers (anxiolytics and antidepressants).

I expect that the prescriptions of analgesics, hypnotics and mood stabilizers increase as the surgery approaches (H1), that I will also find increased medication use of analgesics, but also for hypnotics, anxiolytics and antidepressants in the three month postoperative phase (H2), and that medication use from all medication classes are reduced after THA (H3).

3. Methods

The overarching research methodology for the thesis draws on an established treatment design for assessing the effect of THA, the prospective one-person pre post-design. In paper I and II, data are derived from a prospective treatment study using THA as pain-reducing intervention. Paper I investigates sleep, pain and mood prospectively before and after THA. Paper II is a cross-sectional study utilizing data from the preoperative period, investigating the patient's perceptions about how pain, sleep and mood influence each other. Paper III uses the same treatment design in the same patient population, but through a register-based study of medication use before and after THA, investigating trajectories of prescriptions for analgesics, hypnotics, anxiolytics and antidepressants as affected by the surgery.

3.1 Sample and procedure for Paper I and II

A questionnaire-based, prospective, multicentre treatment study forms the basis for Paper I and II. Between 2014 and 2015, patients from orthopaedic wards in 4 hospitals in Norway were recruited to participate in the study. Firstly, Haukeland University Hospital was the principal study site, where a pilot was conducted in 2013 and where data collection for the main study started in 2014. Subsequently, the Arendal Hospital Sørlandet joined in 2014, and the Hagavik Coastal Hospital and the Diakonhjemmet Hospital in Oslo joined in 2015. All preoperative data collection was finished by November 2015. Participants were recruited consecutively from waiting lists for THA. At the four study sites, a nurse or administrative staff member enclosed an invitation to participate to patients undergoing a primary THA, including information about the study, the questionnaire and informed consent-form, as well as a pre-paid return envelope when sending postal mail informing about the date of surgery to the patients on the waiting list. Patients were asked to complete the questionnaire at home, and return the signed consent form and questionnaire in the pre-paid envelope. In one hospital (Haukeland University Hospital), patients were asked to

return the questionnaire when arriving at the preoperative consultation. Date of surgery was extracted from the Norwegian Arthroplasty Register via the participant's unique identifying code provided in the questionnaire. The participant's address was provided by the respective hospitals. Returned questionnaires were kept by the respective hospitals and collected by the PhD-candidate. One year after the date of surgery, a new questionnaire was sent, this time by the PhD-candidate at the Department of Clinical Psychology. One reminder was sent by postal mail to those who did not respond to the initial invitation.

3.1.1 Participants

A total of 643 questionnaires were distributed to patients on the waiting lists at the four hospitals. At the end of the preoperative data collection, 314 questionnaires were returned. The response rate varied between the hospitals, with response rates of 75% (the Haukeland University Hospital), 72% (the Diakonhjemmet Hospital), 59% (the Hagavik Coastal Hospital), and 23% (the Sørlandet Hospital Arendal), respectively. To ensure that data from the hospital with the lowest response rate (Sørlandet Sykehus Arendal) was representative, sensitivity analyses (*t*-tests) were performed whereby results with all hospitals included were compared to results from all hospitals without the hospital with the lowest response rate. In all cases, the results did not significantly differ, with differences in effect (measured by Cohen's *d* effect size) of less than 0.1. Hence, including data from the hospital with low response rate had negligible effects on the results. Eighteen participants were excluded from the analysis due to missing signed consent forms preoperatively, and five because their THA was cancelled. Thus, the final sample preoperatively consisted of 291 patients, which constitutes the sample in Paper I. At the postoperative time, a consent-form was enclosed together with the questionnaires for the participant with missing consent forms at the preoperative time. This yielded 4 additional patients to be included in the prospective study. Conversely, some patients were excluded as they either withdrew from the study per phone (*n*=10), had their surgery cancelled or moved (*n*=14), had other major surgery (revision THA or other surgeries) in the study period (*n*= 9) and some had changed their address since the preoperative time (*n*=7). Also, 10 patients had their surgery later than the study inclusion period and were subsequently excluded from the prospective analyses. Of

the 262 patients still eligible to be included in the study, 221 patients responded at the postoperative time, giving a postoperative response rate of 83%. The response rate was similar across hospitals (ranging from 8% to 86% at the different study sites). In all, 10 patients were excluded because of incomplete data. Thus, the final sample in the prospective analysis that forms the basis of Paper I was 216 patients (65% female, mean age 67.7 years (SD:9.8; range 32 to 95)).

3.1.2 Measures paper I

A collection of validated questionnaires comprised the measures in Paper I. Hip related outcomes (symptoms, pain, stiffness limitations in daily living (ADL) and quality of life (QoL) were measured by the Hip Osteoarthritis Outcome Scale (HOOS), general pain (items from McGill pain questionnaire), sleep (Bergen Insomnia Scale, BIS) and mood disturbance (Hospital Anxiety and Depression Scale, HADS) prospectively. For Paper II, the abovementioned questionnaires served as clinical background variables. The main outcome variable Paper II was the attribution questionnaire, as described in the following section.

The main questionnaire contained a selection of measures, registering the patient's name and the unique personal identifying number and data on the patient's demographics (age, sex education level, occupation, marital status, income level and number of children). General health was assessed by asking how 1) the participants regarded their present health (1 - poor, 2 - quite poor, 3 - OK, 4 - well or 5 - very well) and 2) how their health was compared to one year earlier (1 - much better, 2 - a bit better, 3 - the same, 4 - a bit worse, 5 - much worse). Duration of pain, sleep problems, anxiety and depression were assessed by asking how many years, if any, their symptoms had been present. Height and weight was assessed and used for calculation of body mass index (kg/m^2 ; BMI) whereby 19.0 - 24,9 is considered normal weight, 25.0 - 29,9 is considered overweight and above 30 is considered obese.

The Hip Disability and Osteoarthritis Outcome Score (HOOS). The HOOS questionnaire was used to evaluate hip related outcomes, and is validated in Norwegian (Nilsson, Lohmander, Klassbo, & Roos, 2003). It consists of 40 items, assessing five separate patient-relevant dimensions: Pain; Symptoms including stiffness and range of motion; Activity limitations-daily living; sport and recreation function; and Hip related quality of life. Standardized response options are provided on a 5-point Likert scale (0-4). Then, a normalized score from 0 to 100 is calculated for each subscale (100 indicating no symptoms, and 0 indicating extreme symptoms) (Nilsson et al., 2003). In Paper I, the Chronbach's alpha for the subscales Symptoms, Pain, ADL, SportRec and Qol was .63, .87, .94, .81 and .75, respectively.

Pain. General pain was assessed using two verbal descriptor scales from the McGill Pain Questionnaire (Melzack, 1975), validated in Norwegian (Kim, Schwartz-Barcott, Holter, & Lorensen, 1995). The two scales assessed the magnitude of the pain by the phrase: "place a cross in the box best describing your pain", with the response alternatives "no pain", "weak", "unpleasant", "bothersome", "terrible" or "unbearable". The frequency of pain was assessed by the phrase: "How often do you have pain?" The response alternatives were "constantly", "daily", "several times a week", "about once a week", "several times a month", "about once a month", "less than once a month" and "never". Chronic pain was assessed by asking if their pain had lasted more than 3 months, "yes" or "no". Participants were subsequently asked to report any diagnosis connected to their hip pain. Comorbid pain was assessed by asking them to rate their pain from 1) the opposite hip, 2) other joints, 3) neck, back or head and 4) other chronic pain conditions, 3) ranging from none=0, a bit=1 or severe=2 (giving a range of composite score from 0 to 8). Moreover, participants were asked to assess to which degree their pain was managed by analgesics, from not at all=0, a small degree=1, a large degree=2 to a very large degree=3.

The Bergen Insomnia Scale (BIS). The BIS (Pallesen et al., 2008) was used to measure last month self-reported symptoms of insomnia. The items are based on the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) inclusion criteria for insomnia (American Psychiatric Association, 2000). The scale has six items, which are scored along an eight-point scale indicating the number of days per week for which a specific symptom is experienced (0-7 days, total scores ranging from 0-42). Participants were categorized as insomniacs if scoring 3 or more on at least one of items 1-4 (assessing

difficulties with sleep initiation, sleep maintenance, early morning awakening and nonrestorative sleep), and 3 or more on at least one of items 5 and 6 (assessing daytime impairment and dissatisfaction with sleep). In addition to prevalence of insomnia diagnosis and the total score, subtypes of insomnia (onset, maintenance and early morning awakening) were categorized according to the single items on the BIS. Normative data from the general population have been collected for the BIS and the scale has been validated using accredited subjective as well as polysomnographic data and found to possess sound psychometric properties. The scale provided a Chronbach's alpha in the present thesis of .91.

The Hospital Anxiety and Depression Scale (HADS). The HADS assesses non-vegetative symptoms of anxiety (HAD_A; seven items) and depression (HAD_D; seven items) experienced during the last week (scored on a four-point scale) (Zigmond & Snaith, 1983). Higher scores indicate greater symptom severity. The HADS holds good case-finding properties for anxiety and depression in patient populations in primary care and hospital settings (Bjelland, Dahl, Haug, & Neckelmann, 2002). The Chronbach's alpha in Paper I and Paper II was .83 and .86 for HAD-A and .81 and .86 for HAD-D, respectively.

3.1.3 Measures Paper II

Paper II utilized the questionnaires from Paper I as background variables. In addition, the paper included a questionnaire developed by the research group.

The Symptom Attribution Questionnaire. In order to assess how participants perceived symptoms of pain, sleep and mood to influence each other, a questionnaire was developed containing 12 statements about how much a given symptom (pain, sleep, mood) changed when another symptom (pain, sleep, mood) worsened or improved. Six statements explored the effect on the other two symptoms when a given symptom worsened, and six statements explored the effect on the other two symptoms when a given symptom improved. The participants were asked to provide responses on a 5-point scale (from 1 to 5) for each statement. For the worsening effect, the perceived effect of increased pain on sleep was investigated with the statement "when my pain is worse than usual, I sleep.. (statement 1a)". The perceived effect of increased pain on mood were investigated with the statement "when my pain is worse than usual, my mood becomes.. (statement 1b)". Secondly, the perceived effect of worsened sleep on pain was assessed with the statement "when my sleep is worse

than usual, my pain becomes.. (statement 2a) and on mood with the statement “when my sleep is worse than usual, my mood becomes” (statement 2b). Lastly, the perceived effect of worsened mood on sleep was assessed with the statement “when my mood is worse than usual, my pain becomes.. (statement 3a) and sleep with the statement “when my mood is worse than usual, my sleep becomes” (statement 3b). In addition, the presence of the converse, improving effect of reduced pain and improved sleep and mood was explored with the six following statements: Firstly, the perceived effect of reduced pain on sleep was investigated with the statement “when my pain is weaker than usual, my sleep becomes.. (statement 1c)”. The perceived effect of reduced pain on mood were investigated with the statement “when my pain is weaker, my mood becomes.. (statement 1d)”. Secondly, the perceived effect of improved sleep on pain was assessed with the statement “when my sleep is better than usual, my pain becomes.. (statement 2c) and on mood with the statement “when my sleep is better than usual, my mood becomes” (statement 2d). Lastly, the perceived effect of improved mood on sleep was assessed with the statement “when my mood is better than usual, my pain becomes.. (statement 3c) and sleep with the statement “when my mood is better than usual, my sleep becomes” (statement 3d).

3.2 Sample and procedure Paper III

This study was a register-based retrospective/prospective study on prescribed medication use before and after THA. Here I merged data from the Norwegian Prescription Database (NorPD) maintained at the Norwegian Institute of Public Health and data from the National Arthroplasty Register in Norway at Haukeland University Hospital. Data from both sources were merged by Statistics Norway, using patients` unique encrypted identifying code, enabling us to analyse the data at the individual level while ensuring personal anonymity.

3.2.1 Participants

In the period 2004 to 2012, a total of 54 402 primary THAs were performed. I excluded surgeries in the opposite hip for the same person, reoperations within the following year, and patients deceased within two years after surgery from the analyses (n= 8700). To be able to analyse medication use during the year following and after surgery, persons undergoing THA in 2004 and 2012 were excluded (n=6014). Thus, the study population comprised 39 688 persons. Data from the National Arthroplasty Register were then merged with prescription data from the Norwegian Prescription Database (Furu, 2008) in a 2-year observation period (divided into 8 quarters (91 days each); 4 before (Q1-Q4), and 4 after (Q5-Q8) surgery for each patient).

3.2.2 Data sources

3.2.2.1 *Norwegian Prescription Database.*

The NorPD is a national health register containing information on all prescription drugs dispensed to all home-dwelling individuals at all pharmacies in Norway from January 2004 to the present time (Furu, 2008). The register covers medications fully paid for by patients, as well as those reimbursed by the government. The database stores detailed information on items dispensed (the dispensed item's generic name, Anatomical Therapeutic Chemical (ATC) code, the defined daily dose of the prescribed drug (DDD) and date of dispensing) (The WHO Collaboration Centre for Drug Statistics Methodology, 2014) as well as basic demographic information about patients (person's unique personal identifying code, age, sex, person's year of death). However, information is lacking at the individual level concerning medications issued for institutionalized patients in nursing homes and hospitals (The Norwegian Institute of Public Health, 2013). We extracted data from NorPD from 2004 to 2012. The medications included in the present study were classified according to the ATC classification system (The WHO Collaboration Centre for Drug Statistics Methodology, 2014).

Analgesics analysed in the present study include M01A – NSAIDs, N02A – opioids and N02B – other analgesics and antipyretics, hereafter referred to as non-opioid analgesics. Three subgroups of psychotropic drugs were included; N05C – hypnotics and sedatives, hereafter referred to as hypnotics, N05B – anxiolytics, and N06A – antidepressants.

3.2.2.2 *Norwegian National Arthroplasty Register*

This person-identifiable health register receives data of operated joint prostheses from all 70 hospitals in Norway performing THA. Completeness is high (97%) for THA (Espehaug et al., 2006). The following information was extracted and used from the register: The persons' unique personal identification code and date of surgery. The following variables were extracted but not analysed in the present study; primary or secondary operation, indication for operation, type of operation, perioperative complications and ASA-class which is the American Society of Anaesthesiologists (ASA) physical status classification system (American Society of Anesthesiologists, 2013). Here, patients were either scored as: 1 healthy person; 2 mild systemic disease; 3 severe systemic disease; 4 severe systemic disease that is a constant threat to life; and 5 moribund person not expected to survive.

3.2.3 **Measures Paper III**

The following medication classes classified according to the Anatomical Therapeutic Chemical Classification system (The WHO Collaboration Centre for Drug Statistics Methodology, 2014) was included in the analyses: Analgesics (M01A- NSAIDs, N02A – Opioids, and N02B – Other analgesics and antipyretics, hereafter called nonopioid analgesics) and three subgroups of psychotropics (N05C – Hypnotics and sedatives, hereafter called hypnotics, N05B – anxiolytics, and N06A – antidepressants). Redeemed prescriptions were used as a proxy for medication use, which was quantified in two ways. Firstly, user rates were defined as number of persons who redeemed one or more

prescriptions during the study period. Secondly, dispensed drug volumes were calculated in terms of number of DDD. The DDD is a technical measuring unit determined on the basis of evaluation of intentional use of the substance in question and is defined as the assumed average daily maintenance dose for a drug used for its main indication in adults (Methology, 2012). The DDD used in paper III refers to the total number of DDDs for each redeemed prescription and is calculated by the NorPD. The dispensed drug volume in DDD was summarized per quarter.

3.3 Statistics

For all analyses, SPSS Statistics, version 21 and 22 were used. In the prospective study which forms the basis of Paper I and Paper II, we conducted sensitivity analyses (*t*-tests) in order to make sure the low response rate in one hospital did not impact our results. Here, results from all hospitals included were compared to results from all hospitals without the hospital with the lowest response rate. In all cases, the results did not significantly differ, with differences in effect (measured by Cohen's *d* effect size) of less than 0.1.

In Paper II and III a Bonferroni correction was applied in order to reduce the risk of a Type 1 error. The new *p*-value in Paper II was set to 0.002, and 0.005 in Paper III. In addition to statistical significance, the magnitude of results was assessed by effect sizes in all studies. Cohen's *d* sizes was calculated by DSTAT (Johnson, 1995) in Paper II and III and by online effect-size calculators in Paper I. According to Cohen (Cohen, 1988) an effect size of 0.2 is regarded as a small, 0.5 a medium, and effect sizes of 0.8 or higher are regarded as large. Effect sizes for continuous variables were corrected for dependence between means. In Paper I, clinical significance was also assessed, generating a total of three ways by which changes in measures before and after THA was assessed. This procedure is described under statistics in Paper I.

3.3.1 Analyses Paper I

In Paper I, person mean substitution was used to impute missing values for participants missing only a single item for questionnaires with 6 or more items (HOOS, BIS, and HAD_A and HAD_B). Means and standard deviations were computed for clinical background variables and insomnia pre- and post-treatment. Proportions of patients fulfilling insomnia, anxiety and depression criteria were also reported. Pearson product moment correlation coefficient were calculated to examine correlations between sleep and pain, hip related factors and mood. To examine changes in continuous variables paired sample *t* tests were used. Exact McNemar tests were performed for comparisons of prevalence and dichotomized variables. Significance level was set to .05. In addition to assessment of statistical significance and effect size, clinical significant change was also calculated: For the BIS total score and individual items (insomnia subtypes), HAD_A and HAD_D and HOOS outcome-scores, reliable change indexes (RCIs) were calculated according to the method of Jacobsen and Truax (1991). An RCI with a magnitude of 1.96 or greater in either direction is statistically reliable at the .05 level (Jacobson & Truax, 1991) and was used as a measure of clinical reliable change. Proportions of patients that clinical significantly improved was reported. For the diagnosis of insomnia, anxiety and depression, “clinical significant improvement” was defined as scoring above cut-off preoperatively and below cut-off postoperatively. “Not clinically improved” was defined as scoring above cut-off on both time-points. “Clinically worsening” was defined as scoring above cut-off postoperatively and below cut-off preoperatively. The categories of clinical significant change in terms of insomnia diagnosis was cross-tabulated against HOOS outcome measures, pain (magnitude, frequency, comorbid pain), anxiety and depression and duration of pain, sleep and mood disorders in order to describe how patients with residual insomnia diagnosis differed from the rest.

3.3.2 Analyses Paper II

In order to display the positive or negative properties of the perceived influence between pain, sleep and mood, the rating scale in the symptom attribution questionnaire was recoded. Here, *much worse* was recoded to -2, *a bit worse* was recoded to -1, *as usual* was recoded to 0 (indicating no change), *a bit better* was recoded to 1 and *much better* was recoded as 2. Descriptive statistics were used to characterize symptom attributions and the difference of the mean from 0 (no change) was measured through one-sample *t*-tests. A paired sample *t*-test was used to compare items in bidirectional relationships in order to assess the directionality of symptom attribution. For example, whether pain influences sleep more than sleep influences pain was assessed by comparing statements 1a and 2a for the worsening relationships between symptoms, and statements 1c and 2c for the improving relationships between symptoms. For the pain-mood relationship, statements 1b and 3a and statements 1d and 3c were compared for the worsening and improving effect of symptoms, respectively. For the sleep-mood relationship, statements 2b and 3b and statements 2d and 3d were compared for the worsening and improving effect of symptoms, respectively.

3.3.3 Analyses Paper III

Trajectories of drug use of all 8 quarters was firstly described by reporting user rates (displayed in percentages) and mean DDDs. Then, drug utilization trends before surgery were examined by comparing Q1 with Q4, immediate postoperative changes by comparing Q4 with Q5, and changes from preoperative to follow-up were examined by comparing Q4 with Q8. Exact McNemar tests were performed for comparison of user rates and paired sample *t* test when comparing drug volumes.

3.4 Ethics

The two studies by which the present thesis is based were both approved by the Regional Committee for Medical and Health Research Ethics in Western Norway (For the prospective study (Study I and Study II: 2014/63/REK Vest) and for the register study (Study III: 2012/312/REK Vest)). The prospective study was in addition approved by each of the hospitals involved. Because of the nature of the data in the register study, this study also needed approval by the Norwegian Directorate for Health and Social Affairs, and by the Norwegian Data Protection Authority (30877/3/MAS and 12/00791-3/RCA).

Signed informed consent was obtained by all participants in Study I and II. Due to the large sample in Study III, obtaining individual consent forms was impractical. Thus, we applied to REK to get an exemption of the demand for informed consent. This was granted based on the following reasons: When patients undergo THA, all patients are asked to be included in the National Arthroplasty Registry. In this consent, it is also included the possibility of merging the NAR to other Registries.

4. Results

4.1 Results Paper I

Preoperative insomnia was positively correlated (significant on $p < 0.001$ level) with anxiety ($r = 0.43$), depression ($r = 0.35$), and negatively correlated with HOOS pain ($r = -0.36$), HOOS ADL ($r = -0.33$), HOOS QoL ($r = -0.29$) and HOOS sportrec ($r = -0.23$). Correlations between insomnia and HOOS symptoms were small, but statistically significant ($p = 0.007$). H1 was therefore confirmed.

THA led to excellent results for hip related outcomes, pain and insomnia, and a reduction in anxiety and depression. H2 was therefore confirmed. Symptoms and pain was significantly reduced and ADL Sport and Rec and QoL was significantly improved ($p < 0.001$) with very large effect sizes ($d = 1.9$ to 2.8) and clinical significant improvement was achieved in the large majority of patients (84% to 95%). Prevalence of patients with an insomnia diagnosis was reduced from 57% preoperatively to 32% postoperatively and the mean score was improved from 16.7 (SD = 11.7) to 11.1 (SD = 10.7) with large and medium effect sizes, respectively. Improvements were also seen in all insomnia subtypes, especially for the parameters “difficulty maintaining sleep”, “not feeling refreshed after sleep” and “unsatisfied with sleep” but with small to medium effect sizes. All insomnia variables were significantly improved on the $p < 0.001$ level. Clinically significant change as measured by RCI on the BIS total score found that 21% of the total sample clinically improved after surgery. Percent achieving RCIs on the insomnia subtypes varied between 11% and 28%, showing the largest improvements in “not feeling refreshed after sleep”. In all, 66 patients (34% of the total sample) showed clinically significant improvement by fulfilling insomnia criteria before surgery but not after, while 46 patients (24% of the total sample size) still had an insomnia diagnosis 12 months post-surgery (non-improvers). In total, 36% (70 patients) had no insomnia diagnosis preoperatively or postoperatively, while 7% of the total sample ($n=14$) fulfilled criteria for an insomnia diagnosis postoperatively and not preoperatively, thus worsening their sleep the year after THA compared to before. Prevalence of patients meeting anxiety diagnosis according to the Hospital Anxiety and Depression Scale was significantly reduced (from 15% to 9%, chi-square = 5.0, $p = 0.023$), and there was a trend

towards a significant reduction in depression diagnosis (from 11% to 7%, chi-square = 2.8, $p = 0.095$). Both anxiety and depression total score were significantly reduced after surgery ($t = 2.7$, $p = 0.008$ and $t = 4.2$, $p < 0.001$, respectively) and approximately 10% of the total sample showed a clinically significant improvement in anxiety and depression. All effect sizes for mood disorders were small.

Patients with persistent insomnia 12 months postoperative reported that their pain and sleep problems had lasted longer compared to the other patients (especially for duration of sleep problems), and more patients reported that sleep problems predated the onset of pain. In addition, the persistent insomniacs reported higher levels and more frequent pain and higher levels of comorbid pain, and higher rates of anxiety and depression. Persistent insomniacs also had worse scores on all HOOS outcome measures. H3 was therefore confirmed.

4.2 Results Paper II

In this novel, exploratory study we asked the participants waiting to undergo THA to rate 12 statements about how worsening or improvements in pain, sleep and mood affected the other symptoms. A substantial portion of patients perceived that worsening of symptoms influenced their pain, sleep and mood. In all, 90% of the patients reported that sleep worsened in the presence of increased pain and 70% reported mood to worsen with increased pain. Close to 45% perceived their pain to worsen with poorer sleep, and almost 60% perceived mood to worsen with poorer sleep. Worse mood was perceived to have the least influence on pain (64.3% perceived there to be no change), but 52% reported mood to negatively influence sleep. The mean on all subscales differed significantly from 0 (all t -values significant on the 0.002-level) with effect sizes ranging from 0.6 to 2.3 (medium to very large effect size).

Patients reported improvement of one symptom to influence the other symptoms to a smaller degree than worsening. Still, reduced pain was perceived to improve sleep and mood in 57% and 52% of the patients, respectively. Improved sleep was also perceived to improve pain in 35% of the patients. Improved sleep had a strong influence on improvements of mood (47%

of the patients). Again, mood was perceived to have the least influence on pain and sleep; improved mood was perceived not to have an effect in 75% for pain and 63% for sleep. All variables differed significantly from 0 (all *t*-values significant on a 0.002-level) with effect sizes ranging from 0.3 = small effect size to 0.9 = large effect size.

Overall, pain stood out as the symptom with the largest perceived influence on the other symptoms, while mood was the symptom perceived by the fewest patients as influencing the other symptoms.

4.3 Results Paper III

Prescription trajectories within a two-year exposure window in a complete population of THA patients showed that all medication subgroups increased in user rates and drug volume through the year prior to surgery, confirming H1. The use of NSAIDs increased only until the third quarter, and then decreased. THA patients in their three-month postoperative phase (Q5) doubled their use of opioid and non-opioid analgesics and hypnotics from Q4, while no change was found in NSAIDs, and antidepressants and anxiolytics significantly decreased in the first postoperative quarter. H2 was therefore confirmed only for opioids, non-opioids and hypnotics. Comparing preoperative levels (Q4) with long-term postoperative levels (Q8), THA was associated with decreased use of analgesics, hypnotics and anxiolytics, but not antidepressants, partially confirming H3.

5. Discussion

5.1 General discussion of the findings

The three adjacent approaches as they appear across the papers in the present thesis collectively support a pain-sleep-mood interrelationship in THA patients where the pain-sleep relationship appear stronger than the pain-mood relationship. This was expected, given the close, reciprocal relationships between the symptoms described in the introductory part of this thesis, however in stark contrast to the attention sleep has been given in this patient group.

Close to 60% of the patients in the present thesis reported insomnia, underlining the central place of sleep disturbance in this patient group. This corresponds to rates found in other chronic pain populations (53-93% depending on the severity of pain) (Brennan & Lieberman, 2009; N. K. Tang et al., 2007). To the best of our knowledge, this is the first study to report insomnia prevalences in THA patients, which makes comparisons to previous results difficult. The two studies to date reporting sleep disturbance in THA patients find that close to 90% report waking up more than twice a week due to pain (Fielden et al., 2003; McHugh et al., 2011). Insomnia rates tend to decrease when stricter diagnostic criteria are employed (N. K. Y. Tang, 2008) such as in the present thesis. Hence the finding that almost 60% report insomnia in our study may accordingly be a conservative estimate of sleep disturbances experienced in this patient group. The reductions in insomnia rates after THA found in Paper I also correspond with improvements in sleep found in previous studies (Bogoch et al., 2010; Fielden et al., 2003). The results from Paper I therefore establish the validity of the relationship between pain and sleep in this patient group, a relationship also found in perceptions of attributions between symptoms as explored in Paper II and in pharmacological symptom management, as explored in Paper III. Furthermore, the results from the three papers align in a convincing way, demonstrating that the relationship between pain and sleep is stronger than the relationship between pain and mood. In fact, given that mood disturbance has received much more attention in THA research than sleep, it is noteworthy that the effect of THA on anxiety and depression is substantially smaller than the effect on sleep. Previous studies find larger and more consistent effects of THA on general

measures of mood (like mental health or mental components of quality of life) than on measures of diagnosis of anxiety and depression. The prevalence of anxiety (15%) and depression (11%) in Paper I is comparable to earlier studies using HADS (Berger et al., 2011; McHugh et al., 2011; Singh & Lewallen, 2010). Interestingly, the results from our prospective study and the medication study (Paper I and Paper III, respectively) align with finding attesting to reductions in anxiety/anxiolytics but not in depression/antidepressants. This is in line with a study conducted by Salmon and colleagues (2001) where they found a significant improvement in QoL mental health six months after surgery, while anxiety improved and depression did not. Other studies using the HADS as a measure of anxiety and depression find no improvements in either scale (Riediger et al., 2010) or improvements in both scales (Duivendoorn et al., 2013). Sleep was not assessed in these studies, so more research is needed to disentangle the role of mood disturbance in the context of pain and sleep disturbance.

Additionally, this thesis offered some new explanations that seem particularly valuable in which the individual results complement each other. Firstly, the close relationship between pain and sleep found in Paper I is mirrored in the perceptions of attributions these patients report in Paper II. Here, the vast majority perceive worsening of pain to worsen sleep. But also interesting, over 50% of these patients perceived improvements in pain to lead to improved sleep which aligns with the improvements in insomnia rates found after THA in Paper I. On the other hand, the results in Paper II also suggests that sleep has a causal role, where many patients perceive poorer sleep to worsen pain, and some patients perceive improved sleep to lessen pain. In turn, these perceptions fit well with the differences in postoperative outcomes based on change-categories of insomnia. Here, persons with persistent insomnia after surgery experience worse pain than persons whose insomnia resolved after the surgery. When these results are seen in connection with the adjacent trajectories found for analgesics and hypnotics in Paper III, the argument of interrelatedness of pain and sleep in THA patients is strengthened even further. Secondly, the insomnia-rate was 57% in Paper I and the prevalence of hypnotic use was 17% in Paper III. Assuming that hypnotic medication was used only by the insomniacs, this equates to a prevalence in hypnotic use of about 30% which is in concordance with prevalences previously found (Allen et al., 2008b). Both insomnia-rates and rates of hypnotic use is

reduced after THA, however the reduction in insomnia versus hypnotic use is proportionately higher for the former after the surgery. The results postoperatively from Paper I might offer a possible explanation for the lack of a more substantial reduction in hypnotic use postoperatively. Given the presence of a proportion of patients with persistent insomnia, we can speculate whether these patients are the ones also being the persistent hypnotic users. A larger proportion of persistent insomniacs had sleep problems predating their pain onset, probably reflecting the presence of a more life long-tendency to sleep poorly (idiopathic insomnia). It is possible that their insomnia would be less affected by arthritis, and subsequently by THA. In turn, this could indicate that corresponding medication use would be less affected by the THA.

Thirdly, in Paper I, we found that 40% of the patients did *not* have insomnia preoperatively despite high levels of pain. Correspondingly, Paper III found that hypnotic use was substantially lower than analgesic rates indicating that not all patients that used analgesics also used hypnotics. This is in accordance with previous research that shows a subset of chronic pain patients with high pain intensity that report to have normal sleep or even regard themselves as “good sleepers” (M. T. Smith, Perlis, Smith, Giles, & Carmody, 2000; N. K. Tang et al., 2007). From the postoperative results in Paper I it can be seen that patients with no insomnia diagnosis either preoperatively or postoperatively have the least comorbid anxiety and comorbid pain, and shortest duration of pain and insomnia complaints. Proportionately, this group also had the least patients where the onset of sleep problems predated their pain onset. This could indicate that these patients have a relatively delimited symptom constellation of pain and functional status unrelated to sleep and mood disturbance.

5.2 Directionality of the pain, sleep and mood relationships

Until recent years, explanatory models of insomnia coexisting with other psychiatric or medical conditions were dominated by the idea that the sleep disturbances were caused by the disorder (Ashworth et al., 2010). With increased knowledge based on experimental and longitudinal studies, it has been established this the relationship is bidirectional (Finan et al., 2013). Recent findings suggest that sleep actually might have a stronger impact on pain than

the reverse (Quartana, Wickwire, Klick, Grace, & Smith, 2010; N. K. Tang, Goodchild, Sanborn, Howard, & Salkovskis, 2012). Neither Paper I nor paper III, allows to comment on which have the strongest influence, as the treatment design only study one direction of causality (the effect of a pain reducing procedure on sleep and mood). Paper II however presents novel insight to the corresponding directionality in perceptions of the mutual influence between pain, sleep and mood. Our findings in Paper II do not support sleep to influence pain more than the reverse, where the percentage of patients who perceives sleep to negatively impact pain was substantially lower (45%) than the percent who perceive pain to negatively impact sleep (90%). This discrepancy might stem from several reasons. Firstly, sample characteristics could influence these results. The present thesis builds on a sample of chronic pain patients in the prolonged process of undergoing a pain-relieving procedure. Therefore it is plausible that the symptom of pain was perceived as a more prominent feature than sleep and mood. In addition, while almost all patients experienced medium or strong pain, only close to 60% of these patients had insomnia preoperatively. Thus, we can expect the perceived effect of pain on sleep and mood to be stronger than the reverse. On the other hand it might be difficult for some patients to discern between the influence of pain and sleep due to the unpredictable fluctuation in the type and intensity of their pain (Hawker et al., 2008). This is supported by a recent daily process study that reported sleep to influence pain more than the reverse, however the pain-relieving effect of good sleep was short-lived (N. K. Tang et al., 2012). Although sleep quality showed an inverse relationship with pain upon waking and during the first half of the day, no association was found during the second half of the day (N. K. Tang et al., 2012). The authors suggest that for some patients, reduced pain might actually lead to over-extending activity whereby leading to more pain the next night. This would cause even more pain during the night, consequently masking the positive effect of good sleep on pain. Furthermore, it is possible that those not perceiving sleep to influence pain was the patients without insomnia. Although few patients have very low insomnia scores, and many scored subclinically, perceptions about interrelationships might depend on the presence or severity of symptoms. This should be further clarified in future studies from this data set. Lastly, in order to explore whether directionality between symptoms depend on which symptom is the main driving force, the attribution questionnaire developed for Paper II should be explored in populations with mainly insomniacs, in populations with mainly mood disturbance patients, and in populations with healthy persons, respectively.

5.3 Methodological discussion

5.3.1 Samples and generalizability

The patient population in the present thesis consisted of persons undergoing THA. This is an established treatment study design where the reported reduction in pain is robust and substantial (Busija et al., 2008; Ethgen et al., 2004; Naal et al., 2015). This enables investigations into whether sleep and mood are affected by these reductions. Primary total hip replacements were chosen as opposed to revision surgery to minimize the risk of other interfering factors such as postoperative complications. In Paper III, the sample comprised a whole population of THA patients as 97% of all THAs are recorded in the Norwegian Arthroplasty Register. In the prospective study comprising Paper I and Paper II, patients were recruited from waiting lists for THA. Here, the response rate varied between the four hospitals. In one hospital, the response rate was markedly lower than the rest (22%). Despite the effort to improve the response rate during the process of data collection in this hospital, we were not able to identify the reason for the low response rate. One possible explanation provided by the staff at the respective hospital was that the patients receive quite a lot of forms to be filled out before the surgery and might prioritize those over participating in research. However, differences in the amount of paperwork delivered at the different hospitals would not be large enough to explain the large difference in response rate alone. There was a discussion whether to exclude this hospital due to its low response rate. However, sensitivity analyses revealed that the results did not significantly differ when excluding this hospital, as opposed to including it in the analyses. Our overall results also correspond with previous research and reports from the Norwegian Arthroplasty Register with regards to demographics (mean age and gender) and hip related symptoms. Hence we included the hospital in the study forming the basis for paper I and paper II. We chose the postoperative assessment at 12 months to ensure that we could identify the full effect of the surgery, as the full benefit of the surgery occurs around 6 months and later postoperatively (Ethgen et al., 2004; Naal et al., 2015).

At recruitment for the prospective study forming the basis of Paper I and Paper II, participants were informed that the study was focused on sleep. On one hand, patients with concerns about their sleep may have been more inclined to take part in the study, but contrary to this most studies in general samples find that persons with problems tend to participate less than their symptom-free counterparts (Torvik, Rognmo, & Tambs, 2012). Regardless, our rates of insomnia correspond to previous studies in chronic patients in general (Brennan & Lieberman, 2009; M. T. Smith et al., 2000) and THA patients in particular (Fielden et al., 2003; McHugh et al., 2011).

5.3.2 Validity and reliability

The prospective study forming the basis for Paper I and Paper II also has strong ecological validity. We did not exclude patients because of medication use and we included all reasons for surgery (OA, RA and others) although previous studies show that rates of pain and sleep disorders vary according to underlying condition (G. J. Lavigne, Nashed, et al., 2011).

In Paper I and II, self-report was used. All questionnaires except our own created attribution questionnaire have previously been validated and show good psychometric properties (see method section above). Although objective measures of sleep would have complemented our understanding of how specific sleep variables change after THA, for example amount of the restorative deep sleep or number of awakenings, subjective self-report measures are sufficient in indicating cases of insomnia.

Several important points should also be discussed regarding validity in the register-based study. Firstly, redeemed prescriptions were used as a proxy of medication use, in line with previous register-data studies (Kjosavik, Ruths, & Hunskaar, 2009, 2012). It is important to note the practical and implied difference between actual medication use (as amounts of medications actually consumed by the patient), prescription rates (what is prescribed by the doctor) and rates of redeemed medications (prescriptions collected at the pharmacy). The doctor will prescribe medications for disorders that he/she considers warrant treatment. However in many instances, patients, especially patients with chronic illnesses, may be prescribed medications to be redeemed “when needed” and hence redeemed

prescriptions may represent an overestimation of actual use. The amount of redeemed medications on the other hand does not necessarily correspond to the amount prescribed to the individual nor to the amount actually consumed by the person. For example, these data do not take into account prescriptions that have been prescribed but not redeemed. Also, medications purchased over-the-counter, which make up a substantial portion of analgesics, is not registered by this method. Conversely, several studies show that patients often have at home large amounts of medications (Sale, Gignac, & Hawker, 2006), by which only some are actually consumed. Lastly, for certain medication classes, especially analgesics and psychotropics, adherence to recommendations about use given by the prescribing doctor is low. For example, chronic pain patients both underuse and overuse medications (Couto, Romney, Leider, Sharma, & Goldfarb, 2009). The best and most thorough way of investigating medication use is to sit with the patients and their box of medications and go through what they actually use, however this is impossible to do in large-scale studies. In conclusion, medication use in home-dwelling elders will be approximate at best in larger samples. In large-scale studies such as the present register study, it is still a valuable outcome measure in describing trends in medication use for a total population of patients.

It is also important to discuss the validity of the medication classes included in this study. Firstly, we followed the division of the major medication classes in the ATC classification system used in Norway, in line with previous reporting from the NorPD (Kjosavik et al., 2012). By doing this we disregard for example that benzodiazepines are present in both the hypnotic and anxiolytic classes. Secondly, there is no one-to-one relationship between the medication class and the underlying disorder. For example, several antidepressants are indicated for treatment for depression, but also for general anxiety disorders, sleep problems (especially in the older patients) and several chronic pain conditions as well (Harris et al., 2011; Pergolizzi et al., 2013). This might explain previous reports where people with mental–physical comorbidity tended to have higher rates of antidepressant, anxiolytic, hypnotic and sedative use than people with mental disorders alone and people with musculoskeletal conditions and other conditions that may involve chronic pain had elevated rates of antidepressant, anxiolytic, hypnotic and sedative use, even in the absence of a comorbid mental disorder (Harris et al., 2011). Caution should therefore be made in directly attributing rates of anxiety, depression and sleep problems based on prescription data alone.

5.4 Strengths

The present thesis has several strengths. The prospective treatment design in Paper I and Paper III reliably induce a change in pain, which might or may not produce a change in other outcome variables. Because these studies examine change within-persons over time, they strengthen causal inferences, by allowing subjects to serve as their own controls and thereby mitigating confounding by stable person or situational factors (West & Hepworth, 1991). A strength is also the use of validated self-report measures of insomnia, mood disturbance and hip related outcomes. Based on the paucity of similar studies, it is also a strength to investigate insomnia and sleep disturbance in THA patients.

The novelty of all three papers should be highlighted. Paper I is to the authors knowledge the first to include assessment of insomnia diagnosis according to clinical diagnostic criteria in THA patients, whereby improving a limitation on many previous studies of sleep in chronic pain populations (Ashworth et al., 2010; Buysse et al., 2006). This strengthen the impact of the findings showing that sleep is a highly relevant patient related outcome after THA. Furthermore, this study is the first to identify a cohort with suboptimal outcomes after surgery based on their persistent insomnia. In contrast to the number of studies that aim to disentangle the relationship between chronic pain, sleep and mood, limited effort has been devoted to investigating how patients themselves perceive how these symptoms influence each other. Paper II thus places itself in a line of studies focusing on obtaining wider knowledge about the sleep-pain domain from the patient's perspective (Hawker et al., 2008; Turk et al., 2008), but it extends the scope to also explore attributions about the influence of sleep and mood on pain, and to illuminate both the attributions related to worsening as well as improvement of symptoms. Paper III is the first study investigating medication use for the frequently comorbid symptom constellation of pain, sleep and mood disturbance in a near complete population of THA patients, thus providing a complete picture of corresponding medication use in these patients. Exploring eight quarters give a temporal description of trajectories before and after THA and reveal details lost with larger exposure-windows.

5.5 Limitations

There are several limitations to the present thesis that should be commented on. Firstly, the outcome measures, which reflect pain, sleep and mood disturbance are not the only explanatory factors for our results. For example, THA also improves other factors in addition to pain and it is likely that reductions in pain does not fully account for the improvement observed in sleep. Sleep improvement probably reflects a synergetic effect of improved hip related function, ADL, mobility and mood, in addition to reduced BMI after surgery. For example, when joint functions are improved, activity during the daytime increase which increase sleep pressure and improves sleep (Menefee et al., 2000). High BMI is in itself associated with a range of adverse outcomes, and pain is shown to impaire relations with others and sleep on a more important degree in obese patients than in non-obese ones (Thomazeau et al., 2014). Weight loss, even very moderate, significantly improves both functional condition and pain in obese adults (Messier et al., 2004) and the reduced BMI after surgerly in the present thesis may play a large part in the overall improved symptoms. Furthermore, other sleep disorders such as sleep apnea and restless legs syndrome might contribute to sleep disturbance (Ancoli-Israel, 2006). Lastly, several analgesics (e.g. NSAIDS, morphine) are shown to have negative impact on sleep architecture (e.g. more awakenings, reductions in the deep non-rapid eye movement (REM) sleep and REM sleep) (G. J. Lavigne, Smith, et al., 2011). Lowered use of analgesics might therefore play one part in the reported improvements in sleep after surgery. Secondly, there are several factors which might have nuanced our results. Including both sexes and all age groups increase ecological validity. However, pain perception and pain expression are found to differ between genders (Greenspan et al., 2007) and so is insomnia rates and rates of mood disturbance. For example, in one study, a larger portion of women (49%) than men (35%) reported preoperative anxiety/depression and the degree of pain relief and satisfaction one year after surgery were related to preoperative anxitety/depression (Rolfson et al., 2009). Further exploration of the data collected for this thesis should examine the presence of gender- or age-differences, and would enhance our understanding of the interconnectedness of pain, sleep and mood even further. Lastly, we regret not including measures of medication use in the prospective study as this would have tied it all together.

5.6 Implications and future directions

There are several specific and general implications of our findings. In Paper I, the direct implication is the importance and utility of including sleep when assessing patients for THA. It is important to note that such an assessment should optimally include other primary sleep disorders such as sleep apnoea or restless legs/periodic leg movement disorder, which may contribute to the expression of insomnia symptoms (S. Smith, Sullivan, Hopkins, & Douglas, 2004; Stehlik, Ulfberg, Hedner, & Grote, 2014). These disorders can easily and time-efficiently be charted by self-report measures such as the Global Sleep Assessment Questionnaire (Roth et al., 2002), by which indications of primary sleep disorders can be further followed-up. We also identified a cohort with sub-optimal outcomes after surgery that might benefit from further follow-up from the health care service. This is especially important given the cyclic relationship between pain and sleep. In Paper II, we identify attributions of symptom causation that could directly lead to certain motivated coping cognitions and behaviour, and ultimately to more positive psychological adjustment (Weiner, 1985). For chronic pain patients who perceive symptoms to interrelate, the door has already been opened to utilize these attributions in the treatment of chronic pain and its comorbid conditions. For patients awaiting THA specifically, these attributions might aid a positive reinforcing cycle of symptom improvement when pain is reduced after surgery. Paper III highlights the need to assess medication use to identify chronic hypnotic use and medications which might increase the risk of adverse interactions between hypnotics and for example, opioids. Furthermore, in addition to supporting decreased medication use be considered when considering the utility of THA, our results also directs attention to the postoperative phase. Here, use of both analgesic and hypnotics dramatically increase, which in turn increase the risk of medication side-effects and development of tolerance and addiction.

One of the more overarching implications from the present thesis is based on the finding of the interrelationship between symptoms found preoperatively in all three studies. The deterioration of pain and functional status the year before surgery corroborates previous findings (Flugsrud et al., 2010) and three specific implications arise from this. Firstly, this supports the notion that THA should not be postponed. Impaired preoperative status and mental health are associated with worse outcome (Bischoff-Ferrari et al., 2004; Camillo et al., 2013; Quintana et al., 2009), and preoperative sleep is found to predict sleep and pain

postsurgery (Bogoch et al., 2010). As the vicious pain-sleep cycle most lightly exacerbate symptom load preoperatively (Camillo et al., 2013), there is a strong personal and economical benefit of providing THA earlier rather than later in the illness trajectory. Despite this, the current attitude has been to postpone replacements of the hip in order to extend its durability and reduce the chances of replacing the artificial joint. However, it could be socioeconomically sound, in addition to the reduced suffering for the patients, to offer the THA sooner rather than later. Secondly, it is important to note that although insomnia is almost halved and hypnotic use significantly reduced after surgery, the present thesis has identified a cohort of persistent insomniacs and hypnotic users. For these patients, it is particularly important to offer non-pharmalogical treatment options postoperatively. As discussed previously, the consequences of untreated insomnia are severe, and could in addition to exacerbating existing comorbid symptoms, also increase the risk of new onset pain (Gupta et al., 2007). With the knowledge that psychological interventions like cognitive behavioural therapy for insomnia work for insomnia, and also reduce pain and pain interference, comes the responsibility to offer this treatment to THA-patients. Thirdly, and lastly, our results, in combination with the previous findings that poor preoperative status and poor sleep affect outcomes, support the extended use of preoperative interventions. Interestingly, general preoperative interventions aiming to improve health directed behavior and improved stiffness, had however no effect on pain, function or quality of life (Crotty et al., 2009). A more specific psychologically-based pain management programme showed better effects on pain intensity, pain distress and sleep disturbance than a waitinglist, but only physical activity and arthritis impact showed an increased postoperative effect compared to the control (Berge et al., 2004). Sleep interventions on the other hand have found to have positive effects on both sleep and pain in knee osteoarthritis (M. T. Smith et al., 2015). Furthermore, short-term improvements in insomnia severity is found to predict long-term reductions in pain severity, arthritis symptoms, fear avoidance, insomnia severity, sleep quality, sleep beliefs/attitudes and fatigue (Vitiello et al., 2014). This shows that sleep interventions might be a way to disrupt the vicious pain-sleep cycle, which may improve outcomes after THA which in turn further improve pain and function and sleep. Since the cost of treating primary and comorbid insomnia is less than the cost of not treating it (Wickwire, Shaya, & Scharf, 2015), we recommend that instead of passively waiting for surgery, sleep should be assessed, identified and treated.

5.7 Conclusions

The present thesis establishes that a significant interrelationship between pain, sleep and mood exists in THA patients, both at the symptom level, the attribution level and regarding pharmacological symptom management. This implies that THA not only reduce pain, it also improves sleep and mood. The link between pain and sleep was found to be stronger than the link between pain and mood. The identification and treatment of sleep disturbance are largely unrecognized opportunities for disease prevention that may improve endogenous central pain modulatory systems, mood, physical function, and ultimately the degree and persistence of pain in osteoarthritis (M. T. Smith, Quartana, Okonkwo, & Nasir, 2009). Furthermore, an understanding of these comorbidities is critical when considering the benefit–risk for joint replacement surgery (Camillo et al., 2013). Given the negative synergetic interaction effect of suffering from chronic pain and insomnia, the reverse positive synergetic effect of treating one to reduce the other serves as a potential benefit of the THA. Including assessment of sleep when considering patients for THA would therefore fit with the trends in perception of THA from a “managing disability” to a more proactive “disability prevention”.

6. References

- Afolalu, E. F., Moore, C., Ramlee, F., Goodchild, C. E., & Tang, N. K. (2016). Development of the Pain-Related Beliefs and Attitudes about Sleep (PBAS) Scale for the Assessment and Treatment of Insomnia Comorbid with Chronic Pain. *J Clin Sleep Med, 12*(9), 1269-1277. doi:10.5664/jcsm.6130
- Albert, S. M., Musa, D., Kwoh, C. K., Hanlon, J. T., & Silverman, M. (2008). Self-care and professionally guided care in Osteoarthritis - Racial differences in a population-based sample. *Journal of Aging and Health, 20*(2), 198-216. doi:10.1177/0898264307310464
- Allen, K. D., Renner, J. B., Devellis, B., Helmick, C. G., & Jordan, J. M. (2008a). Osteoarthritis and sleep: The Johnston County Osteoarthritis Project. *Journal of Rheumatology, 35*(6), 1102-1107.
- Allen, K. D., Renner, J. B., DeVellis, B., Helmick, C. G., & Jordan, J. M. (2008b). Racial differences in sleep medication use: a cross-sectional study of the Johnston County Osteoarthritis Project. *Ann Pharmacother, 42*(9), 1239-1246. doi:10.1345/aph.1L111
- Alonso, J., Angermeyer, M. C., Bernert, S., Bruffaerts, R., Brugha, T. S., Bryson, H., . . . EsemEd/Mhede Investigators, E. S. o. t. E. o. M. D. P. (2004). Psychotropic drug utilization in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMEd) project. *Acta Psychiatr Scand Suppl*(420), 55-64. doi:10.1111/j.1600-0047.2004.00331.x
- American Academy of Sleep Medicine. (2014). *International classification of Sleep Disorders*. Darien, IL: American Academy of Sleep Medicine.
- American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders-IV- TR*. Washington DC: Author.
- American Society of Anesthesiologists. (2013). ASA Physical Status Classification System. Retrieved from <http://www.asahq.org/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System.aspx>
- Ancoli-Israel, S. (2006). The impact and prevalence of chronic insomnia and other sleep disturbances associated with chronic illness. *Am J Manag Care, 12*(8 Suppl), S221-229.
- Ashworth, P. C., Davidson, K. M., & Espie, C. A. (2010). Cognitive-behavioral factors associated with sleep quality in chronic pain patients. *Behav Sleep Med, 8*(1), 28-39. doi:10.1080/15402000903425587
- Avouac, J., Gossec, L., & Dougados, M. (2007). Efficacy and safety of opioids for osteoarthritis: a meta-analysis of randomized controlled trials. *Osteoarthritis and Cartilage, 15*(8), 957-965. doi:10.1016/j.joca.2007.02.006
- Axford, J., Butt, A., Heron, C., Hammond, J., Morgan, J., Alavi, A., . . . Bland, M. (2010). Prevalence of anxiety and depression in osteoarthritis: use of the Hospital Anxiety and Depression Scale as a screening tool. *Clinical Rheumatology, 29*(11), 1277-1283. doi:10.1007/s10067-010-1547-7
- Badura-Brzoza, K., Zajac, P., Kasperska-Zajac, A., Brzoza, Z., Matysiakiewicz, J., Piegza, M., . . . Koczy, B. (2008). Anxiety and depression and their influence on the quality of life

- after total hip replacement: preliminary report. *Int J Psychiatry Clin Pract*, 12(4), 280-284. doi:10.1080/13651500802095012
- Bair, M. J., Robinson, R. L., Katon, W., & Kroenke, K. (2003). Depression and pain comorbidity - A literature review. *Archives of Internal Medicine*, 163(20), 2433-2445. doi:10.1001/archinte.163.20.2433
- Bakken, M. S., Engeland, A., Engesaeter, L. B., Ranhoff, A. H., Hunskaar, S., & Ruths, S. (2013). Increased risk of hip fracture among older people using antidepressant drugs: data from the Norwegian Prescription Database and the Norwegian Hip Fracture Registry. *Age and Ageing*, 42(4), 514-520. doi:10.1093/ageing/aft009
- Bandelow, B., Zohar, J., Hollander, E., Kasper, S., Moller, H. J., Wfsbp Task Force on Treatment Guidelines for Anxiety, O.-C., . . . Vega, J. (2008). World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders - first revision. *World J Biol Psychiatry*, 9(4), 248-312. doi:10.1080/15622970802465807
- Berge, D. J., Dolin, S. J., Williams, A. C., & Harman, R. (2004). Pre-operative and post-operative effect of a pain management programme prior to total hip replacement: a randomized controlled trial. *Pain*, 110(1-2), 33-39.
- Berger, A., Bozic, K., Stacey, B., Edelsberg, J., Sadosky, A., & Oster, G. (2011). Patterns of pharmacotherapy and health care utilization and costs prior to total hip or total knee replacement in patients with osteoarthritis. *Arthritis Rheum*, 63(8), 2268-2275. doi:10.1002/art.30417
- Beswick, A. D., Wylde, V., Gooberman-Hill, R., Blom, A., & Dieppe, P. (2012). What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. *BMJ Open*, 2(1), e000435. doi:10.1136/bmjopen-2011-000435
- Bischoff-Ferrari, H. A., Lingard, E. A., Losina, E., Baron, J. A., Roos, E. M., Phillips, C. B., . . . Katz, J. N. (2004). Psychosocial and geriatric correlates of functional status after total hip replacement. *Arthritis Rheum*, 51(5), 829-835. doi:10.1002/art.20691
- Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res*, 52(2), 69-77. doi:S0022399901002963 [pii]
- Blagestad, T., Pallesen, S., Lunde, L. H., Sivertsen, B., Nordhus, I. H., & Gronli, J. (2012). Sleep in older chronic pain patients: a comparative polysomnographic study. *Clin J Pain*, 28(4), 277-283. doi:10.1097/AJP.0b013e3182313899
- Bogoch, E. R., Olschewski, E., Zangger, P., Henke, M. L., & Smythe, H. A. (2010). Increased tender point counts before and after total hip arthroplasty are associated with poorer outcomes but are not individually predictive. *J Arthroplasty*, 25(6), 945-950. doi:S0883-5403(09)00378-7 [pii]
- 10.1016/j.arth.2009.08.005
- Bolland, B. J., Culliford, D. J., Maskell, J., Latham, J. M., Dunlop, D. G., & Arden, N. K. (2011). The effect of hip and knee arthroplasty on oral anti-inflammatory use and the relationship to body mass index: results from the UK general practice research database. *Osteoarthritis Cartilage*, 19(1), 29-36. doi:S1063-4584(10)00353-5 [pii]
- 10.1016/j.joca.2010.10.012

- Breivik, H., Collett, B., Ventafridda, V., Cohen, R., & Gallacher, D. (2006). Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain*, *10*(4), 287-333. doi:10.1016/j.ejpain.2005.06.009
- Brennan, M. J., & Lieberman, J. A., 3rd. (2009). Sleep disturbances in patients with chronic pain: effectively managing opioid analgesia to improve outcomes. *Curr Med Res Opin*, *25*(5), 1045-1055. doi:10.1185/03007990902797790
- Busija, L., Osborne, R. H., Nilsson, A., Buchbinder, R., & Roos, E. M. (2008). Magnitude and meaningfulness of change in SF-36 scores in four types of orthopedic surgery. *Health Qual Life Outcomes*, *6*, 55. doi:10.1186/1477-7525-6-55
- Buysse, D. J., Ancoli-Israel, S., Edinger, J. D., Lichstein, K. L., & Morin, C. M. (2006). Recommendations for a standard research assessment of insomnia. *Sleep*, *29*(9), 1155-1173.
- Camillo, P., Thompson, P., Goodman, S. B., & Jiang, Y. (2013). The cycle of comorbidities: potential risks with delayed joint replacement. *Orthopaedic Nursing*, *32*(1), 6-13; quiz 14-15.
- Carskadon, M. A., & Dement, W. C. (2011). Monitoring and staging human sleep. In M. H. Kryger, T. Roth, & W. C. Dement (Eds.), *Principles and practice of sleep medicine* (5th ed., pp. 16-26). St. Louis: Elsevier Saunders.
- Chiu, Y., Silman, A., Macfarlane, G., Ray, D., Gupta, A., Dickens, C., . . . McBeth, J. (2005). Poor sleep and depression are independently associated with a reduced pain threshold. Results of a population based study. *Pain*, *115*, 316-321.
- Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.
- Colman, I., Wadsworth, M. E. J., Croudace, T. J., & Jones, P. B. (2006). Three decades of antidepressant, anxiolytic and hypnotic use in a national population birth cohort. *British Journal of Psychiatry*, *189*, 156-160. doi:DOI 10.1192/bjp.bp.105.017434
- Couto, J. E., Romney, M. C., Leider, H. L., Sharma, S., & Goldfarb, N. I. (2009). High rates of inappropriate drug use in the chronic pain population. *Popul Health Manag*, *12*(4), 185-190. doi:10.1089/pop.2009.0015
- Creamer, P. (2000). Osteoarthritis pain and its treatment. *Current Opinion in Rheumatology*, *12*(5), 450-455. doi:Doi 10.1097/00002281-200009000-00019
- Cremins-Smith, J. K., Millington, K., Sledjeski, E., Greene, K., & Delahanty, D. L. (2006). Sleep disruptions mediate the relationship between early postoperative pain and later functioning following total knee replacement surgery. *J Behav Med*, *29*(2), 215-222. doi:10.1007/s10865-005-9045-0
- Crotty, M., Prendergast, J., Battersby, M. W., Rowett, D., Graves, S. E., Leach, G., & Giles, L. C. (2009). Self-management and peer support among people with arthritis on a hospital joint replacement waiting list: a randomised controlled trial. *Osteoarthritis & Cartilage*, *17*(11), 1428-1433.
- Davies, K. A., Macfarlane, G. J., Nicholl, B. I., Dickens, C., Morriss, R., Ray, D., & McBeth, J. (2008). Restorative sleep predicts the resolution of chronic widespread pain: results from the EPIFUND study. *Rheumatology (Oxford)*, *47*(12), 1809-1813. doi:10.1093/rheumatology/ken389
- de Abajo, F. J., Rodriguez, L. A. G., & Montero, D. (1999). Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *British Medical Journal*, *319*(7217), 1106-1109.
- Dean, K. (1986). Lay care in illness. *Soc Sci Med*, *22*(2), 275-284.

- DeGood, D. E., & Kiernan, B. (1996). Perception of fault in patients with chronic pain. *Pain*, *64*(1), 153-159.
- Demierre, M., Castelao, E., & Piot-Ziegler, C. (2011). The long and painful path towards arthroplasty: A qualitative study. *Journal of Health Psychology*, *16*(4), 549-560. doi:10.1177/1359105310385365
- Dieppe, P., Judge, A., Williams, S., Ikwueke, I., Guenther, K. P., Floeren, M., . . . Dreinhofer, K. (2009). Variations in the pre-operative status of patients coming to primary hip replacement for osteoarthritis in European orthopaedic centres. *BMC Musculoskeletal Disord*, *10*, 19. doi:1471-2474-10-19 [pii] 10.1186/1471-2474-10-19
- Dieppe, P. A., & Lohmander, L. S. (2005). Pathogenesis and management of pain in osteoarthritis. *Lancet*, *365*(9463), 965-973. doi:10.1016/s0140-6736(05)71086-2
- Dray, A., & Read, S. J. (2007). Arthritis and pain. Future targets to control osteoarthritis pain. *Arthritis Res Ther*, *9*(3), 212. doi:10.1186/ar2178
- Driban, J. B., Boehret, S. A., Balasubramanian, E., Cattano, N. M., Glutting, J., & Sitler, M. R. (2012). Medication and supplement use for managing joint symptoms among patients with knee and hip osteoarthritis: a cross-sectional study. *BMC Musculoskeletal Disorders*, *13*. doi:10.1186/1471-2474-13-47
- Duivenvoorden, T., Vissers, M. M., Verhaar, J. A., Busschbach, J. J., Gosens, T., Bloem, R. M., . . . Reijman, M. (2013). Anxiety and depressive symptoms before and after total hip and knee arthroplasty: a prospective multicentre study. *Osteoarthritis & Cartilage*, *21*(12), 1834-1840.
- Edinger, J. D., Bonnet, M. H., Bootzin, R. R., Doghramji, K., Dorsey, C. M., Espie, C. A., . . . American Academy of Sleep Medicine Work, G. (2004). Derivation of research diagnostic criteria for insomnia: report of an American Academy of Sleep Medicine Work Group. *Sleep*, *27*(8), 1567-1596.
- Espehaug, B., Furnes, O., Havelin, L. I., Engesaeter, L. B., Vollset, S. E., & Kindseth, O. (2006). Registration completeness in the Norwegian Arthroplasty Register. *Acta Orthop*, *77*(1), 49-56. doi:738520547 [pii] 10.1080/17453670610045696
- Ethgen, O., Bruyere, O., Richey, F., Dardennes, C., & Reginster, J. Y. (2004). Health-related quality of life in total hip and total knee arthroplasty. A qualitative and systematic review of the literature. *J Bone Joint Surg Am*, *86-A*(5), 963-974.
- Feeney, S. L. (2004). The relationship between pain and negative affect in older adults: anxiety as a predictor of pain. *Journal of Anxiety Disorders*, *18*(6), 733-744.
- Felson, D. T., Lawrence, R. C., Dieppe, P. A. et al. . (2000). Osteoarthritis: new insights, part 1: the disease and its risk factors. *Annals of Internal Medicine*, *133*, 635-646.
- Fernandez, A., Saameno, J. A., Pinto-Meza, A., Luciano, J. V., Autonell, J., Palao, D., . . . investigators, D. (2010). Burden of chronic physical conditions and mental disorders in primary care. *Br J Psychiatry*, *196*(4), 302-309. doi:10.1192/bjp.bp.109.074211
- Fielden, J. M., Gander, P. H., Horne, J. G., Lewer, B. M., Green, R. M., & Devane, P. A. (2003). An assessment of sleep disturbance in patients before and after total hip arthroplasty. *J Arthroplasty*, *18*(3), 371-376. doi:10.1054/arth.2003.50056 S0883540302062575 [pii]
- Finan, P. H., Goodin, B. R., & Smith, M. T. (2013). The association of sleep and pain: an update and a path forward. *J Pain*, *14*(12), 1539-1552. doi:10.1016/j.jpain.2013.08.007

- Finan, P. H., & Smith, M. T. (2013). The comorbidity of insomnia, chronic pain, and depression: dopamine as a putative mechanism. *Sleep Med Rev, 17*(3), 173-183. doi:10.1016/j.smrv.2012.03.003
- Fishbain, D. A. (2005). Polypharmacy treatment approaches to the psychiatric and somatic comorbidities found in patients with chronic pain. *American Journal of Physical Medicine & Rehabilitation, 84*(3), S56-S63. doi:10.1097/01.phm.0000154904.83278.32
- Flaherty, J. H. (2008). Insomnia among hospitalized older persons. *Clin Geriatr Med, 24*(1), 51-67, vi. doi:S0749-0690(07)00077-8 [pii] 10.1016/j.cger.2007.08.012
- Flugsrud, G. B., Nordsletten, L., Reinholt, F. P., Risberg, M. A., Rydevik, K., & Uhlig, T. (2010). Artrose. *Tidsskrift for Norsk Legeforening, 130*, 2136-2140.
- Folkehelseinstituttet. (2013). Legemiddelbruk i Norge. Retrieved from <http://www.fhi.no/artikler/?id=70827>
- Folkehelseinstituttet. (2016). *Drug Consumption in Norway 2011-2015*. Retrieved from Oslo: <http://www.legemiddelbruk.no/>
- Furu, K. (2008). Establishment of the nationwide Norwegian Prescription Database. *Nor J Epidemiol, 18*, 129-136.
- Fuzier, R., Serres, I., Bourrel, R., Palmaro, A., Montastruc, J. L., & Lapeyre-Mestre, M. (2014). Analgesic drug consumption increases after knee arthroplasty: a pharmacoepidemiological study investigating postoperative pain. *Pain, 155*(7), 1339-1345. doi:10.1016/j.pain.2014.04.010
- Gallagher, P., Barry, P., & O'Mahony, D. (2007). Inappropriate prescribing in the elderly. *Journal of Clinical Pharmacy and Therapeutics, 32*(2), 113-121. doi:DOI 10.1111/j.1365-2710.2007.00793.x
- Gerrits, M. M., van Oppen, P., van Marwijk, H. W., Penninx, B. W., & van der Horst, H. E. (2014). Pain and the onset of depressive and anxiety disorders. *Pain, 155*(1), 53-59. doi:10.1016/j.pain.2013.09.005
- Gerrits, M. M., Vogelzangs, N., van Oppen, P., van Marwijk, H. W., van der Horst, H., & Penninx, B. W. (2012). Impact of pain on the course of depressive and anxiety disorders. *Pain, 153*(2), 429-436. doi:10.1016/j.pain.2011.11.001
- Gleicher, Y., Croxford, R., Hochman, J., & Hawker, G. (2011). A prospective study of mental health care for comorbid depressed mood in older adults with painful osteoarthritis. *BMC Psychiatry, 11*. doi:10.1186/1471-244x-11-147
- Greenspan, J. D., Craft, R. M., LeResche, L., Arendt-Nielsen, L., Berkley, K. J., Fillingim, R. B., . . . Pain, S. I. G. o. t. I. (2007). Studying sex and gender differences in pain and analgesia: a consensus report. *Pain, 132 Suppl 1*, S26-45. doi:10.1016/j.pain.2007.10.014
- Gupta, A., Silman, A. J., Ray, D., Morriss, R., Dickens, C., MacFarlane, G. J., . . . McBeth, J. (2007). The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study. *Rheumatology (Oxford), 46*(4), 666-671. doi:10.1093/rheumatology/kel363
- Gureje, O. (2007). Psychiatric aspects of pain. *Curr Opin Psychiatry, 20*(1), 42-46. doi:10.1097/YCO.0b013e328010ddf4
- Hajak, G., Muller, W. E., Wittchen, H. U., Pittrow, D., & Kirch, W. (2003). Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and

- zopiclone: a review of case reports and epidemiological data. *Addiction*, 98(10), 1371-1378.
- Hamel, M. B., Toth, M., Legedza, A., & Rosen, M. P. (2008). Joint replacement surgery in elderly patients with severe osteoarthritis of the hip or knee: decision making, postoperative recovery, and clinical outcomes. *Arch Intern Med*, 168(13), 1430-1440. doi:168/13/1430 [pii]
10.1001/archinte.168.13.1430
- Hamilton, N. A., Nelson, C. A., Stevens, N., & Kitzman, H. (2007). Sleep and psychological well-being. *Social Indicators Research*, 82(1), 147-163. doi:10.1007/s11205-006-9030-1
- Harris, M. G., Burgess, P. M., Pirkis, J., Siskind, D., Slade, T., & Whiteford, H. A. (2011). Correlates of antidepressant and anxiolytic, hypnotic or sedative medication use in an Australian community sample. *Aust N Z J Psychiatry*, 45(3), 249-260. doi:10.3109/00048674.2010.531459
- Hawker, G. A., Stewart, L., French, M. R., Cibere, J., Jordan, J. M., March, L., . . . Gooberman-Hill, R. (2008). Understanding the pain experience in hip and knee osteoarthritis - an OARSI/OMERACT initiative. *Osteoarthritis and Cartilage*, 16(4), 415-422. doi:10.1016/j.joca.2007.12.017
- Hinrichs-Rocker, A., Schulz, K., Jarvinen, I., Lefering, R., Simanski, C., & Neugebauer, E. A. M. (2009). Psychosocial predictors and correlates for chronic post-surgical pain (CPSP) - A systematic review. *European Journal of Pain*, 13(7), 719-730. doi:10.1016/j.ejpain.2008.07.015
- Hochberg, M. C., Altman, R. D., April, K. T., Benkhalti, M., Guyatt, G., McGowan, J., . . . Tugwell, P. (2012). American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care & Research*, 64(4), 465-474. doi:10.1002/acr.21596
- Hoogbeem, T. J., den Broeder, A. A., Swierstra, B. A., de Bie, R. A., & van den Ende, C. H. (2012). Joint-pain comorbidity, health status, and medication use in hip and knee osteoarthritis: a cross-sectional study. *Arthritis Care Res (Hoboken)*, 64(1), 54-58. doi:10.1002/acr.20647
- Hossain, M., Parfitt, D. J., Beard, D. J., Darrah, C., Nolan, J., Murray, D. W., & Andrew, G. (2011). Does pre-operative psychological distress affect patient satisfaction after primary total hip arthroplasty? *BMC Musculoskelet Disord*, 12, 122. doi:10.1186/1471-2474-12-122
- Hubbard, C. S., Ornitz, E., Gaspar, J. X., Smith, S., Amin, J., Labus, J. S., . . . Naliboff, B. D. (2011). Modulation of nociceptive and acoustic startle responses to an unpredictable threat in men and women. *Pain*, 152(7), 1632-1640. doi:10.1016/j.pain.2011.03.001
- Hunter, D. J., & Felson, D. T. (2006). Osteoarthritis. *British Medical Journal*, 332(7542), 639-642B. doi:10.1136/bmj.332.7542.639
- Jacobson, N. S., & Truax, P. (1991). Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol*, 59(1), 12-19.
- Jenkins, P. J., Clement, N. D., Hamilton, D. F., Gaston, P., Patton, J. T., & Howie, C. R. (2013). Predicting the cost-effectiveness of total hip and knee replacement: a health economic analysis. *Bone & Joint Journal*, 95-B(1), 115-121.

- Johnson, B. T. (1995). DSTAT: Software for the meta-analytic review of research literature (Version 1.11).
- Jones, C. A., Voaklander, D. C., Johnston, D. W., & Suarez-Almazor, M. E. (2001). The effect of age on pain, function, and quality of life after total hip and knee arthroplasty. *Arch Intern Med*, *161*(3), 454-460. doi:10.1001/arch.161.3.454 [pii]
- Kapstad, H., Rustoen, T., Hanestad, B. R., Moum, T., Langeland, N., & Stavem, K. (2007). Changes in pain, stiffness and physical function in patients with osteoarthritis waiting for hip or knee joint replacement surgery. *Osteoarthritis Cartilage*, *15*(7), 837-843. doi:10.1016/j.joca.2007.01.015 [pii]
- Kim, H. S., Schwartz-Barcott, D., Holter, I. M., & Lorensen, M. (1995). Developing a translation of the McGill pain questionnaire for cross-cultural comparison: an example from Norway. *Journal of Advanced Nursing*, *21*(3), 421-426. doi:10.1111/j.1365-2648.1995.tb02722.x
- Kjosavik, S. R., Ruths, S., & Hunnskaar, S. (2009). Psychotropic drug use in the Norwegian general population in 2005: data from the Norwegian Prescription Database. *Pharmacoepidemiology and Drug Safety*, *18*(7), 572-578. doi:10.1002/pds.1756
- Kjosavik, S. R., Ruths, S., & Hunnskaar, S. (2012). Use of addictive anxiolytics and hypnotics in a national cohort of incident users in Norway. *Eur J Clin Pharmacol*, *68*(3), 311-319. doi:10.1007/s00228-011-1124-2
- Kovac, S. H., Saag, K. G., Curtis, J. R., & Allison, J. (2008). Association of health-related quality of life with dual use of prescription and over-the-counter nonsteroidal antiinflammatory drugs. *Arthritis & Rheumatism-Arthritis Care & Research*, *59*(2), 227-233. doi:10.1002/art.23336
- Kroenke, K., Krebs, E. E., & Bair, M. J. (2009). Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews. *General Hospital Psychiatry*, *31*(3), 206-219. doi:10.1016/j.genhosppsych.2008.12.006
- Lavigne, G., Brousseau, M., Kato, T., Mayer, P., Manzini, C., Guitard, F., & Monplaisir, J. (2004). Experimental pain perception remains equally active over all sleep stages. *Pain*, *110*(3), 646-655. doi:10.1016/j.pain.2004.05.003
- Lavigne, G. J., Nashed, A., Manzini, C., & Carra, M. C. (2011). Does sleep differ among patients with common musculoskeletal pain disorders? *Curr Rheumatol Rep*, *13*(6), 535-542. doi:10.1007/s11926-011-0209-3
- Lavigne, G. J., Smith, M. T., Denis, R., & Zucconi, M. (2011). Pain and sleep. In M. H. Kryger, S. H. Roth, & D. WC (Eds.), *Principles and Practices of Sleep Medicine*. St. Louis: Elsevier Saunders.
- Learmonth, I. D., Young, C., & Rorabeck, C. (2007). The operation of the century: total hip replacement. *Lancet*, *370*(9597), 1508-1519. doi:10.1016/S0140-6736(07)60457-7
- Lingjærde, O. (2006). *Psykofarmaka. Medikamentell behandling av psykiske lidelser*. (5 ed.). Kristiansand: Høyskoleforlaget.
- McHugh, G. A., Campbell, M., & Luker, K. A. (2011). GP referral of patients with osteoarthritis for consideration of total joint replacement: a longitudinal study. *Br J Gen Pract*, *61*(589), e459-468. doi:10.3399/bjgp11X588420
- McWilliams, L. A., Goodwin, R. D., & Cox, B. J. (2004). Depression and anxiety associated with three pain conditions: results from a nationally representative sample. *Pain*, *111*(1-2), 77-83. doi:10.1016/j.pain.2004.06.002

-
- Melzack, R. (1975). The McGill Pain Questionnaire: major properties and scoring methods. *Pain, 1*(3), 277-299.
- Menefee, L. A., Frank, E. D., Doghramji, K., Picarello, K., Park, J. J., Jalali, S., & Perez-Schwartz, L. (2000). Self-reported sleep quality and quality of life for individuals with chronic pain conditions. *Clin J Pain, 16*(4), 290-297.
- Messier, S. P., Loeser, R. F., Miller, G. D., Morgan, T. M., Rejeski, W. J., Sevick, M. A., . . . Williamson, J. D. (2004). Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. *Arthritis Rheum, 50*(5), 1501-1510. doi:10.1002/art.20256
- Methology, W. C. C. f. D. S. (2012). *ATC Classification Index with DDDs*. (Vol. 2014). Oslo: Norwegian Institute of Public Health.
- Michela, J., & Wood, J. (1986). Causal attributions in health and illness. In e. Kendal PC (Ed.), *Advances in cognitive-behavioral research and therapy* (pp. 179-235). New York, NY: Academic Press.
- Mitte, K., Noack, P., Steil, R., & Hautzinger, M. (2005). A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. *J Clin Psychopharmacol, 25*(2), 141-150.
- Moldofsky, H. (2001). Sleep and pain. *Sleep Med Rev, 5*(5), 385-396. doi:S1087-0792(01)90179-0 [pii]
10.1053/smr.2001.0179
- Montin, L., Leino-Kilpi, H., Katajisto, J., Lepisto, J., Kettunen, J., & Suominen, T. (2007). Anxiety and health-related quality of life of patients undergoing total hip arthroplasty for osteoarthritis. *Chronic Illn, 3*(3), 219-227. doi:10.1177/1742395307084405
- Morin, C. M., & Benca, R. (2012). Chronic insomnia. *Lancet, 379*(9821), 1129-1141. doi:10.1016/S0140-6736(11)60750-2
- Naylor, C. D., & Williams, J. I. (1996). Primary hip and knee replacement surgery: Ontario criteria for case selection and surgical priority. *Qual Health Care, 5*(1), 20-30.
- Neogi, T. (2013). The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis Cartilage, 21*(9), 1145-1153. doi:10.1016/j.joca.2013.03.018
- Neutel, C. I. (2005). The epidemiology of long-term benzodiazepine use. *Int Rev Psychiatry, 17*(3), 189-197. doi:10.1080/09540260500071863
- Neutel, C. I., Skurtveit, S., & Berg, C. (2012). What is the point of guidelines? Benzodiazepine and z-hypnotic use by an elderly population. *Sleep Med, 13*(7), 893-897. doi:10.1016/j.sleep.2011.12.014
- NICE. (2004). *Guidance on the use of zalepon, zolpidem and zopiclone for the short-term management of insomnia*. Retrieved from London:
- Nilsdotter, A. K., & Isaksson, F. (2010). Patient relevant outcome 7 years after total hip replacement for OA - a prospective study. *BMC Musculoskelet Disord, 11*, 47. doi:1471-2474-11-47 [pii]
10.1186/1471-2474-11-47
- Nilsdotter, A. K., Lohmander, L. S., Klassbo, M., & Roos, E. M. (2003). Hip disability and osteoarthritis outcome score (HOOS)--validity and responsiveness in total hip replacement. *BMC Musculoskelet Disord, 4*, 10. doi:10.1186/1471-2474-4-10
- Norwegian Arthroplasty Register. (2016). *Norwegian National Advisory Unit on Arthroplasty and Hip Fractures 2016 Annual Report*. Retrieved from

- Naal, F. D., Impellizzeri, F. M., Lenze, U., Wellauer, V., von Eisenhart-Rothe, R., & Leunig, M. (2015). Clinical improvement and satisfaction after total joint replacement: a prospective 12-month evaluation on the patients' perspective. *Quality of Life Research, 24*(12), 2917-2925.
- Ohayon, M. M. (2005). Relationship between chronic painful physical condition and insomnia. *J Psychiatr Res, 39*(2), 151-159. doi:10.1016/j.jpsychires.2004.07.001
- Onen, S. H., Alloui, A., Gross, A., Eschallier, A., & Dubray, C. (2001). The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. *J Sleep Res, 10*(1), 35-42.
- Pallesen, S., Bjorvatn, B., Nordhus, I. H., Sivertsen, B., Hjørnevik, M., & Morin, C. M. (2008). A new scale for measuring insomnia: the Bergen Insomnia Scale. *Percept Mot Skills, 107*(3), 691-706.
- Patten, S. B., Williams, J. V. A., & Wang, J. L. (2006). Mental disorders in a population sample with musculoskeletal disorders. *Bmc Musculoskeletal Disorders, 7*. doi:10.1186/1471-2474-7-37
- Pergolizzi, J. V., Jr., Raffa, R. B., Taylor, R., Jr., Rodriguez, G., Nalamachu, S., & Langley, P. (2013). A review of duloxetine 60 mg once-daily dosing for the management of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain due to chronic osteoarthritis pain and low back pain. *Pain Pract, 13*(3), 239-252. doi:10.1111/j.1533-2500.2012.00578.x
- Pinto, P. R., McIntyre, T., Ferrero, R., Almeida, A., & Araujo-Soares, V. (2013). Risk factors for moderate and severe persistent pain in patients undergoing total knee and hip arthroplasty: a prospective predictive study. *PLoS ONE [Electronic Resource], 8*(9), e73917.
- Quartana, P. J., Wickwire, E. M., Klick, B., Grace, E., & Smith, M. T. (2010). Naturalistic changes in insomnia symptoms and pain in temporomandibular joint disorder: a cross-lagged panel analysis. *Pain, 149*(2), 325-331. doi:10.1016/j.pain.2010.02.029
- Quintana, J. M., Escobar, A., Aguirre, U., Lafuente, I., & Arenaza, J. C. (2009). Predictors of health-related quality-of-life change after total hip arthroplasty. *Clin Orthop Relat Res, 467*(11), 2886-2894. doi:10.1007/s11999-009-0868-9
- Riediger, W., Doering, S., & Krismer, M. (2010). Depression and somatisation influence the outcome of total hip replacement. *Int Orthop, 34*(1), 13-18. doi:10.1007/s00264-008-0688-7
- Roesch, S. C., & Weiner, B. (2001). A meta-analytic review of coping with illness: do causal attributions matter? *J Psychosom Res, 50*(4), 205-219.
- Rolfson, O., Dahlberg, L. E., Nilsson, J. A., Malchau, H., & Garellick, G. (2009). Variables determining outcome in total hip replacement surgery. *J Bone Joint Surg Br, 91*(2), 157-161. doi:10.1302/0301-620X.91B2.20765
- Roth, T., Zammit, G., Kushida, C., Doghramji, K., Mathias, S. D., Wong, J. M., & Buysse, D. J. (2002). A new questionnaire to detect sleep disorders. *Sleep Med, 3*(2), 99-108. doi:S1389945701001319 [pii]
- Sale, J. E. M., Gignac, M., & Hawker, G. (2006). How "bad" does the pain have to be? A qualitative study examining adherence to pain medication in older adults with osteoarthritis. *Arthritis & Rheumatism, 55*(2), 272-278. doi:10.1002/art.21853
- Salmon, P., Hall, G. M., Peerbhoy, D., Shenkin, A., & Parker, C. (2001). Recovery from hip and knee arthroplasty: Patients' perspective on pain, function, quality of life, and

- well-being up to 6 months postoperatively. *Archives of Physical Medicine & Rehabilitation*, 82(3), 360-366.
- Sawyer, P., Bodner, E. V., Ritchie, C. S., & Allman, R. M. (2006). Pain and pain medication use in community-dwelling older adults. *Am J Geriatr Pharmacother*, 4(4), 316-324. doi:S1543-5946(06)00079-1 [pii]
10.1016/j.amjopharm.2006.12.005
- Schrimpf, M., Liegl, G., Boeckle, M., Leitner, A., Geisler, P., & Pieh, C. (2015). The effect of sleep deprivation on pain perception in healthy subjects: a meta-analysis. *Sleep Med*, 16(11), 1313-1320. doi:10.1016/j.sleep.2015.07.022
- Shan, L., Shan, B., Graham, D., & Saxena, A. (2014). Total hip replacement: a systematic review and meta-analysis on mid-term quality of life. *Osteoarthritis Cartilage*, 22(3), 389-406. doi:10.1016/j.joca.2013.12.006
- Sharp, L. K., & Lipsky, M. S. (2002). Screening for depression across the lifespan: a review of measures for use in primary care settings. *Am Fam Physician*, 66(6), 1001-1008.
- Singh, J. A., & Lewallen, D. (2010). Predictors of pain and use of pain medications following primary Total Hip Arthroplasty (THA): 5,707 THAs at 2-years and 3,289 THAs at 5-years. *BMC Musculoskelet Disord*, 11, 90. doi:1471-2474-11-90 [pii]
10.1186/1471-2474-11-90
- Sivertsen, B., Krokstad, S., Mykletun, A., & Overland, S. (2009). Insomnia symptoms and use of health care services and medications: the HUNT-2 study. *Behav Sleep Med*, 7(4), 210-222. doi:10.1080/15402000903190199
- Sivertsen, B., Krokstad, S., Overland, S., & Mykletun, A. (2009). The epidemiology of insomnia: associations with physical and mental health. The HUNT-2 study. *J Psychosom Res*, 67(2), 109-116. doi:10.1016/j.jpsychores.2009.05.001
- Sivertsen, B., Lallukka, T., Petrie, K. J., Steingrimsdottir, O. A., Stubhaug, A., & Nielsen, C. S. (2015). Sleep and pain sensitivity in adults. *Pain*, 156(8), 1433-1439. doi:10.1097/j.pain.000000000000131
- Sivertsen, B., Overland, S., Pallesen, S., Bjorvatn, B., Nordhus, I. H., Maeland, J. G., & Mykletun, A. (2009). Insomnia and long sleep duration are risk factors for later work disability. The Hordaland Health Study. *J Sleep Res*, 18(1), 122-128. doi:10.1111/j.1365-2869.2008.00697.x
- Sivertsen, B., Pallesen, S., Glozier, N., Bjorvatn, B., Salo, P., Tell, G. S., . . . Overland, S. (2014). Midlife insomnia and subsequent mortality: the Hordaland health study. *BMC Public Health*, 14, 720. doi:10.1186/1471-2458-14-720
- Smith, M. T., Finan, P. H., Buenaver, L. F., Robinson, M., Haque, U., Quain, A., . . . Haythornthwaite, J. A. (2015). Cognitive-behavioral therapy for insomnia in knee osteoarthritis: a randomized, double-blind, active placebo-controlled clinical trial. *Arthritis Rheumatol*, 67(5), 1221-1233. doi:10.1002/art.39048
- Smith, M. T., & Haythornthwaite, J. A. (2004). How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. *Sleep Med Rev*, 8(2), 119-132. doi:10.1016/S1087-0792(03)00044-3
- Smith, M. T., Perlis, M. L., Smith, M. S., Giles, D. E., & Carmody, T. P. (2000). Sleep quality and presleep arousal in chronic pain. *J Behav Med*, 23(1), 1-13.
- Smith, M. T., Quartana, P. J., Okonkwo, R. M., & Nasir, A. (2009). Mechanisms by which sleep disturbance contributes to osteoarthritis pain: a conceptual model. *Curr Pain Headache Rep*, 13(6), 447-454.

- Smith, S., Sullivan, K., Hopkins, W., & Douglas, J. (2004). Frequency of insomnia report in patients with obstructive sleep apnoea hypopnea syndrome (OSAHS). *Sleep Med*, 5(5), 449-456. doi:10.1016/j.sleep.2004.03.005
- Stehlik, R., Ulfberg, J., Hedner, J., & Grote, L. (2014). High prevalence of restless legs syndrome among women with multi-site pain: a population-based study in Dalarna, Sweden. *Eur J Pain*, 18(10), 1402-1409. doi:10.1002/ejp.504
- Tang, N. K. (2009). Cognitive-behavioral therapy for sleep abnormalities of chronic pain patients. *Curr Rheumatol Rep*, 11(6), 451-460.
- Tang, N. K., Goodchild, C. E., Sanborn, A. N., Howard, J., & Salkovskis, P. M. (2012). Deciphering the temporal link between pain and sleep in a heterogeneous chronic pain patient sample: a multilevel daily process study. *Sleep*, 35(5), 675-687a. doi:10.5665/sleep.1830
- Tang, N. K., Wright, K. J., & Salkovskis, P. M. (2007). Prevalence and correlates of clinical insomnia co-occurring with chronic back pain. *J Sleep Res*, 16(1), 85-95. doi:JSR571 [pii]
10.1111/j.1365-2869.2007.00571.x
- Tang, N. K. Y. (2008). Insomnia Co-Occurring with Chronic Pain: Clinical Features, Interaction, Assessments and Possible Interventions. *Reviews in Pain*, 2(1), 2-7. doi:10.1177/204946370800200102
- The IASP Taxonomy Working Group. (2013). *Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Second edition (Revised)*. Washington: IASP Press.
- The Norwegian Institute of Public Health. (2013). The Norwegian prescription database. Retrieved from <http://www.norpd.no/>
- The WHO Collaboration Centre for Drug Statistics Methodology. (2014). ATC/DDD index 2014. Retrieved from http://www.whocc.no/atc_ddd_index/
- Theadom, A., & Cropley, M. (2010). 'This constant being woken up is the worst thing' - experiences of sleep in fibromyalgia syndrome. *Disabil Rehabil*, 32(23), 1939-1947. doi:10.3109/09638281003797331
- Thomazeau, J., Perin, J., Nizard, R., Bouhassira, D., Collin, E., Nguyen, E., . . . Lloret-Linares, C. (2014). Pain management and pain characteristics in obese and normal weight patients before joint replacement. *Journal of Evaluation in Clinical Practice*, 20(5), 611-616.
- Torvik, F. A., Rognum, K., & Tambs, K. (2012). Alcohol use and mental distress as predictors of non-response in a general population health survey: the HUNT study. *Soc Psychiatry Psychiatr Epidemiol*, 47(5), 805-816. doi:10.1007/s00127-011-0387-3
- Toye, F., Seers, K., Allcock, N., Briggs, M., Carr, E., Andrews, J., & Barker, K. (2013). Patients' experiences of chronic non-malignant musculoskeletal pain: a qualitative systematic review. *Br J Gen Pract*, 63(617), e829-841. doi:10.3399/bjgp13X675412
- Tracey, I. (2010). Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. *Nat Med*, 16(11), 1277-1283. doi:nm.2229 [pii]
10.1038/nm.2229
- Tracey, I., & Mantyh, P. W. (2007). The cerebral signature for pain perception and its modulation. *Neuron*, 55(3), 377-391. doi:S0896-6273(07)00533-8 [pii]
10.1016/j.neuron.2007.07.012
- Tsang, A., Von Korff, M., Lee, S., Alonso, J., Karam, E., Angermeyer, M. C., . . . Watanabe, M. (2008). Common Chronic Pain Conditions in Developed and Developing Countries:

- Gender and Age Differences and Comorbidity With Depression-Anxiety Disorders. *Journal of Pain*, 9(10), 883-891. doi:10.1016/j.jpain.2008.05.005
- Turk, D. C., Dworkin, R. H., Revicki, D., Harding, G., Burke, L. B., Cella, D., . . . Rappaport, B. A. (2008). Identifying important outcome domains for chronic pain clinical trials: an IMMPACT survey of people with pain. *Pain*, 137(2), 276-285. doi:10.1016/j.pain.2007.09.002
- Vandekerckhove, M., & Cluydts, R. (2010). The emotional brain and sleep: an intimate relationship. *Sleep Med Rev*, 14(4), 219-226. doi:10.1016/j.smr.2010.01.002
- Vitiello, M. V., McCurry, S. M., Shortreed, S. M., Baker, L. D., Rybarczyk, B. D., Keefe, F. J., & Von Korff, M. (2014). Short-term improvement in insomnia symptoms predicts long-term improvements in sleep, pain, and fatigue in older adults with comorbid osteoarthritis and insomnia. *Pain*, 155(8), 1547-1554. doi:10.1016/j.pain.2014.04.032
- Vogl, M., Leidl, R., Plotz, W., & Gutacker, N. (2015). Comparison of pre- and post-operative health-related quality of life and length of stay after primary total hip replacement in matched English and German patient cohorts. *Quality of Life Research*, 24(2), 513-520.
- Weiner, B. (1985). An attributional theory of achievement motivation and emotion. *Psychol Rev*, 92(4), 548-573.
- West, S. G., & Hepworth, J. T. (1991). Statistical issues in the study of temporal data: daily experiences. *J Pers*, 59(3), 609-662.
- Wickwire, E. M., Shaya, F. T., & Scharf, S. M. (2015). Health economics of insomnia treatments: The return on investment for a good night's sleep. *Sleep Med Rev*, 30, 72-82. doi:10.1016/j.smr.2015.11.004
- Wilson, K. G., Eriksson, M. Y., D'Eon, J. L., Mikail, S. F., & Emery, P. C. (2002). Major depression and insomnia in chronic pain. *Clin J Pain*, 18(2), 77-83.
- Wittchen, H. U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jonsson, B., . . . Steinhausen, H. C. (2011). The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol*, 21(9), 655-679. doi:10.1016/j.euroneuro.2011.07.018
- Woolhead, G., Gooberman-Hill, R., Dieppe, P., & Hawker, G. (2010). Night pain in hip and knee osteoarthritis: a focus group study. *Arthritis Care & Research*, 62(7), 944-949.
- Wylde, V., Hewlett, S., Learmonth, I. D., & Dieppe, P. (2011). Persistent pain after joint replacement: prevalence, sensory qualities, and postoperative determinants. *Pain*, 152(3), 566-572. doi:S0304-3959(10)00708-6 [pii] 10.1016/j.pain.2010.11.023
- Zautra, A. J., Johnson, L. M., & Davis, M. C. (2005). Positive affect as a source of resilience for women in chronic pain. *J Consult Clin Psychol*, 73(2), 212-220. doi:10.1037/0022-006X.73.2.212
- Zhang, W., Moskowitz, R. W., Nuki, G., Abramson, S., Altman, R. D., Arden, N., . . . Tugwell, P. (2008). OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis and Cartilage*, 16(2), 137-162. doi:10.1016/j.joca.2007.12.013
- Zhang, W., Nuki, G., Moskowitz, R. W., Abramson, S., Altman, R. D., Arden, N. K., . . . Tugwell, P. (2010). OARSI recommendations for the management of hip and knee osteoarthritis Part III: changes in evidence following systematic cumulative update

of research published through January 2009. *Osteoarthritis and Cartilage*, 18(4), 476-499. doi:10.1016/j.joca.2010.01.013

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatr Scand*, 67(6), 361-370.

Insomnia is reduced after total hip arthroplasty and is related to preoperative and postoperative patient related factors.

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Abstract

Objective: The personal and socioeconomic burden of pain-associated insomnia is increasingly recognized. Despite the high prevalence of sleep disturbance in patients undergoing total hip arthroplasty (THA), limited effort has been aimed at illuminating sleep as an outcome after surgery. Here, we examined insomnia before and after THA.

Design: A questionnaire-based, multicentre prospective study of insomnia, assessing mood disturbance and hip related outcomes before and 12 months after THA. In total, 216 patients (56% female, mean age 67 years (SD=14.2) completed the Bergen Insomnia Scale, the Hip Osteoarthritis Outcome Scale and the Hospital Anxiety and Depression Scale on both occasions.

Results: THA led to excellent hip related outcomes. In addition, THA reduced insomnia prevalence from 57% preoperatively to 32% postoperatively ($p<0.001$, $d=0.9$) and clinically significant improvement was demonstrated in 34% of the patients when tested by reliable change index. Preoperatively, insomnia severity was negatively correlated with hip related function and positively correlated with anxiety and depression. Twelve months after surgery, persistent insomniacs showed worse patient related outcomes in terms of pain, mood disturbance and hip related factors.

Conclusion: High prevalence (57%) of insomnia was found in patients waiting for THA. The prevalence nearly halved 12 months after surgery. Our preliminary attempt to shed light on vulnerabilities associated with persistent insomnia after THA identified a cohort of patients that experience suboptimal responses to THA.

Introduction

The majority of patients undergoing total hip arthroplasty (THA) report sleep disturbances of a severity that warrant clinical attention [1]. The most common sleep disturbance is insomnia, characterized by difficulty initiating or maintaining sleep, waking up too early, or experiencing chronically non-restorative sleep. Insomnia is associated with an array of negative consequences such as impaired daytime function, cognitive impairments, physical and mental health complaints, increased health care utilization, work disability and mortality [2-7].

The relationship between sleep and pain is well established and likely bidirectional [8-14]. The few studies to date in patients eligible for THA report a high rate of sleep disturbances [1, 15] and improvements in several sleep parameters are reported after surgery [1, 16, 17]. These findings are in line with improvements in sleep following effective management of chronic pain [18]. Sleep prior to THA has moreover been found to be a predictor for post-operative pain and sleep disturbance after surgery [16]. In addition, sleep disruptions one month after THA was in one study associated with greater disability 3 months postoperative [19]. Collectively, this identifies sleep as a highly relevant patient related outcome after THA.

Although THA has been shown to improve sleep, still one third of patients report continued sleep disturbance after THA [1]. Sleep disturbance like insomnia has been known to exacerbate pain and symptoms of mood disorders, and may lead to worse long-term outcomes after THA [19]. Knowledge about characteristics of those experiencing insomnia after THA is therefore important as it may help tailoring treatment after surgery and may help inform health care professionals about patients with suboptimal outcomes after THA.

As life expectancy increases, the rates of THA are expected to continue to increase [20]. Optimizing patient related outcomes of THA is therefore pertinent. The main objective

of the present study was accordingly to assess the effect of THA on insomnia. Based on the robust relationship between pain and sleep we expected lowered rates of insomnia after THA. We also report prevalence of insomnia preoperatively and its association with other patient related factors such as pain, mood and hip related factors. Lastly, in order to explore what differentiates those with persistent sleep disturbance after surgery from those whose insomnia have resolved, descriptive characterizations of all patient related outcomes were tabulated based on change-category postoperatively. Our overall aim is to illuminate sleep as a patient related outcome after THA.

PATIENTS AND METHODS

Study design and participants A questionnaire-based prospective, multi-centre study evaluating pain, symptoms of different sleep disorders, anxiety and depression in patients before and 12 months after undergoing THA was conducted. Participants were recruited from four different orthopaedic departments in hospitals across Norway (Haukeland University Hospital, Diakonhjemmet Hospital, Coastal Hospital Hagevik and Sørlandet Hospital Arendal) between May 2014 and November 2015.

Procedure The participants were recruited consecutively by a hospital administrative staff in each hospital by including the questionnaire when providing them with the date for the operation via postal mail. Patients willing to participate were asked to complete the questionnaire at home and to return it and to sign the consent form. They either brought with them the documents when arriving at the pre-operative consultation or sent them via postal mail in an enclosed prepaid envelope. The patients on average completed the questionnaire one month before surgery. Date of surgery was extracted from the Norwegian Arthroplasty Register via the participant's unique identifying code provided in the questionnaire. The

participant's address was provided by the respective hospitals. The study was approved by the Regional Committee for Medical and Health Research Ethics in Western Norway (2014/63/REK Vest) and was in addition approved by each of the hospitals involved.

Questionnaires. Demographic variables comprised name and the unique personal identifying number, occupation, marital status, income level and number of children. General health was assessed by asking how the participants regarded their present health (poor, quite poor, okay, well or very well) and also in comparison to one year earlier (much better, a bit better, the same, a bit worse, much worse). The duration of pain, sleep problems, anxiety and depression was assessed by asking how many years, if any, their symptoms have been present. Height and weight were assessed and used for calculation of Body Mass Index (kg/m^2 ; BMI) whereby 19-24,9 is considered normal weight, 25-29,9 is considered overweight and above 30 is considered obese.

The Hip Disability and Osteoarthritis Outcome Score (HOOS) was used to evaluate hip related outcomes. It consists of 40 items, assessing five separate patient-relevant dimensions: Pain; Symptoms including stiffness and range of motion; Activity limitations-daily living (hereby referred to as ADL); Sport and Recreation Function; and Hip Related Quality of Life (QoL). Standardized response options are provided on a 5-point Likert scale (0-4). A normalized score from 0 to 100 is finally calculated for each subscale (100 indicating no symptoms, and 0 indicating extreme symptoms) [21]. In the present study, Chronbach's alpha for the subscales Symptoms, Pain, ADL, SportRec and QoL was .63, .87, .94, .81 and .75, respectively.

Pain. General pain was assessed by asking the participants to rate the intensity and frequency of their pain. The patients were asked to indicate if their pain was chronic (>3 months), to what degree their pain was managed by analgesics (from not at all=0, a small degree=1, a large degree=2 to a very large degree=3) and to report any diagnosis connected to

their hip pain. Comorbid pain was assessed by rating their pain from 1) the opposite hip, 2) other joints, 3) neck, back or head and 4) other chronic pain conditions, 3) ranging from none=0, a bit=1 or severe=2 (giving a range of composite scores from 0 to 8).

The Bergen Insomnia Scale (BIS). The BIS measures last month self-reported symptoms of insomnia [22]. The six items are based on the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) inclusion criteria for insomnia [23] and are scored along an eight-point scale indicating the number of days per week for which a specific symptom is experienced (0–7 days, total scores ranging from 0–42). Participants were categorized as insomniacs if scoring 3 or more on at least one of items 1–4 (assessing difficulties with sleep initiation, sleep maintenance, early morning awakening and nonrestorative sleep), and 3 or more on at least one of items 5 and 6 (assessing daytime impairment and dissatisfaction with sleep). Subtypes of insomnia (difficulty initiating sleep, difficulty maintaining sleep, early awakenings, not feeling refreshed after sleep, sleep negatively affected work or unsatisfied with sleep) were categorized according to the single items on the BIS. The BIS has been validated against accredited subjective and polysomnographic data and found to possess sound psychometric properties [22]. The Chronbach's alpha in the present study was .91.

The Hospital Anxiety and Depression Scale (HADS) was used to assesses non-vegetative symptoms of anxiety (HAD-A; seven items) and depression (HAD-D; seven items) experienced during the last week (scored on a four-point scale) [24]. Higher scores indicate greater symptom severity. The HADS holds good case-finding properties for anxiety and depression in patient populations in primary care and hospital settings and have previously demonstrated acceptable reliability [25]. The Chronbach's alpha in the present study was .83 for HAD-A and .81 for HAD-D.

Data analysis. Analyses were performed using SPSS Statistics, version 22. Means and standard deviations were computed for clinical background variables and insomnia pre- and post-treatment. For questionnaires with 6 or more items (HOOS, BIS, and HAD-A and HAD-D), person mean substitution was used to impute missing values for participants missing only a single item. Scores were not imputed for participants missing two or more items on these questionnaires, or for single standing items (i.e., pain frequency or intensity). Pearsons r was used to assess correlations between insomnia and hip related factors and mood disturbance preoperatively. To examine changes in continuous variables a paired sample t -test was used. Exact McNemar test was performed for comparisons of prevalence and dichotomized variables pre vs. post. Significance level was set to .05. Additionally, in order to measure the magnitude of the improvement, effect sizes (Cohen's d) were calculated for all outcome measures and interpreted according to Cohen [26] whereby 0.2 equates to a small effect, 0.5 to a medium effect and effect sizes of 0.8 and larger represent a strong effect. Effect sizes for continuous variables were corrected for dependence between means [27]. Clinical significant change was also examined: For the BIS total score, HAD-A and HAD-D and the HOOS outcome-scores, reliable change indexes (RCIs) were calculated according to the method of Jacobsen and Truax (1991) [28]. In accordance with this method, previously reported Chronbach's alphas was used for the calculations of RCIs [22, 25, 29]. RCI scores provide a measure of the change in standardised units, the direction of change, and whether it's reliable; an RCI of 1.00 is half as big a change as a RCI of 2.00, positive RCIs indicate improvement whereas negative RCIs signify worsening. An RCI with a magnitude of 1.96 or greater in either direction is statistically reliable at the .05 level [28], and percentages meeting this criteria was calculated for the BIS total score and the six individual items. For the diagnosis of insomnia, anxiety and depression, "clinical significant improvements" was defined as scoring above cut-off preoperatively and below cut-off postoperatively. "Not clinically

improved” was defined as scoring above cut-off on both time-points. “Clinically worsening” was defined as scoring above cut-off postoperatively and below cut-off preoperatively. Proportions of patients that clinical significantly improved was reported for all outcomes. Lastly, the categories of clinical significant change of insomnia diagnosis were cross-tabulated against HOOS outcome measures, pain (magnitude, frequency, comorbid pain), anxiety and depression and duration of pain, sleep and mood disorders in order to describe how patients with residual insomnia diagnosis differed from the rest.

RESULTS

Preoperative characteristics. A total of 643 patients who entered the waiting lists for THA were invited to participate, of which 312 with complete data and signed consent was included in the study. The response rate preoperatively differed between the four hospitals, with response rates of 75.2%, 72.0%, 58.7%, and 23.2%, respectively. Sensitivity analysis showed that including data from the hospital with the lowest response rate had negligible effects on the results. All participants received the same questionnaire 12 months after the surgery. Of these, 31 patients were excluded based on postponed or cancelled operations, revision surgery in the study period or wrong address and 10 patients withdrew from the study by phone. Of the 271 patients still eligible to be included in the prospective analysis, 226 responded with complete data at both time points. This gives a response rate at the postoperative time of 83.4% (ranging from 80.7% to 86.4% at the different study sites). Of these, 10 patients were excluded due to missing data. Thus, the final sample in the prospective analysis comprised 216 patients. Patient demographics and clinical characteristics preoperatively are shown in Table 1, 2 and 4, respectively. The majority of the sample was female (65.0%) with a mean age of 67.7 years (SD=9.8; range 32 to 95). Compared to the responders postoperatively, non-responders were older and more frequently men. Of those

reporting any diagnosis associated with their pain, 82.0% reported osteoarthritis, 4.0% rheumatoid arthritis and 14.0% reported other chronic pain diagnosis. Mean BMI was 29.4 (SD 18.3) which is considered borderline obese. The majority (46.7%) reported that their health was good, while 29.4% reported that their health was quite poor or poor. In all, 33.8% considered their health to be the same as one year ago, while 58.5% considered their health to be a bit or much worse than one year ago. The majority reported pain to be bothersome (68.5%) or horrible/unbearable (16.4%). More than 90% reported their pain to occur daily or constant. Many also reported pain unrelated to their operated hip either in the opposite hip (48.7%), in other joints (51.4%), their back, head or neck (49.5%) or other chronic pain conditions (16.2%). Patients had poor hip related scores measured by HOOS subscales (normalized mean scores on symptoms, pain, ADL, Sport Rec and QoL all ranging between 40.9 (SD=17.6) and 23.4 (SD=18.0), where 100 indicate no symptoms and 0 indicate extreme symptoms). In all, 15.0% and 10.7% scored above cut-off symptoms indicating anxiety and depression, respectively. Insomnia was negatively correlated with HOOS Symptoms ($r=-0.19$, $p=0.007$), HOOS Pain, ($r=-0.36$, $p<0.001$), HOOS ADL ($r=-0.33$, $p<0.001$), HOOS SportRec ($r=-0.23$, $p=0.001$), HOOS QoL ($r=-0.29$, $p<0.001$) and positively correlated with symptoms of anxiety and depression ($r=0.43$ and $r=0.35$, respectively, both significant on the $p<0.001$ level), see Table 3.

Changes in hip related outcomes, general pain and mood disturbance after THA.

As shown in Table 4, THA led to excellent results for hip related outcomes. Symptoms and pain was significantly reduced and ADL Sport and Rec and QoL were significantly improved ($p<0.001$) with very large effect sizes ($d=1.9$ to 2.8). The large majority (83.7% to 94.8%) showed clinically significant improvement in terms of hip related outcomes. Twelve months after surgery, mean BMI was also reduced from borderline obese (mean=29.5) to the lower

spectrum of overweight (mean=26.8). The prevalence of patients satisfying the criteria for anxiety diagnosis according to the Hospital Anxiety and Depression Scale was significantly reduced ($p=0.023$), and there was a trend towards a significant reduction in the proportion satisfying the criteria for depression ($p=0.095$). Both anxiety and depression total scores were significantly reduced after surgery ($p < 0.023$) and approximately 10% of the total sample showed a clinically significant improvement of anxiety and depression. All effect sizes for mood disorders were small.

Changes in insomnia after THA. Insomnia symptoms measured by the BIS were significantly improved (see Table 5). Prevalence of patients with an insomnia diagnosis was reduced from 57.1% to 32.2%, and the mean score improved from 16.7 (SD=11.7) to 11.1 (SD=10.7) with large and medium effect sizes, respectively. Improvements were also seen in all insomnia subtypes, especially for the parameters “difficulty maintaining sleep”, “not feeling refreshed after sleep” and “being unsatisfied with sleep” but with small to medium effect sizes. All insomnia variables were significantly improved on the $p < 0.001$ level. Clinically significant change as measured by RCI on the BIS total score showed that 20.6% of the total sample clinically improved after surgery. RCIs for the insomnia subtypes varied between 11.3 % and 27.6 %, respectively, showing the largest improvements in “not feeling refreshed after sleep”. In all, 66 patients (33.7% of the total sample) showed clinically significant improvement, while 46 patients (23.5% of the total sample) still had an insomnia diagnosis 12 months post-surgery (non-improvers) (see Table 6). In all, 35.7% of the total sample (70 patients) had no insomnia diagnosis preoperatively or postoperatively, while 7.1% of the total sample ($N=14$) suffered from insomnia only postoperatively, thus worsening their sleep.

Characteristics of post-operative insomniacs compared to those whose insomnia resolved after the surgery.

Patients with persistent insomnia 12 months after surgery reported that their pain and sleep problems had lasted longer compared to the other patients (especially for duration of sleep problems), and more patients reported that sleep problems predated the onset of pain (see Table 6). In addition, they reported higher levels and more frequent pain and higher levels of comorbid pain, and higher rates of anxiety and depression. Persistent insomniacs also had worse scores on all HOOS outcome measures.

DISCUSSION

The present study confirms the high prevalence of insomnia in the THA-patient group, and supports previous studies that report sleep to be improved after THA. Still, and in concordance with a previous study by Fielden [1], about one third of the patients reported persistent insomnia 12 months after surgery. The persistent insomniacs in the present study reported higher levels of pain and mood disturbance and less improved hip related outcomes compared to the rest. Collectively, these results support sleep as an important THA-related outcome, and at the same time identifies a cohort of patients that might benefit from further multi-modal treatment in order to optimize outcomes after THA.

The large majority of chronic pain patients reported disturbed sleep (70-90%) preoperatively. The insomnia prevalence found preoperatively in the present study was comparable to what described previously in chronic pain patients (57% and 53%, respectively) [2]. In the adult Norwegian population aged 60 or more, the most recent prevalence estimates according to the DSM-IV criteria is found to be 12.2% in men and

16.7% in women [30]. Preoperative insomnia correlated further with all hip related factors and mood disturbance, and is likely to exacerbate all symptoms before surgery. Collectively this reveals the magnitude of sleep problems in this population and highlight the necessity to address insomnia in THA patients.

The fact that insomnia rates in the present study became almost halved following THA is a substantial finding and correspond with one previous report in THA patients [1]. It is important to note that improved sleep is not merely related to well-being in general. Sleep is vital for restoration, and restorative sleep is involved in the resolution of chronic pain [12]. Conversely, sleep deprivation leads to hyperalgesia and lowers pain thresholds [31] and appears to be associated with persistence of pain [13]. Previous studies find that sleep disturbance is associated with up to a two-fold risk for developing new chronic musculoskeletal pain or turning acute pain into chronic pain [32, 33]. Insomnia is also a public health issue, associated with substantially elevated use of health care services, medication and alcohol overuse [4]. Insomnia increases the risk of sickness absence and disability retirement (e.g. [6]) and increases the risk of mortality three fold [7]. Moreover, when insomnia and chronic pain co-occur, their joint impact increases health risks and leads to increased health care costs and elevated disability in a synergistic manner [34, 35]. It comes therefore as no surprise that treatment of insomnia disorder is highly cost effective as assessed by quality of adjusted years of life (QAYL) measurements [36]. THA is in itself cost effective in improving QAYL without taking into account the added benefit of improved sleep [37]. Including assessments of insomnia when considering patients for THA would therefore fit with the contemporary view of THA as proactive “disability prevention” [38].

After surgery, 33% still fulfilled the diagnosis criteria for insomnia. While THA restores function and pain and mental health to normative population values [39, 40], age-matched healthy populations only report 4-6% insomnia rates when DSM-IV diagnostic

criteria are applied. [41, 42]. The elevated insomnia rates found postoperatively in some patients thus suggest further comorbidities, which is confirmed by the present study. Patients with persistent insomnia after THA showed elevated rates of anxiety and depression, more pain, both hip related and comorbid, and longer duration of symptoms compared to those who's insomnia resolved. The worsened outcomes in persistent insomniacs 12 months after the surgery could have several causes. Persistent insomnia could be due to less improved pain and function after surgery, thus reflecting a subgroup of non-optimal outcomes after THA. Alternatively, the indication for surgery in these patients could be wrong. An alternative explanation is that persistent insomnia reflects the presence of idiopathic insomnia, or a life-long vulnerability to poor sleep. Accordingly, insomnia could in these patients be unrelated to arthritis and the THA procedure. The fact that the frequency of patients reporting onset of sleep disturbance to predate the onset of pain supports this presumption. Although our analysis does not permit any conclusions about cause and effect it is likely that pain, mood disturbance and sleep problems continue to exacerbate each other after the surgery (described in the sleep and pain literature as the pain-sleep vicious cycle) [14]. Further analysis is warranted to disentangle the temporal relationship between pain, sleep and mood disturbance in this patient group. It is important that those with persistent insomnia still improve in hip related outcomes. Insomniacs with idiopathic origin should therefore not be denied THA based on the risk of suboptimal outcomes. The present results rather illuminate that there is a relative large minority of hip pain patients which might need additional follow-up to maximize outcomes after THA.

THA also improves other factors in addition to pain, and it is likely that reductions in pain does not fully account for the improvement observed in sleep. Sleep improvement probably reflects a synergetic effect of improved hip related function, ADL, mobility and mood, in addition to reduced BMI after surgery. For example, when joint functions are

improved, activity during the daytime increase which increase sleep pressure and improvement in sleep. Furthermore, several analgesics (e.g. NSAIDS, morphine) are shown to have a negative impact on sleep architecture (e.g. more awakenings, reduction in the slow wave sleep and rapid eye movement sleep) [43]. In keeping with this a recent large, register based study on medication use before and after THA showed that analgesic use (opioids, NSAIDs and non-opioids) became significantly reduced after THA [44]. Lowered use of analgesics might therefore play one part in the reported improvements in sleep following THA.

Some limitations of the study should be noted. The data collected relied exclusively on the participants` self-report and were therefore subject to possible reporting or recall bias. At recruitment, participants were informed through the title of the study and information sheet that the study focused on sleep and mood disturbances, and patients with concerns about these issues may have been more inclined to take part in the study than those with less focus on these topics. This raises the risk of self-selection bias. However, our results are comparable with studies of THA-patients focusing less on sleep disturbance [1]. Secondly, it is important to note that one of the hospitals included in the study had a very low response rate preoperatively (22%) due to unknown factors. In order to ensure that our data were representative, sensitivity analyses were performed for the clinical background variables and showed no major changes in results when data from the respective hospital was removed from the analyses. There was large variability in disease severity at the time of surgery [45], illustrating the importance of including multiple hospitals when investigating THA symptomatology. Lastly, our analyses do not permit conclusions regarding how sleep disturbance and pain interact. In future work, one should attempt to disentangle the respective contribution of sleep and pain related to THA.

Despite the limitations, the present study has several assets that deserve mention. This study is the largest, and to the authors knowledge the first to investigate insomnia before and after THA. A validated self-report measure of insomnia was used [22]. Although objective measures would have complemented our understanding of how specific sleep variables change after THA (e.g. slow wave sleep), subjective self-report measures are sufficient in identifying cases of insomnia. In addition, the subjective experience of sleep disturbance is the central aspect of this prevalent sleep disorder. This is illustrated by the fact that objective sleep measures do not necessarily match the severity of the patient's complaint, and that subjective assessment of sleep and negative impact on daytime functioning have to be present in order to fulfil an insomnia diagnosis [22]. Questionnaires are also the best tool for time-efficient and large-scale screening of sleep disorders. Our study confirms the usefulness of screening for sleep problems in THA patients.

In the present study, we found that THA leads to improvements in insomnia. Sleep is therefore a highly relevant patient related outcome after THA and further investigations are warranted in order to clarify the specific contribution of sleep on different outcomes in these patients. Our preliminary attempt to shed light on vulnerabilities associated with persistent insomnia after THA identified a cohort of patients that report suboptimal hip-related and other outcomes. The patients not showing improvements in insomnia after the surgery had a more chronic course of pain, sleep and mood disturbance, lasting longer than the rest of the patients. This suggests that THA should not be postponed. Collectively, the present study highlights the utility of including sleep when considering patients for THA but also underscores the importance of routinely examination of sleep in THA patients in order to detect risk factors for reduced outcomes after THA.

Author contributions

TB, SP, JG, GH and IHN were involved in the conception and design of the study, while TH, GH, RB, MH and PA was involved in acquisition of data. Data management and all analyses were undertaken by TB, however all authors was involved with analysis decisions. All authors contributed to data interpretation and preparation of the manuscript. All authors approved the final version of the manuscript.

Conflict of interest

All authors declare that there are no conflicts of interest.

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REFERENCES

1. Fielden, J.M., et al., *An assessment of sleep disturbance in patients before and after total hip arthroplasty*. Journal of Arthroplasty, 2003. **18**(3): p. 371-6.
2. Tang, N.K., K.J. Wright, and P.M. Salkovskis, *Prevalence and correlates of clinical insomnia co-occurring with chronic back pain*. J Sleep Res, 2007. **16**(1): p. 85-95.
3. Ohayon, M.M., *Relationship between chronic painful physical condition and insomnia*. J Psychiatr Res, 2005. **39**(2): p. 151-9.
4. Sivertsen, B., et al., *Insomnia symptoms and use of health care services and medications: the HUNT-2 study*. Behav Sleep Med, 2009. **7**(4): p. 210-22.
5. Sivertsen, B., et al., *The epidemiology of insomnia: associations with physical and mental health. The HUNT-2 study*. J Psychosom Res, 2009. **67**(2): p. 109-16.
6. Sivertsen, B., et al., *Insomnia and long sleep duration are risk factors for later work disability. The Hordaland Health Study*. J Sleep Res, 2009. **18**(1): p. 122-8.
7. Sivertsen, B., et al., *Midlife insomnia and subsequent mortality: the Hordaland health study*. BMC Public Health, 2014. **14**: p. 720.
8. Edwards, R.R., et al., *Duration of sleep contributes to next-day pain report in the general population*. Pain, 2008. **137**(1): p. 202-7.
9. Vitiello, M.V., et al., *Cognitive behavioral therapy for insomnia improves sleep and decreases pain in older adults with co-morbid insomnia and osteoarthritis*. J Clin Sleep Med, 2009. **5**(4): p. 355-62.
10. Chiu, Y., et al., *Poor sleep and depression are independently associated with a reduced pain threshold. Results of a population based study*. Pain, 2005. **115**: p. 316-321.

11. Sivertsen, B., et al., *Sleep and pain sensitivity in adults*. Pain, 2015. **156**(8): p. 1433-9.
12. Davies, K.A., et al., *Restorative sleep predicts the resolution of chronic widespread pain: results from the EPIFUND study*. Rheumatology (Oxford), 2008. **47**(12): p. 1809-13.
13. Jansson-Frojmark, M. and K. Boersma, *Bidirectionality between pain and insomnia symptoms: A prospective study*. British Journal of Health Psychology, 2012. **17**: p. 420-431.
14. Blågestad, T., et al., *How Perceived Pain Influence Sleep and Mood More Than The Reverse: A Novel, Exploratory Study with Patients Awaiting Total Hip Arthroplasty*. Frontiers in Psychology, 2016. **7**: p. 1689.
15. McHugh, G.A., M. Campbell, and K.A. Luker, *GP referral of patients with osteoarthritis for consideration of total joint replacement: a longitudinal study*. Br J Gen Pract, 2011. **61**(589): p. e459-68.
16. Bogoch, E.R., et al., *Increased tender point counts before and after total hip arthroplasty are associated with poorer outcomes but are not individually predictive*. J Arthroplasty, 2010. **25**(6): p. 945-50.
17. Berge, D.J., et al., *Pre-operative and post-operative effect of a pain management programme prior to total hip replacement: a randomized controlled trial*. Pain, 2004. **110**(1-2): p. 33-9.
18. Brennan, M.J. and J.A. Lieberman, 3rd, *Sleep disturbances in patients with chronic pain: effectively managing opioid analgesia to improve outcomes*. Curr Med Res Opin, 2009. **25**(5): p. 1045-55.

19. Cremeans-Smith, J.K., et al., *Sleep disruptions mediate the relationship between early postoperative pain and later functioning following total knee replacement surgery*. Journal of Behavioral Medicine, 2006. **29**(2): p. 215-22.
20. Norwegian Arthroplasty Register, *Norwegian National Advisory Unit on Arthroplasty and Hip Fractures 2016 Annual Report*. 2016, Helse Bergen HF, Department of Orthopaedic Surgery, Haukeland University Hospital.
21. Nilsdotter, A.K., et al., *Hip disability and osteoarthritis outcome score (HOOS)-- validity and responsiveness in total hip replacement*. BMC Musculoskeletal Disord, 2003. **4**: p. 10.
22. Pallesen, S., et al., *A new scale for measuring insomnia: the Bergen Insomnia Scale*. Percept Mot Skills, 2008. **107**(3): p. 691-706.
23. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders-IV- TR*. 2000, Washington DC: Author.
24. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale*. Acta Psychiatr Scand, 1983. **67**(6): p. 361-70.
25. Bjelland, I., et al., *The validity of the Hospital Anxiety and Depression Scale. An updated literature review*. J Psychosom Res, 2002. **52**(2): p. 69-77.
26. Cohen, J., *Statistical power analysis for the behavioral sciences*. 2nd ed. 1988, Hillsdale, NJ: Lawrence Erlbaum Associates.
27. Morris, S.B. and R.P. DeShon, *Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs*. Psychol Methods, 2002. **7**(1): p. 105-25.
28. Jacobson, N.S. and P. Truax, *Clinical significance: a statistical approach to defining meaningful change in psychotherapy research*. J Consult Clin Psychol, 1991. **59**(1): p. 12-9.

29. Klässbo, M., E. Larsson, and E. Mannevik, *Hip disability and osteoarthritis outcome score* An extension of the Western Ontario and McMaster Universities Osteoarthritis Index. *Scandinavian Journal of Rheumatology*, 2003. **32**(1): p. 46-51.
30. Pallesen, S., et al., *A 10-year trend of insomnia prevalence in the adult Norwegian population*. *Sleep Med*, 2014. **15**(2): p. 173-9.
31. Lautenbacher, S., B. Kundermann, and J.C. Krieg, *Sleep deprivation and pain perception*. *Sleep Med Rev*, 2006. **10**(5): p. 357-69.
32. Canivet, C., et al., *Sleeping Problems as a Risk Factor for Subsequent Musculoskeletal Pain and the Role of Job Strain: Results from a One-Year Follow-Up of the Malmo Shoulder Neck Study Cohort*. *International Journal of Behavioral Medicine*, 2008. **15**(4): p. 254-262.
33. Kaila-Kangas, L., et al., *Sleep disturbances as predictors of hospitalization for back disorders - A 28-year follow-up of industrial employees*. *Spine*, 2006. **31**(1): p. 51-56.
34. Lallukka, T., et al., *The joint contribution of pain and insomnia to sickness absence and disability retirement: a register-linkage study among Norwegian and Finnish employees*. *Eur J Pain*, 2014. **18**(6): p. 883-92.
35. Wilson, K.G., et al., *Major depression and insomnia in chronic pain*. *Clin J Pain*, 2002. **18**(2): p. 77-83.
36. Wickwire, E.M., F.T. Shaya, and S.M. Scharf, *Health economics of insomnia treatments: The return on investment for a good night's sleep*. *Sleep Med Rev*, 2015. **30**: p. 72-82.
37. Jenkins, P.J., et al., *Predicting the cost-effectiveness of total hip and knee replacement: a health economic analysis*. *Bone & Joint Journal*, 2013. **95-B**(1): p. 115-21.

38. Losina, E., et al., *The Dramatic Increase in Total Knee Replacement Utilization Rates in the United States Cannot Be Fully Explained by Growth in Population Size and the Obesity Epidemic*. Journal of Bone and Joint Surgery-American Volume, 2012. **94a**(3): p. 201-207.
39. Shan, L., et al., *Total hip replacement: a systematic review and meta-analysis on mid-term quality of life*. Osteoarthritis Cartilage, 2014. **22**(3): p. 389-406.
40. Ethgen, O., et al., *Health-related quality of life in total hip and total knee arthroplasty. A qualitative and systematic review of the literature*. J Bone Joint Surg Am, 2004. **86-A**(5): p. 963-74.
41. Roth, T., *Insomnia: definition, prevalence, etiology, and consequences*. J Clin Sleep Med, 2007. **3**(5 Suppl): p. S7-10.
42. Tang, N.K.Y., *Insomnia Co-Occurring with Chronic Pain: Clinical Features, Interaction, Assessments and Possible Interventions*. Reviews in Pain, 2008. **2**(1): p. 2-7.
43. Lavigne, G., D. McMillan, and M. Zucconi, *Pain and sleep*, in *Principles and practice of sleep medicine*, K. MH, T. Roth, and W. Dement, Editors. 2005, Elsevier: Philadelphia. p. 1246-1255.
44. Blagestad, T., et al., *Prescription trajectories and effect of total hip arthroplasty on the use of analgesics, hypnotics, antidepressants, and anxiolytics: results from a population of total hip arthroplasty patients*. Pain, 2016. **157**(3): p. 643-51.
45. Dieppe, P., et al., *Variations in the pre-operative status of patients coming to primary hip replacement for osteoarthritis in European orthopaedic centres*. BMC Musculoskelet Disord, 2009. **10**: p. 19.

Table 1. Baseline demographic characteristics of the study participants compared to non-responders at the postoperative time

	Responders postoperatively N=216	Non-responders postoperatively N=43
Age (SD), range	67.7 (9.8), 32-95	73.1 (19.2), 37-92
Sex (% female)	65.0	46.5
Education (%)		
No schooling completed	0.5	0.0
Nursery school	19.0	2.4
High school graduate	18.5	14.3
Trade/technical/vocational training	26.0	50.0
Bachelor's degree	24.0	19.0
Master's or doctorate degree	10.5	14.3
<i>Work status (%)</i>		
Employed (Full time or part time)	17.0	27.9
Homemaker	1.0	0.0
Unemployed or work assessment allowance	1.0	4.7
On sick leave	1.0	14.0
Disability benefit	10.5	7.0
Retired	64.0	46.5
<i>Marital status (%)</i>		
Married/cohabitant/partner	78.3	69.0
Single/separated/divorced/widow/widower	21.7	31.0

Number of children (%)

None	6.4	11.9
1-2	47.8	50.0
3 or more	45.8	38.2

Income (NOK. %)

0 - 199 999	1.6	12.5
200 000 - 399 999	49.0	45.0
400 000 - 599 999	25.0	30.0
600 000 or more	4.9	12.5

Reason for operation (%)

Osteoarthritis	81.6	68.0
Rheumatoid Arthritis	4.0	8.0
Other	14.4	24.0

Table 2. Health and general pain preoperatively and 12 months postoperatively

	Preoperatively	Postoperatively
BMI, mean (SD)	29.4 (18.3)	26.8 (4.3)
Health (%)		
Excellent	2.3	7.0
Very good	21.5	22.4
Good	46.7	43.0
Quite poor	21.5	21.5
Poor	7.9	6.1
Health compared to a year ago (%)		
Much better than a year ago	2.4	50.7
A bit better than a year ago	5.2	23.3
About the same as a year ago	33.8	15.8
A bit worse than a year ago	39.0	9.3
Much worse than a year ago	19.5	0.9
General pain		
Magnitude (%)		
No pain	0.5	25.7
Weak	3.8	36.9
Unpleasant	10.8	18.2
Bothersome	68.5	16.8
Horrible	15.0	1.4
Unbearable	1.4	0.9
Frequency (%)		

Constant	29.1	6.7
Daily	63.8	24.8
Multiple times a week	5.6	16.7
Once a week	0.5	4.3
Multiple times a month	0.0	5.2
Once a month	0.5	6.2
Less than once a month	0.5	12.9
Never	0.0	23.3
Chronic (<3 months)		
Yes (%)	98.6	58.2
Additional pain to the hip being replaced		
Yes (%)	71.0	65.1
Opposite hip	28.7	27.3
Other joints	51.4	35.2
Back, head or neck	49.5	41.2
Other chronic pain conditions	16.2	20.3
Magnitude of comorbid pain (SD)	2 (1.4)	1.9 (1.5)
Effect of analgesics (%)		
None	8.5	15.6
To a small degree	53.5	41.9
To a large degree	36.5	35.6
Completely	1.5	6.9
Duration of symptoms (mean (SD), range)		
Pain	7.8 (8.9), 1-50	
Sleep	7.0 (9.3), 1-60	

Anxiety	11.6 (13.1), 1-60
Depression	5.7 (6.2), 1-25
Onset of sleep problems predating onset of pain (%)	
Pain before sleep	60.7
Pain and sleep simultaneously	23.8
Sleep before pain	15.5

BMI = Body Mass Index (kg/m²) whereby 19-24.9 is considered normal weight, 25-29.9 is considered overweight and above 30 is considered obese.

Table 3. Correlations between Insomnia, hip related symptoms and mood disturbance preoperatively

	Insomnia*	
	<i>r</i>	sig (2-tailed)
Anxiety	0.43	p < .001
Depression	0.35	p < .001
HOOS Symptom	-0.19	p = .007
HOOS Pain	-0.36	p < .001
HOOS ADL	-0.33	p < .001
HOOS SportRec	-0.23	p = .001
HOOS QoL	-0.29	p < .001

Correlation measured by Pearsons *r* (two tailed).

* Total score of the Bergen Insomnia Scale

Anxiety and depression total scores measured by the Hospital Anxiety and Depression Scale.

HOOS= total score of the Hip Osteoarthritis Outcome Scale. ADL = Activity of daily living. SportRec = Sport and Recreational activities. QoL = Quality of Life. Normal scores from 0-100, (100 indicating no symptoms, and 0 indicating extreme symptoms). Negative correlations indicate that higher insomnia scores are correlated with worse HOOS outcomes.

Table 4. Changes in hip related outcomes and mood disturbance

	Pre-operative		Post-operative		Chi-square	<i>t</i>	95% CI of the difference		Test statistics		Effect size (<i>d</i>)	Clinically improved (percent)
	Mean	SD	Mean	SD			<i>Lower</i>	<i>Upper</i>	<i>df</i>	<i>sig (2-tailed)</i>		
Hip related outcomes												
Symptom	34.8	15.2	76.6	19.3		-28.3	-44.7	-38.9	215	<i>p</i> < .001	2.4	87.2
Pain	39.8	14.9	84.1	16.6		-33.1	-47.1	-41.8	205	<i>p</i> < .001	2.7	94.8
ADL	40.9	17.6	81.4	18.0		-26.8	-43.0	-37.3	198	<i>p</i> < .001	2.2	92.0
Sport Rec	23.4	18.0	65.3	25.9		-21.6	-45.6	-38.0	200	<i>p</i> < .001	1.9	83.7
QoL	24.7	14.3	73.5	20.9		-30.4	-52.5	-46.1	204	<i>p</i> < .001	2.8	87.6
Anxiety												
Mean (SD)	4.1	3.6	3.6	3.4		2.7	0.1	0.8	210	<i>p</i> = .008	0.1	9.1
Cutoff <8 (%)	15.0		9.4		5.0					<i>p</i> = .023	0.3	8.6
Depression												
Mean (SD)	3.5	3.3	2.8	3.1		4.2	0.4	1.1	209	<i>p</i> < .001	0.3	11.2
Cutoff <8 (%)	10.7		6.6		2.8					<i>p</i> = .095	0.2	8.1

Hip related outcomes measured by the Hip Osteoarthritis Outcome Scale (HOOS). ADL = Activity of daily living. SportRec = Sport and Recreational activities. QoL = Quality of Life. Normal scores from 0-100, (100 indicating no symptoms, and 0 indicating extreme symptoms).

Anxiety and depression measured by the Hospital Anxiety and Depression Scale (HADS).

Chi-Square = McNemar with Yates correction for continuity.

t = paired samples t-test.

Effect size measured by Cohen's d , whereby 0.2 equates to a small effect, 0.5 to a medium effect and effect sizes of 0.8 and larger represent a strong effect.

Table 5. Preoperative and postoperative prevalence of insomnia diagnosis and insomnia subtypes

			Test statistic				sig (2-tailed)	Effect size (d)	Clinically improved (percent)
	Pre-operative	Post-operative	Chi-Square	t	95% CI of the difference				
					Lower	Upper			
Cutoff									
Insomnia*	57.1	32.2	32.5				p < .001	0.9	33.7
Insomnia total score									
mean (SD)	16.7 (11.7)	11.1 (10.7)		8.5	4.6	7.4	193 p < .001	0.6	20.6
Insomnia subtypes									
mean (SD)									
Difficulty initiating sleep									
mean (SD)	2.7 (2.2)	1.9 (2.1)		5.9	0.5	1.1	196 p < .001	0.4	15.3
Difficulty maintaining sleep									
mean (SD)	3.2 (2.4)	2.1 (2.2)		7.1	0.8	1.4	196 p < .001	0.5	21.9
Early awakenings									
mean (SD)	3.0 (2.4)	2.0 (2.2)		5.8	0.7	1.3	196 p < .001	0.4	24.0

Not feeling refreshed after sleep	3.0	(2.4)	1.8	(2.1)	7.7	0.9	1.5	196	p < .001	0.5	27.6
Affected work	1.6	(2.2)	1.0	(1.8)	4.3	0.3	0.9	195	p < .001	0.3	11.3
Unsatisfied with sleep	3.1	(2.5)	1.9	(2.2)	7.2	0.9	1.7	196	p < .001	0.6	22.1

*As defined by DSM-IV, presented as %.

T-test for paired samples. Chi-Square statistic = McNemar Test. Continuity Corrected.

Effect size: Cohen's *d*.

CI = confidence interval.

Table 6. Characteristics of postoperative patient related factors by change-category for Insomnia-diagnosis

Patient related factors postoperatively	Unimproved (N=46)	Clinical significant improved	Clinical significantly worsened	No insomnia (N=70)
		(N=66)	(N=14)	
Sex (% female)	76,1	63,6	78,6	52,9
Age; mean (SD)	69.1 (9.4)	66 (9.1)	60,5 (7.3)	66.7 (11.1)
Anxiety diagnosis; n (%)	10 (27,7)	5 (7.6)	1 (7.1)	0
Depression diagnosis; n (%)	7 (15,6)	0	1 (7.1)	3 (4.3)
Hip related factors; mean,(SD)				
HOOS_Symptom	73.3 (17.6)	79.8 (18.0)	74.6 (22.5)	78.9 (18.5)
HOOS_Pain	79.6 (17.0)	86.7 (15.5)	81.0 (19.7)	86.8 (15.2)
HOOS_ADL	75.5 (18.0)	85.0 (15.8)	74.0 (17.5)	84.7 (16.7)
HOOS_SportRec	58.9 (26.0)	73.8 (23.9)	64.2 (19.0)	65.9 (25.5)
HOOS_QoL	69.4 (18.9)	78.1 (20.0)	70.1 (20.2)	76.4 (20.2)
Sum comorbid pain	2.9 (1.3)	1.7 (1.5)	2.1 (1.4)	1.5 (1.4)
Strenght of pain	2.7 (1.1)	2.1 (1)	2.5 (1.3)	2.1 (1.1)
Frequency of pain	3.9 (2.4)	5.2 (2.5)	4.1 (2.7)	5.1 (2.7)
Duration of symptoms; mean, (SD)				

Years of pain	9.8 (9.7)	7.01(7.3)	8.3 (10.4)	6.9 (9.3)
Years of sleep problems	10.6 (13.5)	4.9 (6.0)	9.7 (8.9)	4.4 (7.9)
Years of anxiety	12.6 (18.29)	12.5 (9.2)	2 (-)	5.6 (6.4)
Years of depression	6.3 (8.3)	6.6 (6.3)	2 (-)	1.3 (0.5)
Onset of sleep disturbance; n (%)				
Before pain	9 (25)	5 (9)	3 (25)	3 (7)
Concurrently with pain	10 (28)	17 (29)	0	8 (18)
After pain	17 (47)	37 (63)	9 (75)	34 (76)

% = percent of subcategory. Clinically significant improvement = Insomnia diagnosis preoperatively, but not postoperatively. Clinically significant worsening = No insomnia diagnosis preoperatively, but postoperatively. Unimproved = Insomnia diagnosis both preoperatively and postoperatively. No insomnia = No insomnia diagnosis either preoperatively or postoperatively. Anxiety and Depression measured by Hospital Anxiety and Depression Scale. HOOS= Hip Osteoarthritis Outcome Scale (0 to 100; 100 indicating no symptoms, and 0 indicating extreme symptoms). ADL = Activity of daily living. SportRec = Sport and Recreational activities. QoL = Quality of Life.



How Perceived Pain Influence Sleep and Mood More Than The Reverse: A Novel, Exploratory Study with Patients Awaiting Total Hip Arthroplasty

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Objectives: Attributions about how comorbid symptoms worsen or improve each other are central cognitive components of chronic pain that are shown to facilitate or impede the recovery process. Still, these attributions have been poorly illuminated in chronic pain patients. The present study explored perceptions of how sleep, pain, and mood influence each other in patients awaiting total hip arthroplasty (THA).

Design and Methods: In this cross-sectional study, 291 patients (mean age 67.8, 65.3% female) rated 12 statements about how much a given symptom (pain, sleep, mood) changed when another symptom (pain, sleep, mood) worsened or improved on a response scale ranging from much worse (−2) via no change (0) to much better (2). Sleep (Bergen Insomnia Scale), pain (McGill Pain Questionnaire), anxiety and depression (Hospital Anxiety and Depression Scale) were assessed as background variables.

Results: Of the patients in the study, 56% reported symptoms indicating insomnia. Anxiety and depression were indicated in 16 and 10%, respectively. Over 80% rated their pain as horrible/unbearable and reported that pain occurred always/daily. When experiencing increased pain, a majority perceived that sleep (90%) and mood (70%) worsened, whilst experiencing reduced pain improved sleep and mood in 50%. Poor sleep increased pain and worsened mood in 45 and 60% of the patients, respectively. Better sleep was perceived to reduce pain and improve mood in 50%. Worsened mood increased pain (46%) and worsened sleep (52%). Improved mood decreased pain and improved sleep in 25 and 35%, respectively.

Discussion: In this study, a novel approach was used to investigate perceptions of reciprocal relationships between symptoms. We found that THA patients perceived interrelationships between pain, sleep and mood. These perceived interrelations were stronger when symptoms worsened than when symptoms improved. They also held stronger beliefs about the effect of pain on sleep and mood, than the effect of sleep and

mood on pain. Attributions are central in illness perception and ultimately affect illness behavior. For patients who perceive symptoms to interrelate, the door has already been opened to utilize these attributions in treatments aiming to disrupt vicious cycles, hence supporting the use of multimodal treatments.

Keywords: chronic pain, sleep, mood, attribution, reciprocal relationships between symptoms

INTRODUCTION

Pain in patients eligible for total hip arthroplasty (THA) is normally caused by arthritis (Hamel et al., 2008). The experience and expression of such pain is commonly modulated by the presence of comorbid conditions like sleep and mood disturbances (Chiu et al., 2005; Lautenbacher et al., 2006; Roehrs et al., 2006; Haack et al., 2007; Smith et al., 2007; O'Brien et al., 2011; Blågestad et al., 2012) as well as expectancies and appraisals about these conditions (Tracey, 2010; Bjorkedal and Flaten, 2012). Chronic pain patients often attribute specific causal relationships in terms of how these conditions influence each other (Morin et al., 1998; Hawker et al., 2008; Tang et al., 2009; Theadom and Cropley, 2010). Shown to shape symptom expression, such attributions also influence a person's overall perceived symptom load (Petrie et al., 2007). Attributions typically enable a person to predict and influence future events, and are, accordingly, found to predict thoughts and behavior aimed at getting well, or motivation to perform preventive health behavior (Michela and Wood, 1986). In chronic pain specifically, such attributions are found to be central cognitive facilitators or impediments to the recovery process (Dean, 1986; Michela and Wood, 1986; DeGood and Kiernan, 1996; Roesch and Weiner, 2001).

Sleep and mood disturbances are frequently experienced as a consequence of pain in chronic pain patients (Brennan and Lieberman, 2009), and often interact to worsen pain (Chiu et al., 2005; Zautra et al., 2005; Vitiello et al., 2009; Ong et al., 2010; Theadom and Cropley, 2010; Sivertsen et al., 2015). Conversely, there is also recent research highlighting the amplifying effect of improvements of sleep and mood involved in the recovery from chronic pain (Zautra et al., 2005; Davies et al., 2008; Ashworth et al., 2010; Ong et al., 2010). Sleep and mood are therefore central components both in expression of illness, and as part of the multimodality treatment of chronic pain patients. There is emerging evidence that chronic pain patients with comorbid sleep problems are aware of the bidirectional relationship between the constructs (Tang et al., 2009; Ramlee et al., 2016). Hence, there is great potential in assessing and utilizing attributions to aid accurate understanding and treatment of chronic pain and its comorbid conditions.

Attributions about the perceived relationship between pain, sleep and mood have been poorly illuminated empirically. A few studies have explored the perceived effect of pain on sleep and mood and found, first, that good sleep and emotional well-being are rated as very important for chronic pain patients (Turk et al., 2008). Furthermore, many pain patients are convinced that their sleep problems result from their pain (Morin et al., 1998; Hawker et al., 2008), and consequently when they experience

severe pain, it is difficult for them to sleep (Edwards et al., 2011; Tang et al., 2012a). In line with this, chronic pain patients often believe that their sleep problem will disappear when their pain is gone (Morin et al., 1998). Of the studies to date, only one has explored this reciprocal relationship from the perspective of sleep, finding that fibromyalgia patients directly associate poor sleep with feelings of pain and fatigue, in addition to reduced coping abilities (Theadom and Cropley, 2010). Knowledge of attributions about the perceived mutual influence of mood, pain and sleep is lacking in chronic pain patients. Also missing are studies exploring attributions about how improvements, and not only worsening, of symptoms, are perceived to influence other symptoms. Finally, in order to investigate whether bidirectional relationships exist in how patients attribute reciprocal symptom influence, these multidirectional attributions need to be explored within the same individuals.

To improve our understanding of attributions of symptoms in chronic pain patients, we developed an instrument to explore how patients waiting to undergo THA perceived pain, sleep and mood to influence each other. The questionnaire contained 12 statements assessing two main aspects of symptom influence: (1) how levels of pain influence sleep and mood, but also, conversely, the influence of sleep and mood on pain, and (2) the perceived effect on pain, sleep and mood both when symptoms are worse than usual and when symptoms are better than usual. Based on the responses to these statements, bidirectional relationships between pain, sleep and mood were investigated.

MATERIALS AND METHODS

Study Design

This questionnaire-based study was part of a prospective, multi-center study that evaluated pain, sleep, anxiety, depression and symptom attribution in patients 6–0 weeks before THA. These results are reported elsewhere.

Participants

Participants were recruited from four different orthopedic departments in hospitals across Norway (Haukeland University Hospital, Diakonhjemmet Hospital, Coastal Hospital Hagevik and Sørlandet Hospital Arendal) between May 2014 and November 2015. A total of 643 patients who entered the waiting lists for THA were invited to participate and 314 patients accepted. The response rate differed between the hospitals, with response rates of 75.2, 72.0, 58.7, and 23.2%, respectively. Due to the low response rate in the last hospital, sensitivity analyses were performed whereby results with all hospitals included were compared to results from all hospitals without the hospital

with the lowest response rate. In all cases, the results did not significantly differ, with differences in effect (measured by Cohen's *d* effect size) of less than 0.1. Hence, including data from the hospital with low response rate had negligible effects on the results. Eighteen participants were excluded from the analysis due to missing signed consent form pre-operatively, and five because their THA was canceled. Thus, the final sample consisted of 291 participants.

Procedure

The participants were recruited consecutively from the waiting lists for THA. When sending the notice of the date for their operation, an administrative staff member at the respective hospital enclosed information about the study, provided a questionnaire consisting of several validated scales as well as an informed consent form. Patients willing to participate were asked to complete the questionnaire at home and return the questionnaire and signed consent form when arriving at the pre-operative consultation. At one hospital, the patients were asked to return the questionnaire in a prepaid return envelope. Date of surgery was extracted from the Norwegian Arthroplasty Register via the participant's unique identifying code provided in the questionnaire. The participant's address was provided by the respective hospitals.

The study was approved by The Regional Committee for Medical and Health Research Ethics in Western Norway (2014/63/REK Vest) and was also approved at each of the hospitals involved.

Materials

The questionnaire contained a selection of measures that registered the participant's name, identifying code and data on the participant's demographics (age, sex, ethnicity, education level, employment, income, marital status, and number of children) and self-reported health. The following clinical background variables were assessed; pain intensity and frequency [from the McGill Pain Questionnaire (Melzack, 1975), in addition to reporting additional pain in the hip being replaced], sleep [Bergen Insomnia Scale (BIS; Pallesen et al., 2008)], symptoms of anxiety and depression [Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983)], and specific hip-related outcomes [Hip Osteoarthritis Outcome Scale (Nilsdotter et al., 2003)]. In addition, the participants completed a questionnaire assessing attribution of symptoms specifically designed for this study. These questionnaires are briefly described in the following paragraphs.

General pain was assessed using two verbal descriptor scales from the McGill Pain Questionnaire (Melzack, 1975), validated in Norwegian (Kim et al., 1995). The magnitude of pain was assessed by the phrase: "place a cross in the box fitting your pain," with the response alternatives "no pain," "weak," "unpleasant," "bothersome," "terrible" or "unbearable." The frequency of pain was assessed by the phrase: "How often do you have pain?" The response alternatives were "constantly," "daily," "several times a week," "about once a week," "several times a month," "about once a month," "less than once a month" and "never." Patients were also asked whether the pain was chronic (> 3 months), if they had

additional pain to the hip being replaced and whether they felt that analgesics relieved their pain.

Sleep was assessed using the BIS which measures self-reported symptoms of insomnia corresponding to the criteria for insomnia in the Diagnostic and Statistical Manual of Mental Disorders-IV-TR (American Psychiatric Association, 2000). The scale includes six items that are scored on an eight-point scale indicating the number of days per week for which a specific symptom is experienced (0–7 days, total scores ranging from 0 to 42). The BIS is validated using subjective as well as polysomnographic data and is found to possess good psychometric properties (Pallesen et al., 2008). Participants were categorized as insomniacs if scoring 3 or more on at least one of items 1–4, and 3 or more on at least one of items 5 and 6. The scale provided a Cronbach's alpha of 0.91 in the present study.

The Hospital Anxiety and Depression Scale (HADS) was used to assess the presence of anxiety and depression. The HADS contains 14 items describing non-vegetative symptoms of anxiety and depression (scoring range 0–21 for both anxiety and depression subscales) (Zigmond and Snaith, 1983). Higher scores indicate greater symptom severity. A score of 8 or higher on the HADS subscales of anxiety and depression respectively is considered a clinical cut-off. A validated Norwegian version of the HADS was used in the present study (Bjelland et al., 2002), for which the Cronbach's alpha for each subscale was 0.86.

The Hip Osteoarthritis Outcome Scale (HOOS) evaluated hip related outcomes through 5 subscales [pain, symptoms, functioning in activities of daily living (ADL), functioning in sport and recreation, and hip-related quality of life]. Standardized response alternatives are provided on a 5-point Likert scale (0–4). Then, a normalized score from 0 to 100 is calculated for each subscale (100 indicating no symptoms, and 0 indicating extreme symptoms) (Nilsdotter et al., 2003). The Cronbach's alpha coefficient was 0.96 in the present study.

The main outcome variable was symptom attribution. In order to assess how participants perceived symptoms of pain, sleep and mood to influence each other, a questionnaire was developed containing 12 statements about how much a given symptom (pain, sleep, mood) changed when another symptom (pain, sleep, mood) worsened or improved. Six statements explored the effect on the other two symptoms when a given symptom worsened, and six statements explored the effect on the other two symptoms when a given symptom improved. The participants were asked to provide responses on a 5-point scale (from 1 to 5) for each statement. **Table 1** presents the 12 statements together with the response alternatives.

Data Analysis

Analyses were performed using SPSS, version 21. For the symptom attribution questionnaire, the rating scale was recoded in order to display the positive or negative properties of the perceived influence. *Much worse* was recoded to -2 , *a bit worse* was recoded to -1 , *as usual* was recoded to 0 (indicating no change), *a bit better* was recoded to 1 and *much better* was recoded as 2. Descriptive statistics were used to characterize symptom attributions and the difference of the mean from 0 (no change) was measured through one-sample

TABLE 1 | Symptom attribution questionnaire.

	Response alternatives				
	Much better	A bit better	No change	A bit worse	Much worse
When my pain is worse than usual, my sleep becomes. . .					
When my pain is worse than usual, my mood becomes. . .					
When my sleep is worse than usual, my pain becomes. . .					
When my sleep is worse than usual, my mood becomes. . .					
When my mood is worse than usual, my pain becomes. . .					
When my mood is worse than usual, my sleep becomes. . .					
When my pain is weaker than usual, my sleep becomes. . .					
When my pain is weaker than usual, my mood becomes. . .					
When my sleep is better than usual, my pain becomes. . .					
When my sleep is better than usual, my mood becomes. . .					
When my mood is better than usual, my pain becomes. . .					
When my mood is better than usual, my sleep becomes. . .					

t-tests. A paired sample *t*-test was used to compare items in bidirectional relationships in order to assess the directionality of symptom attribution. All statements are listed in **Table 1**. For example, whether pain influences sleep more than sleep influences pain was assessed by comparing statements 1a and 2a for the worsening relationships between symptoms, and statements 1c and 2c for the improving relationships between symptoms. For the pain-mood relationship, statements 1b and 3a and statements 1d and 3c were compared for the worsening and improving effect of symptoms, respectively. For the sleep-mood relationship, statements 2b and 3b and statements 2d and 3d were compared for the worsening and improving effect of symptoms, respectively. Pairs with one or more missing values were removed from analyses (excluded pairwise). To measure the magnitude of the effect, effect sizes (Cohen's *d*) were estimated using DSTAT (Johnson, 1995). An effect size of 0.2 is regarded as a small, 0.5 a medium, and effect sizes of 0.8 or higher are regarded as large (Cohen, 1988). A Bonferroni-correction was applied due to multiple comparisons, setting the new critical *p*-value to 0.002.

RESULTS

Description of Baseline Characteristics

Table 2 presents the participants' characteristics. The mean age was 67.9 years and 65.3% were female. The majority were retired, married/cohabiting, and had 2 or 3 children. The majority had an income between 100 000 and 399 999 NOK (equivalent to approximately 12 000–50 000 USD). Clinical background variables are presented in **Table 3**. On the PPI, most participants rated their pain to be horrible (66.3%) or unbearable (16.2%), and over 90% rated their pain to occur daily or be present

constantly. Over 70% also reported additional pain in the hip being replaced. In total, 54.0% reported symptoms indicating insomnia (the average BIS score was 16.4, *SD* = 12.0). Symptoms indicating caseness of anxiety or depression were reported by 16.2 and 10.3%, respectively. According to the hip-specific outcome measure (HOOS), the self-reported hip-related pain, function, quality of life, ADL and sports and recreation were poor (between 40 and 24 on a scale of 100–0 where 100 indicates no symptoms, and 0 indicates extreme symptoms).

Attributions between Pain, Sleep and Mood When Symptoms Worsened

A substantial portion of patients perceived that worsening of symptoms influenced their pain, sleep and mood (**Table 4, Figure 1**). Ninety per cent of the patients reported that sleep worsened in the presence of increased pain and 70% reported mood to worsen with increased pain. Close to 45% perceived their pain to worsen with poorer sleep, and almost 60% perceived mood to worsen with poorer sleep. Worse mood was perceived to have the least influence on pain (64.3% perceived there to be no change), but 51.9% reported mood to influence sleep. As displayed in **Table 5**, the mean on all subscales differed significantly from 0 (all *t*-values significant on the 0.002-level) with effect sizes ranging from 0.6 to 2.3 (medium to very large effect size).

Attributions between Pain, Sleep and Mood When Symptoms Improved

Patients reported improvement of one symptom to influence the other symptoms to a smaller degree than did worsening of it (**Table 4, Figure 1**). Still, reduced pain was perceived to improve sleep and mood in 56.7 and 51.8% of the patients, respectively. Improved sleep was also perceived to improve pain

in 35.4% of the patients. Improved sleep had a strong influence on improvements of mood and was reported by 47.2% of the patients. Again, mood was perceived to have the least influence on pain and sleep; improved mood was perceived not to have an effect in 74.9% for pain and 63.2% for sleep. Regardless, all variables differed significantly from 0 (all t -values significant on a 0.002-level). **Table 5** displays the effect sizes (ranging from 0.3 = small effect size to 0.9 = large effect size).

Directionality of Attributions When Symptoms Worsened

When symptoms worsened, pain was significantly perceived to influence sleep more than sleep influenced pain ($t = -19.2$, $df = 279$). The effect size was large ($d = 1.1$) (**Table 6, Figure 2**). Increased pain was also perceived to influence mood significantly more than worsened mood influenced pain ($t = -10.5$, $df = 269$). This effect size was medium ($d = 0.6$). There was no significant difference to which degree

the participants perceived sleep and mood to influence each other.

Directionality Attributions When Symptoms Improved

Reduced pain significantly influenced sleep more than improved sleep influenced pain (**Table 6, Figure 3**, $t = 5.7$, $df = 272$). The effect size was small to medium ($d = 0.4$). Reduced pain also influenced mood more than improved mood influenced pain ($t = 10.3$, $df = 268$) with a medium effect size ($d = 0.6$). Lastly, improved sleep was perceived to influence mood more than improved mood influenced sleep ($t = 8.0$, $df = 269$) with a medium effect size ($d = 0.5$).

TABLE 2 | Demographics (N = 291).

Age	67.9 (SD: 11.1), range 23–96
Sex	65.3% female
Education (%)	
No schooling completed	0.3
Nursery school	15.8
High school graduate	16.2
Trade/technical/vocational training	29.2
Bachelor's degree	25.4
Master's degree	10.1
Doctorate degree	1.0
Work status (%)	
Full time 100 %	15.1
Part time	3.4
Homemaker	0.7
Unemployed	0.7
Student	0.3
On sick leave 100%	7.6
On sick leave <100%	1.7
Work assessment allowance	1.4
Disability benefit	8.6
Retired	59.8
Marital status (%)	
Married/cohabitant/partner	74.6
Single/separated/divorced/widow/widower	24.7
Number of children (%)	
None	9.9
1–2	48.1
3–4	36.4
5 or more	5.2
Income (NOK, %)	
0–199 999	15.4
200 000–399 999	44.7
400 000–599 999	25.1
600 000 or more	8.6

TABLE 3 | Clinical background variables (N = 291).

Pain	
Magnitude (%)	
Weak, unpleasant or bothersome	14.5
Horrible	66.3
Unbearable	16.2
Frequency (%)	
Constant or daily	89.3
Once or multiple times a week	7.2
Once or multiple times a month	0.6
Less than once a month	1.0
Chronic (pain lasting <3 months, %)	96.9
Experiencing additional pain to the replaced hip (%)	70.4
Effect of analgesics (%)	
None or to a small degree	56.0
To a large degree or completely	34.7
Health (%)	
Excellent or very good	24.0
Good or quite good	64.3
Poor	10.7
Health compared to a year ago (%)	
Much or a bit better than a year ago	7.2
About the same as a year ago	31.3
A bit or much worse than a year ago	59.1
Insomnia (BIS)	
Sum (mean)	16.4
Cutoff-insomnia* (%)	54.0
Anxiety (HAD-A < 8, %)	16.2
Mean (SD)	4.3 (SD: 3.9)
Depression (HAD-D < 8, %)	10.3
Mean (SD)	3.5 (SD: 3.19)
Hip related measures - HOOS	
Symptoms	34.35
Pain	39.22
ADL	40.05
Sportrec	23.02
QoL	24.78

*As defined by DSM-IV; BIS, Bergen Insomnia Scale; HADS, Hospital Anxiety and Depression Scale; HOOS, Hip Osteoarthritis Outcome Scale. Normal scores from 0–100, (100 indicating no symptoms, and 0 indicating extreme symptoms).

DISCUSSION

In contrast to the number of studies that aim to disentangle the relationship between chronic pain, sleep and mood, limited effort has been devoted to investigating how patients themselves perceive how these symptoms influence each other. The present study explored perceived bi-directional influences of pain, sleep and mood when symptoms worsened or improved in patients awaiting THA. We found that a large majority perceived sleep and mood to worsen when experiencing worse pain than usual and less intense pain than usual was perceived to improve sleep and mood. A significant proportion of the patients perceived pain

to worsen with poorer sleep, and better sleep was perceived to reduce pain. Overall, pain stood out as the symptom with the largest perceived influence on the other symptoms, while mood was the symptom perceived by the fewest patients as influencing the other symptoms.

Worsening Symptom Attribution

We found that almost all of the patients in the present study perceived increased pain to lead to poorer sleep, corroborating the impact of pain on sleep in previous qualitative and quantitative studies (Smith et al., 2000; Breivik et al., 2006; Hawker et al., 2008; Ashworth et al., 2010; Theadom and

TABLE 4 | Description of attributions of the effect between pain, sleep and mood (N = 291).

Attributions when symptoms worsen	Level of effect (%)						
	Mean (from -2 to 2)	SD	Much worse	A bit worse	No change	A bit better	Much better
When my pain is worse than usual, my sleep becomes...	-1.4	0.6	49.1	40.9	6.5	0.0	0.0
When my pain is worse than usual, my mood becomes...	-0.9	0.6	14.4	56.4	24.1	0.3	0.0
When my sleep is poorer than usual, my pain becomes...	-0.6	0.7	11.3	32.6	51.9	0.3	0.0
When my sleep is poorer than usual, my mood becomes...	-0.7	0.7	11.3	45.7	37.5	0.3	0.0
When my mood is worse than usual, my pain becomes...	-0.4	0.6	7.9	22.0	64.3	0.0	0.0
When my mood is worse than usual, my sleep becomes...	-0.7	0.7	13.4	38.5	41.2	0.3	0.0

Attributions when symptoms improve	Level of effect (%)						
	Mean (from -2 to 2)	SD	Much better	A bit better	No change	A bit worse	Much Worse
When my pain is weaker than usual, my sleep becomes...	0.7	0.9	17.5	39.2	30.6	6.5	0.3
When my pain is weaker than usual, my mood becomes...	0.8	0.8	21.6	30.2	40.5	1.4	0.3
When my sleep is better than usual, my pain becomes...	0.4	0.7	7.6	27.8	56.4	2.7	1.4
When my sleep is better than usual, my mood becomes...	0.7	0.8	18.9	28.2	46.4	1.0	0.3
When my mood is better than usual, my pain becomes...	0.2	0.5	2.7	13.7	74.9	2.1	0.7
When my mood is better than usual, my sleep becomes...	0.3	0.6	4.5	23.4	63.2	3.1	0.0

TABLE 5 | Strength of relationships between symptoms

Attributions when symptoms worsen	Difference from 0 (indicating no change)					
	t	df	95% CI of the difference		Sig	Effect size
When my pain is worse than usual, my sleep becomes...	-39.0	280	-1.5	-1.4	0.000	2.3
When my pain is worse than usual, my mood becomes...	-23.2	276	-1.0	-0.8	0.000	1.4
When my sleep is poorer than usual, my pain becomes...	-13.7	279	-0.7	-0.5	0.000	0.8
When my sleep is poorer than usual, my mood becomes...	-17.8	275	-0.8	-0.6	0.000	1.1
When my mood is worse than usual, my pain becomes...	-10.4	273	-0.5	-0.3	0.000	0.6
When my mood is worse than usual, my sleep becomes...	-16.1	271	-0.8	-0.6	0.000	1.0

Attributions when symptoms improve	Difference from 0 (indicating no change)					
	t	df	95% CI of the difference		Sig	Effect size
When my pain is weaker than usual, my sleep becomes...	13.7	273	0.6	0.8	0.000	0.8
When my pain is weaker than usual, my mood becomes...	15.1	273	0.7	0.9	0.000	0.9
When my sleep is better than usual, my pain becomes...	8.9	278	0.3	0.5	0.000	0.5
When my sleep is better than usual, my mood becomes...	13.8	275	0.6	0.8	0.000	0.8
When my mood is better than usual, my pain becomes...	5.2	273	0.1	0.2	0.000	0.3
When my mood is better than usual, my sleep becomes...	8.4	273	0.2	0.4	0.000	0.5

CI, Confidence Interval. Effect size, Cohen's d.

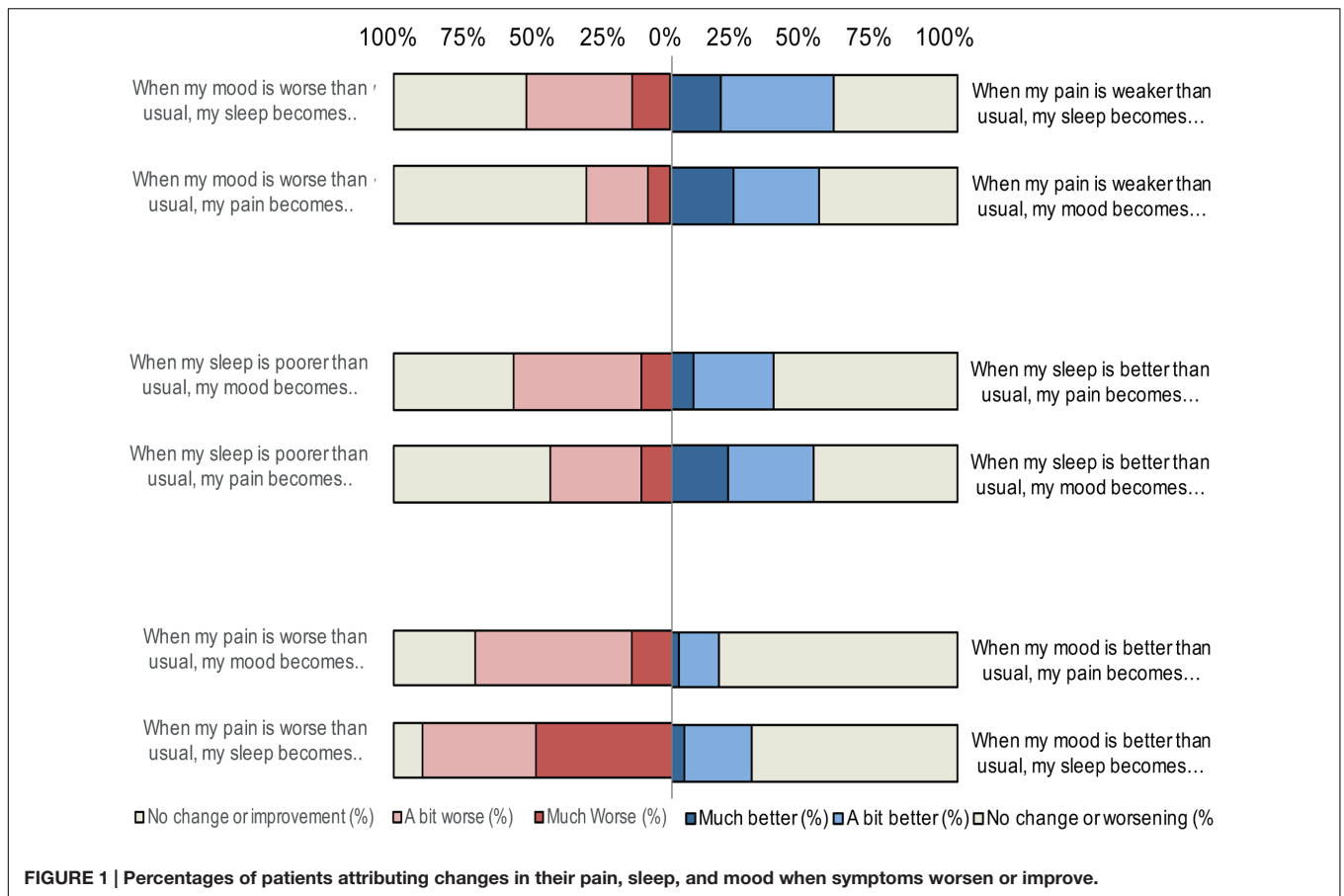


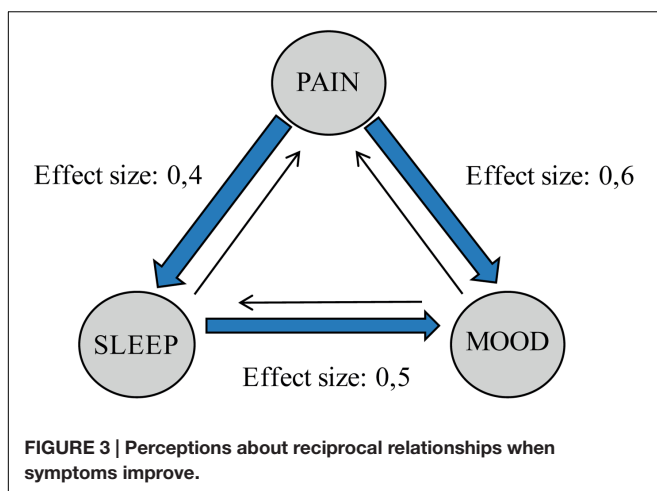
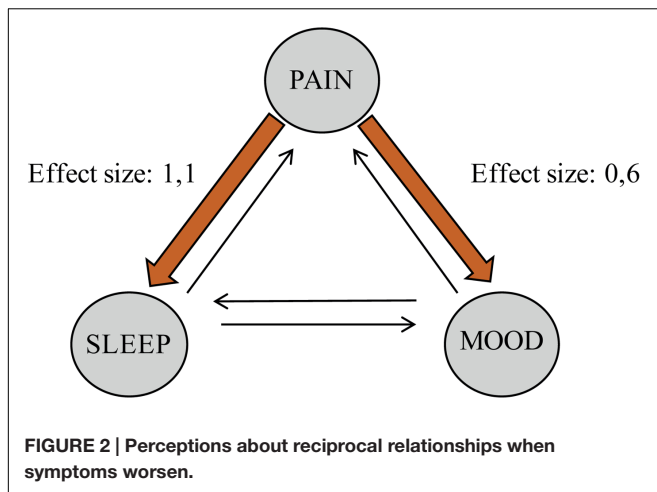
TABLE 6 | Directionality of symptom attribution between pain, sleep and mood (N = 291).

When symptoms worsen	95 % CI		t	df	Sig	Effect size
Pain affects sleep (1a) Sleep affects pain (2a)	-1.0	-0.8	-19.2	279	0.000	1.1
Pain affects mood (1b) Mood affects pain (3a)	-0.6	-0.4	-10.5	269	0.000	0.6
Sleep affects mood (2b) Mood affects sleep (3b)	-0.1	0.1	-0.17	267	0.868	
When symptoms Improve	95 % CI		t	df	Sig	Effect size
Pain affects sleep (1c) Sleep affects pain (2c)	0.2	0.4	5.7	272	0.000	0.4
Pain affects mood (1d) Mood affects pain (3c)	0.5	0.7	10.3	268	0.000	0.6
Sleep affects mood (2d) Mood affects sleep (3d)	0.3	0.5	8.0	269	0.000	0.5

CI, Confidence Interval. Effect size, Cohen's d.

Cropley, 2010; Henderson et al., 2013; Thomazeau et al., 2014). For example, many chronic pain patients firmly believe that when they are in pain, it is simply impossible for them to get comfortable and go to sleep (Edwards et al., 2011; Tang et al.,

2012a). The rate of patients perceiving pain to negatively impact sleep was higher in the present study than found in chronic pain patients in general (90% vs. 65%) (Breivik et al., 2006); also, the intensity and frequency of pain was higher in the present



sample. The present study highlights the importance of effective treatments for chronic pain.

One third of our patients perceived pain and mood to worsen with poorer sleep, mirroring one qualitative study where a poor night's sleep was found to be directly associated with increased pain (Theadom and Cropley, 2010). Our results are also in line with increasing numbers of observational and experimental studies establishing an effect of sleep on pain. However, more than half of the patients in our study did not perceive poorer sleep to increase pain. One of the most distressing features of chronic pain is the unpredictable fluctuation in its type and intensity (Hawker et al., 2008), and it may thus be difficult for patients to perceive how these symptoms are influenced by sleep and mood. This is supported by a recent daily process study that reported the pain-relieving effect of good sleep to be short-lived. Although sleep quality showed an inverse relationship with pain upon waking and during the first half of the day, no association was found during the second half of the day (Tang et al., 2012c). The authors suggest that for some patients, reduced pain might actually lead to over-extending activity. This would cause even more pain during the night, consequently masking the positive effect of good sleep on pain. Hence,

perceived improvement of pain as a result of good sleep might be masked by the fluctuations or other sources of increasing pain. In addition, many clinicians do not regularly assess, diagnose or treat comorbid sleep problems in pain patients, since they are under the false impression that treatment of the underlying organic /psychiatric condition will resolve any residual sleep complaints (Ozminkowski et al., 2007). This lack of focus might contribute to these patients' perception of illness.

Although depression, anxiety and negative mood are closely related to chronic pain (Lin et al., 2003; Argoff, 2007; Montin et al., 2007; O'Brien et al., 2010; Wylde et al., 2011; Hoozeboom et al., 2012), worse mood than usual was perceived by the fewest patients to impact pain and sleep in our study. In a study of middle-aged women with chronic pain, an increase in negative affect during the previous week predicted greater pain during subsequent weeks (Zautra et al., 2005). One could assume that patients would perceive this same effect to a larger degree than what we found. Our results might indicate, as suggested by Lavigne (2005), that negative mood affects sleep and pain in a more indirect way. Alternatively, if the perception about reciprocal relationships between symptoms depend on the presence of the symptom in question, our results might simply reflect lower rates of anxiety and depression compared to pain and sleep complaints in the present study. Future investigations of symptom attributions in chronic pain patients with larger samples of comorbid anxiety and depression would clarify this matter.

Improving Symptom Attribution

The present study is to the authors' knowledge the first to explore how improvement in one symptom (pain, sleep, or mood) is perceived to influence other symptoms. We found that a majority of our patients perceive reduction of pain to improve sleep and mood. Although chronic pain is intractable by definition, this underlines the importance of optimal pain management, whereby reducing pain may also improve comorbid symptoms (Turk and Cohen, 2010). More noteworthy is the finding that one third perceived better sleep than usual to improve pain. The role of sound sleep is key in chronic pain patients. Firstly, restorative sleep is shown to be involved in the resolution of chronic pain (Davies et al., 2008), and chronic pain patients that are "good sleepers" report less pain at night, less negative consequences from their pain and less depression or pain-related anxiety (Ashworth et al., 2010). Accordingly, the concurrent treatment of pain-related sleep problems is found either to reduce pain itself, or to reduce pain interference, which might be an important aspect of pain in chronic pain patients (Edinger et al., 2005; Vitiello et al., 2009; Jungquist et al., 2010; Tang et al., 2012b). Furthermore, positive emotions are seen as resilience factors decreasing the negative impact of chronic pain conditions (Zautra et al., 2005; Ong et al., 2010). In a study investigating positive and negative affect in women with chronic pain, people who tend to have higher levels of positive affect also had less pain over time (Zautra et al., 2005). Hence, adequate sleep and positive mood seems to be a buffer involved not only in the biological foundation of pain perception (Davies et al., 2008), but also in the ability to cope with daily pain

(Theadom and Cropley, 2010). Positive emotions and good sleep may therefore play an important role in fostering recovery after episodes of severe pain (Zautra et al., 2001).

Taken together, the present findings have implications for the assessment and treatment of chronic pain and pain-related sleep and mood disturbances. That symptoms interact to worsen and improve each other forms the basis of multimodality treatments. This emphasizes the benefit of interventions aiming at disrupting vicious circles between symptoms (Argoff, 2007; Smith et al., 2009). The results of the present study support the use of interventions that target sleep and mood in addition to pain. Furthermore, attributions are found to be central cognitive facilitators or impediments to the recovery process (Dean, 1986; DeGood and Kiernan, 1996; Roesch and Weiner, 2001). According to attribution theory, individuals with chronic illness who make internal, unstable and controllable attributions also believe they can do something to minimize the impact of their illness. This leads directly to certain motivated coping cognitions and behavior, and ultimately to more positive psychological adjustment (Weiner, 1985). For chronic pain patients who perceive symptoms to interrelate, the door has already been opened to utilize these attributions in the treatment of chronic pain and its comorbid conditions. For our patients awaiting THA specifically, these attributions might aid a positive reinforcing cycle of symptom improvement when pain is reduced after surgery.

The limitations of the study should be noted. Firstly, due to the lack of previous studies that include the key attribution elements aimed at in the present study, a questionnaire was constructed for this purpose. It is therefore not previously validated. The questions used for assessing reciprocal relationships between pain, sleep and mood should be validated in other types of samples (e.g., normal subjects as well as in patients suffering from sleep and mood disorders). In the process of developing the questionnaire, mood was intentionally chosen as a general symptom-effector instead of specifying anxiety and depression, for several reasons. By broadening the term into “mood,” we are convinced that aspects of disturbed mood such as “helplessness” or “frustrations” often experienced by these patients would be included in addition to aspects of anxiety and depression. Furthermore, there is no equivalent positive category to diagnoses such as anxiety and depression, and we also wanted to capture eventual positive attributions of improved mood, beyond the absence of negative symptoms. Another limitation is that since the patients completed the questionnaires without assistance from the researchers we had no way to ensure that participants understood the intention of the attribution questionnaire. Third, it is important to note that one of the hospitals included in the study had a very low response rate (22%), due to unknown factors. In order to ensure representativeness of our data, sensitivity analyses were performed and showed no major changes in results when the respective hospital was removed from analyses.

Despite the limitations, there are several strengths of this novel study. It places itself in a line of studies focusing on

obtaining wider knowledge about the sleep-pain domain from the patient’s perspective (Hawker et al., 2008; Turk et al., 2008), but it extends the scope to also explore attributions about sleep and mood, and to illuminate both the attributions related to worsening as well as improvement of symptoms. The natural path forward is to extend this newly acquired perspective into different chronic pain populations or populations where pain is a frequently experienced comorbid symptom.

CONCLUSION

The present study found that patients awaiting THA perceive pain, sleep and mood to influence each other when symptoms worsen or improve. Pain was perceived to have a stronger influence on sleep and mood, than sleep and mood had on pain. Attributions of symptom dynamics as investigated in the present study may play a key role in overall pain experience and illness behavior.

AUTHOR CONTRIBUTIONS

TB designed the study, developed the main questionnaire, recruited the hospitals participating in the study and collected the data. She also analyzed the data and wrote the manuscript. SP supervised the project, including participating in the design of the study and developing the main questionnaire. He also took part in deciding the choice of analyses, and critically reviewed the manuscript. JG also supervised the project, including participating in the design of the study and developing the main questionnaire. she also took part in deciding the choice of analyses, and critically reviewed the manuscript. NT took part in deciding the choice of analyses, the interpretation of the results and critically reviewed the manuscript. IN was the main supervisor of the project and participated in the design of the study and the development of the main questionnaire. She also took part in deciding the choice of analyses, and critically reviewed the manuscript. All authors have approved of the final version of the manuscript to be published.

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REFERENCES

- American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders-IV-TR*. Washington DC: American Psychiatric Association.
- Argoff, C. E. (2007). The coexistence of neuropathic pain, sleep, and psychiatric disorders: a novel treatment approach. *Clin. J. Pain* 23, 15–22. doi: 10.1097/01.aip.0000210945.27052.b300002508-200701000-00003
- Ashworth, P. C., Davidson, K. M., and Espie, C. A. (2010). Cognitive-behavioral factors associated with sleep quality in chronic pain patients. *Behav. Sleep Med.* 8, 28–39. doi: 10.1080/15402000903425587
- Bjelland, I., Dahl, A. A., Haug, T. T., and Neckelmann, D. (2002). The validity of the hospital anxiety and depression Scale. An updated literature review. *J. Psychosom. Res.* 52, 69–77. doi: 10.1016/S0022-3999(01)00296-3
- Bjorkedal, E., and Flaten, M. A. (2012). Expectations of increased and decreased pain explain the effect of conditioned pain modulation in females. *J. Pain Res.* 5, 289–300. doi: 10.2147/JPR.S33559
- Blagestad, T., Pallesen, S., Lunde, L. H., Sivertsen, B., Nordhus, I. H., and Gronli, J. (2012). Sleep in older chronic pain patients: a comparative polysomnographic study. *Clin. J. Pain* 28, 277–283. doi: 10.1097/AJP.0b013e3182313899
- Breivik, H., Collett, B., Ventafridda, V., Cohen, R., and Gallacher, D. (2006). Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur. J. Pain* 10, 287–333. doi: 10.1016/j.ejpain.2005.06.009
- Brennan, M. J., and Lieberman, J. A. III. (2009). Sleep disturbances in patients with chronic pain: effectively managing opioid analgesia to improve outcomes. *Curr. Med. Res. Opin.* 25, 1045–1055. doi: 10.1185/03007990902797790
- Chiu, Y., Silman, A., Macfarlane, G., Ray, D., Gupta, A., Dickens, C., et al. (2005). Poor sleep and depression are independently associated with a reduced pain threshold. Results of a population based study. *Pain* 115, 316–321. doi: 10.1016/j.pain.2005.03.009
- Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences*, 2nd Edn. Hillsdale, NJ: Lawrence Erlbaum Associates.
- Davies, K. A., Macfarlane, G. J., Nicholl, B. I., Dickens, C., Morriss, R., Ray, D., et al. (2008). Restorative sleep predicts the resolution of chronic widespread pain: results from the EPiFUND study. *Rheumatology (Oxford)* 47, 1809–1813. doi: 10.1093/rheumatology/ken389
- Dean, K. (1986). Lay care in illness. *Soc. Sci. Med.* 22, 275–284. doi: 10.1016/0277-9536(86)90076-6
- DeGood, D. E., and Kiernan, B. (1996). Perception of fault in patients with chronic pain. *Pain* 64, 153–159. doi: 10.1016/0304-3959(95)00090-9
- Edinger, J. D., Wohlgemuth, W. K., Krystal, A. D., and Rice, J. R. (2005). Behavioral insomnia therapy for fibromyalgia patients: a randomized clinical trial. *Arch. Intern. Med.* 165, 2527–2535. doi: 10.1001/archinte.165.21.2527
- Edwards, M. J., Tang, N. K., Wright, A. M., Salkovskis, P. M., and Timberlake, C. M. (2011). Thinking about thinking about pain: a qualitative investigation of rumination in chronic pain. *Pain Manag.* 1, 311–323. doi: 10.2217/pmt.11.29
- Haack, M., Sanchez, E., and Mullington, J. M. (2007). Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. *Sleep* 30, 1145–1152.
- Hamel, M. B., Toth, M., Legedza, A., and Rosen, M. P. (2008). Joint replacement surgery in elderly patients with severe osteoarthritis of the hip or knee: decision making, postoperative recovery, and clinical outcomes. *Arch. Intern. Med.* 168, 1430–1440. doi: 10.1001/archinte.168.13.1430
- Hawker, G. A., Stewart, L., French, M. R., Cibere, J., Jordan, J. M., March, L., et al. (2008). Understanding the pain experience in hip and knee osteoarthritis—an OARSI/OMERACT initiative. *Osteoarthritis Cartilage* 16, 415–422. doi: 10.1016/j.joca.2007.12.017
- Henderson, J. V., Harrison, C. M., Britt, H. C., Bayram, C. F., and Miller, G. C. (2013). Prevalence, causes, severity, impact, and management of chronic pain in Australian general practice patients. *Pain. Med.* 14, 13461361. doi: 10.1111/pme.12195
- Hoogbeem, T. J., den Broeder, A. A., Swierstra, B. A., de Bie, R. A., and van den Ende, C. H. (2012). Joint-pain comorbidity, health status, and medication use in hip and knee osteoarthritis: a cross-sectional study. *Arthritis Care Res. (Hoboken)* 64, 54–58. doi: 10.1002/acr.20647
- Johnson, B. T. (1995). *DSTAT: Software for the Meta-Analytic Review of Research Literature (Version 1.11)*. Hillsdale, NJ: Erlbaum.
- Jungquist, C. R., O'Brien, C., Matteson-Rusby, S., Smith, M. T., Pigeon, W. R., Xia, Y., et al. (2010). The efficacy of cognitive-behavioral therapy for insomnia in patients with chronic pain. *Sleep Med.* 11, 302–309. doi: 10.1016/j.sleep.2009.05.018
- Kim, H. S., Schwartz-Barcott, D., Holter, I. M., and Lorensen, M. (1995). Developing a translation of the McGill pain questionnaire for cross-cultural comparison: an example from Norway. *J. Adv. Nurs.* 21, 421–426. doi: 10.1111/j.1365-2648.1995.tb02722.x
- Lautenbacher, S., Kundermann, B., and Krieg, J. C. (2006). Sleep deprivation and pain perception. *Sleep Med. Rev.* 10, 357–369. doi: 10.1016/j.smrv.2005.08.001
- Lavigne, G. J. (2005). *Principles and Practices in Sleep Med.* Amsterdam: Elsevier.
- Lin, E. H., Katon, W., Von Korff, M., Tang, L., Williams, JW Jr, Kroenke, K., et al. (2003). Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial. *JAMA* 290, 2428–2429. doi: 10.1001/jama.290.18.2428290/18/2428
- Melzack, R. (1975). The McGill pain questionnaire: major properties and scoring methods. *Pain* 1, 277–299. doi: 10.1016/0304-3959(75)90044-5
- Michela, J., and Wood, J. (1986). “Causal attributions in health and illness,” in *Advances in Cognitive-Behavioral Research and Therapy*, ed. P. C. Kendall (New York, NY: Academic Press), 179–235.
- Montin, L., Leino-Kilpi, H., Katajisto, J., Lepisto, J., Kettunen, J., and Suominen, T. (2007). Anxiety and health-related quality of life of patients undergoing total hip arthroplasty for osteoarthritis. *Chronic Illn.* 3, 219–227. doi: 10.1177/1742395307084405
- Morin, C. M., Gibson, D., and Wade, J. (1998). Self-reported sleep and mood disturbance in chronic pain patients. *Clin. J. Pain* 14, 311–314. doi: 10.1097/00002508-199812000-00007
- Nilsdotter, A. K., Lohmander, L. S., Klassbo, M., and Roos, E. M. (2003). Hip disability and osteoarthritis outcome score (HOOS)—validity and responsiveness in total hip replacement. *BMC Musculoskelet. Disord.* 4:10. doi: 10.1186/1471-2474-4-10
- O'Brien, E. M., Waxenberg, L. B., Atchison, J. W., Gremillion, H. A., Staud, R. M., McCrae, C. S., et al. (2010). Negative mood mediates the effect of poor sleep on pain among chronic pain patients. *Clin. J. Pain* 26, 310–319. doi: 10.1097/AJP.0b013e3181c328e9
- O'Brien, E. M., Waxenberg, L. B., Atchison, J. W., Gremillion, H. A., Staud, R. M., McCrae, C. S., et al. (2011). Intraindividual variability in daily sleep and pain ratings among chronic pain patients: bidirectional association and the role of negative mood. *Clin. J. Pain* 27, 425–433. doi: 10.1097/AJP.0b013e318208c8e4
- Ong, A. D., Zautra, A. J., and Reid, M. C. (2010). Psychological resilience predicts decreases in pain catastrophizing through positive emotions. *Psychol. Aging* 25, 516–523. doi: 10.1037/a0019384
- Ozminkowski, R. J., Wang, S., and Walsh, J. K. (2007). The direct and indirect costs of untreated insomnia in adults in the United States. *Sleep* 30, 263–273.
- Pallesen, S., Bjorvatn, B., Nordhus, I. H., Sivertsen, B., Hjørnevik, M., and Morin, C. M. (2008). A new scale for measuring insomnia: the Bergen Insomnia Scale. *Percept. Mot. Skills* 107, 691–706. doi: 10.2466/PMS.107.7.691-706
- Petrie, K. J., Jago, L. A., and Devcich, D. A. (2007). The role of illness perceptions in patients with medical conditions. *Curr. Opin. Psychiatry* 20, 163–167. doi: 10.1097/YCO.0b013e328014a871
- Ramlee, F., Afolalu, E., and Tang, N. (2016). Do people with chronic pain judge their sleep differently? A qualitative study. *Behav. Sleep Med.* 1–16. doi: 10.1080/15402002.2016.1188393 [Epub ahead of print].
- Roehrs, T., Hyde, M., Blaisdell, B., Greenwald, M., and Roth, T. (2006). Sleep loss and REM sleep loss are hyperalgesic. *Sleep* 29, 145–151.
- Roesch, S. C., and Weiner, B. (2001). A meta-analytic review of coping with illness: do causal attributions matter? *J. Psychosom. Res.* 50, 205–219. doi: 10.1016/S0022-3999(01)00188-X
- Sivertsen, B., Lallukka, T., Petrie, K. J., Steingrimsdottir, O. A., Stubhaug, A., and Nielsen, C. S. (2015). Sleep and pain sensitivity in adults. *Pain* 156, 1433–1439. doi: 10.1097/j.pain.0000000000000131
- Smith, M. T., Edwards, R. R., McCann, U. D., and Haythornthwaite, J. A. (2007). The effects of sleep deprivation on pain inhibition and spontaneous pain in women. *Sleep* 30, 494–505.
- Smith, M. T., Perlis, M. L., Smith, M. S., Giles, D. E., and Carmody, T. P. (2000). Sleep quality and presleep arousal in chronic pain. *J. Behav. Med.* 23, 1–13. doi: 10.1023/A:1005444719169
- Smith, M. T., Quartana, P. J., Okonkwo, R. M., and Nasir, A. (2009). Mechanisms by which sleep disturbance contributes to osteoarthritis pain: a conceptual model. *Curr. Pain Headache Rep.* 13, 447–454. doi: 10.1007/s11916-009-0073-2

- Tang, N. K., Goodchild, C. E., Hester, J., and Salkovskis, P. M. (2012a). Pain-related insomnia versus primary insomnia: a comparison study of sleep pattern, psychological characteristics, and cognitive-behavioral processes. *Clin. J. Pain* 28, 428–436. doi: 10.1097/AJP.0b013e31823711bc
- Tang, N. K., Goodchild, C. E., and Salkovskis, P. M. (2012b). Hybrid cognitive-behaviour therapy for individuals with insomnia and chronic pain: a pilot randomised controlled trial. *Behav. Res. Ther.* 50, 814–821. doi: 10.1016/j.brat.2012.08.006
- Tang, N. K., Goodchild, C. E., Sanborn, A. N., Howard, J., and Salkovskis, P. M. (2012c). Deciphering the temporal link between pain and sleep in a heterogeneous chronic pain patient sample: a multilevel daily process study. *Sleep* 35, 675A–687A. doi: 10.5665/sleep.1830
- Tang, N. K., Salkovskis, P. M., Hodges, A., Soong, E., Hanna, M. H., and Hester, J. (2009). Chronic pain syndrome associated with health anxiety: a qualitative thematic comparison between pain patients with high and low health anxiety. *Br. J. Clin. Psychol.* 48(Pt 1), 1–20. doi: 10.1348/014466508X336167
- Theadom, A., and Cropley, M. (2010). ‘This constant being woken up is the worst thing’—experiences of sleep in fibromyalgia syndrome. *Disabil. Rehabil.* 32, 1939–1947. doi: 10.3109/09638281003797331
- Thomazeau, J., Perin, J., Nizard, R., Bouhassira, D., Collin, E., Nguyen, E., et al. (2014). Pain management and pain characteristics in obese and normal weight patients before joint replacement. *J. Eval. Clin. Pract.* 20, 611–616. doi: 10.1111/jep.12176
- Tracey, I. (2010). Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. *Nat. Med.* 16, 1277–1283. doi: 10.1038/nm.2229
- Turk, D. C., and Cohen, M. J. (2010). Sleep as a marker in the effective management of chronic osteoarthritis pain with opioid analgesics. *Semin. Arthritis Rheum.* 39, 477–490. doi: 10.1016/j.semarthrit.2008.10.006
- Turk, D. C., Dworkin, R. H., Revicki, D., Harding, G., Burke, L. B., Cella, D., et al. (2008). Identifying important outcome domains for chronic pain clinical trials: an IMMPACT survey of people with pain. *Pain* 137, 276–285. doi: 10.1016/j.pain.2007.09.002
- Vitiello, M. V., Rybarczyk, B., Von Korff, M., and Stepanski, E. J. (2009). Cognitive behavioral therapy for insomnia improves sleep and decreases pain in older adults with co-morbid insomnia and osteoarthritis. *J. Clin. Sleep Med* 5, 355–362.
- Weiner, B. (1985). An attributional theory of achievement motivation and emotion. *Psychol. Rev.* 92, 548–573. doi: 10.1037/0033-295X.92.4.548
- Wylde, V., Hewlett, S., Learmonth, I. D., and Dieppe, P. (2011). Persistent pain after joint replacement: prevalence, sensory qualities, and postoperative determinants. *Pain* 152, 566–572. doi: 10.1016/j.pain.2010.11.023
- Zautra, A., Smith, B., Affleck, G., and Tennen, H. (2001). Examinations of chronic pain and affect relationships: applications of a dynamic model of affect. *J. Consult. Clin. Psychol.* 69, 786–795. doi: 10.1037/0022-006X.69.5.786
- Zautra, A. J., Johnson, L. M., and Davis, M. C. (2005). Positive affect as a source of resilience for women in chronic pain. *J. Consult. Clin. Psychol.* 73, 212–220. doi: 10.1037/0022-006X.73.2.212
- Zigmond, A. S., and Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatr. Scand.* 67, 361–370. doi: 10.1111/j.1600-0447.1983.tb09716.x

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Prescription trajectories and effect of total hip arthroplasty on the use of analgesics, hypnotics, antidepressants, and anxiolytics: results from a population of total hip arthroplasty patients

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Abstract

Total hip arthroplasty (THA) has been shown to reduce pain and improve function. In addition, it is suggested that THA improves sleep and alleviates symptoms of anxiety and depression. Patients with chronic pain are frequent users of analgesic and psychotropic drugs and thereby risk adverse drug events. The impact of THA on such drug use has not been thoroughly investigated. Based on merged data from the Norwegian Prescription Database and the Norwegian Arthroplasty Register, this study sought to investigate redeemed medications in a complete population (N = 39,688) undergoing THA in 2005 to 2011. User rates and redeemed drug volume of analgesics (nonsteroid anti-inflammatory drugs (NSAIDs), opioids, and nonopioids) and psychotropics (hypnotics, anxiolytics, and antidepressants) were calculated for 4 quarters before and 4 quarters after surgery. We analysed preoperative prescription trends (Q1 vs Q4), postoperative prescription (Q4 vs Q5), and long-term effect of surgery (Q4 vs Q8). Before surgery, use of all drug groups increased from Q1 to Q4. Use of opioids, nonopioids, and hypnotics dramatically increased from Q4 to Q5. Long-term (Q4 vs Q8) surgery reduced prescriptions of analgesics, hypnotics, and anxiolytics, but not antidepressants. Overall, the present results extend the positive effects of THA to include reduced reliance on medication to alleviate symptoms.

Keywords: Register study, Total hip arthroplasty, Analgesics, Psychotropics

1. Introduction

Most patients waiting for total hip arthroplasty (THA) report constant pain and use of pain medications.^{10,43} Nocturnal pain is a key indication for THA,⁴⁴ and 80% of all patients report awakening at night because of pain before surgery.⁴³ The prevalence of anxiety and depression in these patients is between 5% and 15%.^{10,43} Consistently successful in relieving pain and

improving function,^{39,33} THA has also been found to have additional positive effects including reduction of sleep problems^{12,26,61} and alleviation of symptoms of anxiety and depression,^{31,22} all leading to improved quality of life. Notably, preoperative mental health and sleep problems have been found to predict postoperative levels of pain, functional level, and quality of life.^{12,22} Overall, this reflects mutual relationships between pain, sleep, and mental health.^{9,11,15,18,24,34,48,51,54}

Analgesics and psychotropic drugs are often prescribed to control pain, sleep problems, and mental health.⁴³ However, little is known about the corresponding use of analgesics and psychotropic drugs before and after THA. Self-reported analgesic use in these patients is as high as 97%.⁵² Prescription rates are lower, not including over-the-counter medications. Most THA patients received prescriptions for nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids during the 2-year period before surgery.^{10,38} The use of medication increased over time as the date of surgery approached.¹⁰ To our knowledge, only 1 study has investigated changes in the use of analgesics after THA, reporting reduced user rates of NSAIDs during the year after surgery.¹³

Total hip arthroplasty patients experience increasing levels of pain leading up to surgery, elevated postoperative pain during a 3-month recovery phase and lower level than presurgery pain at 6 to 12 months after surgery.^{2,33,37,45,53} If prescription patterns follow pain trajectories, analysis of short prescription intervals is necessary to elucidate trajectories of medication use. Knowledge about the use of medication in THA patients in large-scale,

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pre–post designs is warranted, given the risk of adverse drug reactions, drug–drug interactions, and/or postoperative costs associated with pharmacotherapy for chronic pain and frequent comorbid symptoms.^{4,8,23,41,56}

Based on information from 2 nationwide registers, the Norwegian Prescription Database (NorPD) and the Norwegian Hip Arthroplasty Register, the aim of this study was to extend previous research on THA and medication use by analysing prescription patterns of 3 groups of analgesics and 3 groups of psychotropics over a 2-year window of exposure; 1 year before and 1 year after surgery. Specifically, we investigated prescription trends leading up to surgery, changes in medication use in the recovery period after surgery, and long-term effects of surgery on medication use. We hypothesized that (1) use of these medications would increase before surgery, (2) drug use would further increase in the postoperative phase, and (3) that THA would reduce use of medications 1 year after surgery.

2. Materials and methods

2.1. Study population

The health care system in Norway is public and hip replacements are all financed by the compulsory insurance scheme.⁴⁹ Patients who undergo elective surgery are referred to a hospital by a general practitioner. Prioritization generally follows 3 criteria: the degree of severity, the expected efficiency of treatment, and the cost in relation to the expected outcome of the treatment.⁵ A total of 54,402 primary THAs were performed in the period 2004 to 2012. We excluded surgeries in the opposite hip for the same person ($n = 6509$), reoperations within the following year ($n = 742$), and patients deceased within 2 years after surgery ($n = 1449$) from the analyses. To be able to analyse medication use during the year before and after surgery, persons undergoing THA in 2004 and 2012 were excluded ($n = 6014$). Thus, the study population comprised 39,688 persons. Data were then merged with prescription data from the NorPD, including redeemed prescriptions 1 year before and 1 year after the date of surgery.

2.2. Study design and data sources

This study was a register-based prospective study using data from the NorPD maintained at the Norwegian Institute of Public Health and data from the National Arthroplasty Register in Norway at Haukeland University Hospital used. Data from both sources were merged by Statistics Norway, using patients' unique encrypted identifying code, enabling us to analyse the data at the individual level while ensuring personal anonymity.

2.2.1. Norwegian prescription database

The NorPD is a national health register containing information on all prescription drugs dispensed to all home-dwelling individuals at all pharmacies in Norway from January 2004 to this time.³⁰ The register covers medications fully paid for by patients, and those reimbursed by the government. The database stores detailed information on items dispensed (the dispensed item's generic name, Anatomical Therapeutic Chemical code, the defined daily dose (DDD) of the prescribed drug, and date of dispensing)⁴⁷ and basic demographic information about patients (person's unique personal identifying code, age, sex, and person's year of death) about patients. However, information is lacking at the individual level concerning medications issued for institutionalized patients in nursing homes and hospitals.³⁵ We extracted data from NorPD

from 2004 to 2012. The medications included in this study were classified according to the Anatomical Therapeutic Chemical classification system.⁴⁷ Analgesics analysed in this study include M01A—NSAIDs, N02A—opioids, and N02B—other analgesics and antipyretics, hereafter called as nonopioid analgesics. Three subgroups of psychotropic drugs were included; N05C—hypnotics and sedatives, hereafter called as hypnotics, N05B—anxiolytics, and N06A—antidepressants.

2.2.2. Norwegian national arthroplasty register

This person-identifiable health register receives data of operated joint prostheses from all 70 hospitals in Norway performing THA. Completeness is high (97%) for THA.²⁵ We extracted the following information from the register: the persons' unique personal identification code, date of operation, primary or secondary operation, indication for operation, type of operation, and perioperative complications. The patients were scored preoperatively by the American Society of Anesthesiologists (ASA) physical status classification system³ as either: 1 healthy person; 2 mild systemic disease; 3 severe systemic disease; 4 severe systemic disease that is a constant threat to life; and 5 moribund person not expected to survive.

2.3. Medication use

Two measures of medication use were included. User rates were defined as number of persons who redeemed 1 or more prescriptions during the period studied. Furthermore, dispensed drug volumes were quantified as number of DDD. The DDD is a technical measuring unit determined on the basis of evaluation of international use of the substance in question and is defined as the assumed average daily maintenance dose for a drug used for its main indication in adults.⁴⁷ The DDD used in this article refers to the total number of DDDs for each redeemed prescription and is calculated by the NorPD. The dispensed drug volume in DDD was summarized per quarter.

2.4. Analysis strategy and statistics

Analyses were performed using SPSS Statistics, version 21. To examine changes in drug use over time, the 2-year observation period was divided into 8 quarters (91 days each); 4 before (Q1–Q4), and 4 after (Q5–Q8) surgery for each patient. Drug utilization trends before surgery were examined by comparing Q1 with Q4, immediate postoperative changes by comparing Q4 with Q5, and changes from preoperative to follow-up were examined by comparing Q4 with Q8. Exact McNemar tests were performed for comparison of user rates and paired sample *t* tests when comparing drug volumes. The analyses for user rates and drug volumes were supplemented by effect size (Cohen *d*) calculation using DSTAT and interpreted according to Cohen¹⁶ whereby 0.2 equates to a small effect, 0.5 to a medium effect, and effect sizes larger than 0.8 to a strong effect. A Bonferroni correction was applied because of multiple comparisons, setting the new critical *P* value to 0.005. Effect sizes for DDDs were corrected for dependence between means.⁵⁰

2.5. Ethics and approvals

The study was approved by the Regional Committee for Medical and Health Research Ethics, The Norwegian Directorate for Health and Social Affairs, and by The Norwegian Data Protection Authority.

3. Results

3.1. Study population

Demographic characteristics of the study population are presented in **Table 1**. The mean age of persons undergoing THR was 68.5 years, 80.4% of the study population was above 60 years and 66.4% were female. The main reason for undergoing surgery was primary osteoarthritis (77.4%), and 79.1% of the study population was classified as belonging to ASA class 1 or 2 preoperatively.

3.2. Analgesic and psychotropic drug use related to total hip arthroplasty

At least 1 type of analgesic drug was redeemed by 49.3% of the study population during the year before THA: 37.9% were dispensed NSAIDs, 16.3% opioids, and 12.4% nonopioid analgesics, **Table 2**. In the same period, 23.1% redeemed any psychotropics, 14.3% redeemed hypnotics (1.8% benzodiazepines, 12.5% Z-hypnotics, and 0.2% melatonin, data not shown), 7.8% redeemed antidepressants, and 7.6% redeemed anxiolytics, respectively. The drug utilization trajectories for all medication subgroups during the 4 quarters before, and the 4 quarters after THA are illustrated in **Figure 1** for user rates and **Figure 2** for DDDs.

3.2.1. Preoperative drug utilization trends (Q1 vs Q4)

User rates and redeemed drug volumes of analgesics increased from quarter 1 to quarter 4 preoperatively (**Figs. 1 and 2**). The increase was most pronounced for user rates and drug volume of opioids (from 16.3% to 27.8%, $P < 0.001$ and from 6.3 to 11.4 DDD, $P < 0.001$) and nonopioid analgesics (from 12.4% to 21.0%, $P < 0.001$ and from 4.6 to 9.4 DDD, $P < 0.001$). Effect sizes were small to medium (opioids: $d = 0.35$ for user rates and $d = 0.22$ for DDD; nonopioids: $d = 0.29$ for user rates and $d = 0.21$ for DDD, **Tables 2 and 3**). For NSAIDs, an increase from quarter 1 to quarter 4 (37.9% vs 39.4% and 32.9 vs 35.3 DDD) the change was also statistically significant ($P < 0.001$).

Table 1
Characteristics of study population at the time of surgery.

	n (%)
Sex	
Men	13,350 (33.6)
Women	26,338 (66.4)
Age, y	
Mean (SD)	68.5 (11.5)
Range	11-98
0-39	703 (1.8)
40-59	7056 (17.8)
60-69	11,960 (30.1)
70-79	13,329 (33.6)
80+	6640 (16.7)
Primary cause of operation	
Primary arthritis	30,737 (77.4)
ASA-class	
1	10,402 (26.2)
2	21,003 (52.9)
3	6965 (17.5)
4	113 (0.3)
Missing	1201 (3)

1 = healthy person, 2 = mild systemic disease, 3 = severe systemic disease, 4 = severe systemic disease that is a constant threat to life or moribund person.

ASA, American Society of Anesthesiologists physical status classification system.

Regarding psychotropic use, hypnotics and anxiolytics increased in user rates and drug volume during the preoperative period (hypnotics: from 14.3% to 16.8%, $P < 0.001$ and from 11.8 to 14.3 DDD, $P < 0.001$; anxiolytics: from 7.6% to 8.6% $P < 0.001$ and from 3.7 to 4.2 DDD, $P < 0.001$) while antidepressants increased significantly in drug volume only (from 8.9 to 9.8 DDD, $P < 0.001$, **Tables 2 and 3**). For changes in psychotropic user rates and drug volume effect sizes were small ($d = 0.11-0.02$).

3.2.2. Immediate postoperative changes (Q4 vs Q5)

Significant changes in medication use from quarter 4 to quarter 5 were detected (**Tables 2 and 3**). Analgesic use (both user rates and drug volume) increased the quarter after surgery regarding opioids (27.8% vs 65.4%, $P < 0.001$ and 11.4 vs 15.1 DDD, $P < 0.001$) and nonopioid analgesics (21.0% vs 60.5%, $P < 0.001$ and 9.4 vs 17.8 DDD, $P < 0.001$) Effect sizes were large for both user rates of opioids ($d = 0.8$) and nonopioids ($d = 0.85$). For NSAIDs, user rates (from 39.4% to 23.0%) and drug volumes (from 35.3 to 13.9 DDD) decreased significantly, with an effect size of 0.40 for user rates and 0.37 for drug volume. User rates of hypnotics increased from 16.8% to 25.0%, but the corresponding change in drug volume was small, from 14.3 to 15.4 DDDs, however were statistically significant ($P < 0.001$). Effect sizes were small ($d = 0.27$ for user rates and 0.03 for drug volume). Conversely, a decrease was found for antidepressants (user rates: from 8.0% to 7.2%, $P < 0.001$ and drug volume: 9.8-7.9 DDD, $P < 0.001$) and for anxiolytics (drug volume: 4.2 vs 3.6 DDD, $P < 0.001$).

3.2.3. Changes from preoperative to follow-up (Q4 vs Q8)

Total hip arthroplasty was associated with reductions in use of medications in the long-term, as shown in **Table 3**. The use of analgesics decreased from quarter 4 to quarter 8, with user rates being halved for opioids (from 27.8% to 14.1%, $P < 0.001$, $d = 0.41$) and NSAIDs (from 39.4% to 18.0%, $P < 0.001$, $d = 0.54$). User rates of nonopioid analgesics decreased (from 21.0% to 13.1%, $P < 0.001$, $d = 0.25$) in the same period. Moreover, drug volumes were reduced, especially for NSAIDs showing 35.3 DDD in quarter 4 to 13.6 DDD in quarter 8 ($P < 0.001$, $d = 0.37$). User rates and drug volumes for redeemed hypnotics and anxiolytics significantly decreased from quarter 4 to quarter 8, (hypnotics: 16.8% vs 16%, $P < 0.001$ and 14.3 vs 13.3 DDD, $P < 0.001$; anxiolytics: 8.6% vs 7.8%, $P < 0.001$ and 4.2 vs 3.7 DDD, $P < 0.001$) but with very small effect sizes. No significant changes were found for antidepressants (**Table 3, Figs. 1 and 2**).

4. Discussion

Prescription trajectories within a 2-year exposure window in a complete population of THA patients showed an increase in the use of analgesics (opioids and nonopioids) and hypnotics during the year before surgery, peaking in the postoperative recovery phase and decreasing after THA long-term, thus following the same trajectories as pain described in the THA literature.^{37,44,53}

All medication subgroups increased in user rates and drug volume through the year before surgery. Increased pain has been reported the year before THA,^{2,45} and our results support a previous study showing increased use of NSAIDs and opioids the year before total hip and knee arthroplasty.¹⁰ The use of NSAIDs increased only until the third quarter, and then decreased. Nonsteroid anti-inflammatory drugs have several adverse side effects, especially in the elderly,^{41,56} and patients

Table 2
Number and percentage of patients who have redeemed at least 1 prescription and amounts of redeemed medication (measured in DDDs) in 4 quarters preoperative (Q1-Q4) and 4 quarters postoperative (Q5-Q8).

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
User rates, percent (95% CI)								
Analgesics								
Any	49.3 (48.8-49.8)	53.7 (53.2-54.2)	59.8 (59.3-60.3)	58.5 (58.0-59.0)	86.7 (86.4-87.1)	35.1 (34.6-35.6)	34.4 (34.0-34.9)	32.8 (32.3-33.24)
Opioids	16.3 (15.9-16.6)	18.8 (18.4-19.2)	23.8 (23.4-24.2)	27.8 (27.3-28.2)	65.4 (64.9-65.8)	14.7 (14.4-15.0)	14.4 (14.2-14.8)	14.1 (13.7-14.4)
NSAIDs	37.9 (37.4-38.4)	40.6 (40.1-41.1)	44.2 (43.7-44.7)	39.4 (38.9-39.9)	23.0 (22.5-23.4)	19.3 (19.0-19.7)	19.3 (18.9-19.6)	18.0 (17.6-18.4)
Nonopioid analgesics	12.4 (12.1-12.8)	14.8 (14.5-15.2)	19.4 (19.0-19.7)	21.0 (20.6-21.4)	60.5 (60.1-61.0)	14.4 (14.1-14.8)	13.7 (13.4-14.1)	13.1 (12.8-13.5)
Psychotropics								
Any	23.1 (22.7-23.8)	23.4 (22.9-23.8)	24.3 (23.9-24.7)	25.8 (25.3-26.2)	32.5 (32.1-33.0)	24.3 (23.8-24.7)	24.4 (24.0-24.8)	24.6 (24.2-25.0)
Hypnotics	14.3 (14.0-14.7)	14.7 (14.3-15.0)	15.5 (15.2-15.9)	16.8 (16.4-17.1)	25.0 (24.6-25.5)	16.1 (15.7-16.5)	15.8 (15.5-16.2)	16.0 (15.6-16.3)
Antidepressants	7.8 (7.5-8.1)	7.7 (7.4-7.9)	7.9 (7.7-8.2)	8.0 (7.6-8.3)	7.2 (6.9-7.4)	7.8 (7.5-8.2)	8.1 (7.8-8.3)	8.2 (8.0-8.5)
Anxiolytics	7.6 (7.4-7.9)	7.7 (7.4-7.9)	7.9 (7.6-8.2)	8.6 (8.3-8.8)	8.5 (8.2-8.7)	7.7 (7.5-8.0)	7.8 (7.5-8.1)	7.9 (7.7-8.2)
Drug volume (DDDs), mean (SD)								
Analgesics								
Any	43.8 (69.1)	48.4 (72.6)	56.7 (77.2)	56.0 (78.3)	46.8 (56.4)	26.5 (56.9)	25.9 (55.3)	24.9 (55.6)
Opioids	6.3 (26.5)	7.1 (28.0)	9.0 (30.1)	11.4 (33.7)	15.1 (29.6)	6.0 (27.1)	5.7 (25.3)	5.8 (27.4)
NSAIDs	32.9 (57.5)	35.6 (59.4)	39.8 (62.0)	35.3 (59.2)	13.9 (36.8)	14.6 (39.8)	14.5 (39.3)	13.6 (38.3)
Nonopioid analgesics	4.6 (15.7)	5.8 (17.8)	8.0 (21.0)	9.4 (23.4)	17.8 (23.1)	5.9 (18.8)	5.7 (18.5)	5.6 (18.3)
Psychotropics								
Any	24.4 (68.7)	24.8 (70.9)	25.9 (71.0)	28.3 (75.8)	26.9 (67.0)	26.0 (70.4)	26.4 (71.2)	27.0 (75.3)
Hypnotics	11.8 (38.6)	12.1 (39.2)	12.8 (40.0)	14.3 (42.8)	15.4 (39.5)	13.3 (39.3)	13.3 (39.5)	13.6 (42.6)
Antidepressants	8.9 (40.3)	9.0 (41.5)	9.2 (41.7)	9.8 (43.7)	7.9 (37.0)	9.0 (40.3)	9.5 (41.4)	9.6 (41.8)
Anxiolytics	3.7 (20.4)	3.7 (22.6)	3.8 (21.2)	4.2 (24.1)	3.6 (21.1)	3.8 (21.8)	3.7 (21.6)	3.8 (22.4)

Persons may have redeemed medications from more than 1 medication class (N = 39,688).

CIs, Confidence Intervals; DDDs, defined daily doses; NSAIDs, nonsteroid anti-inflammatory drugs.

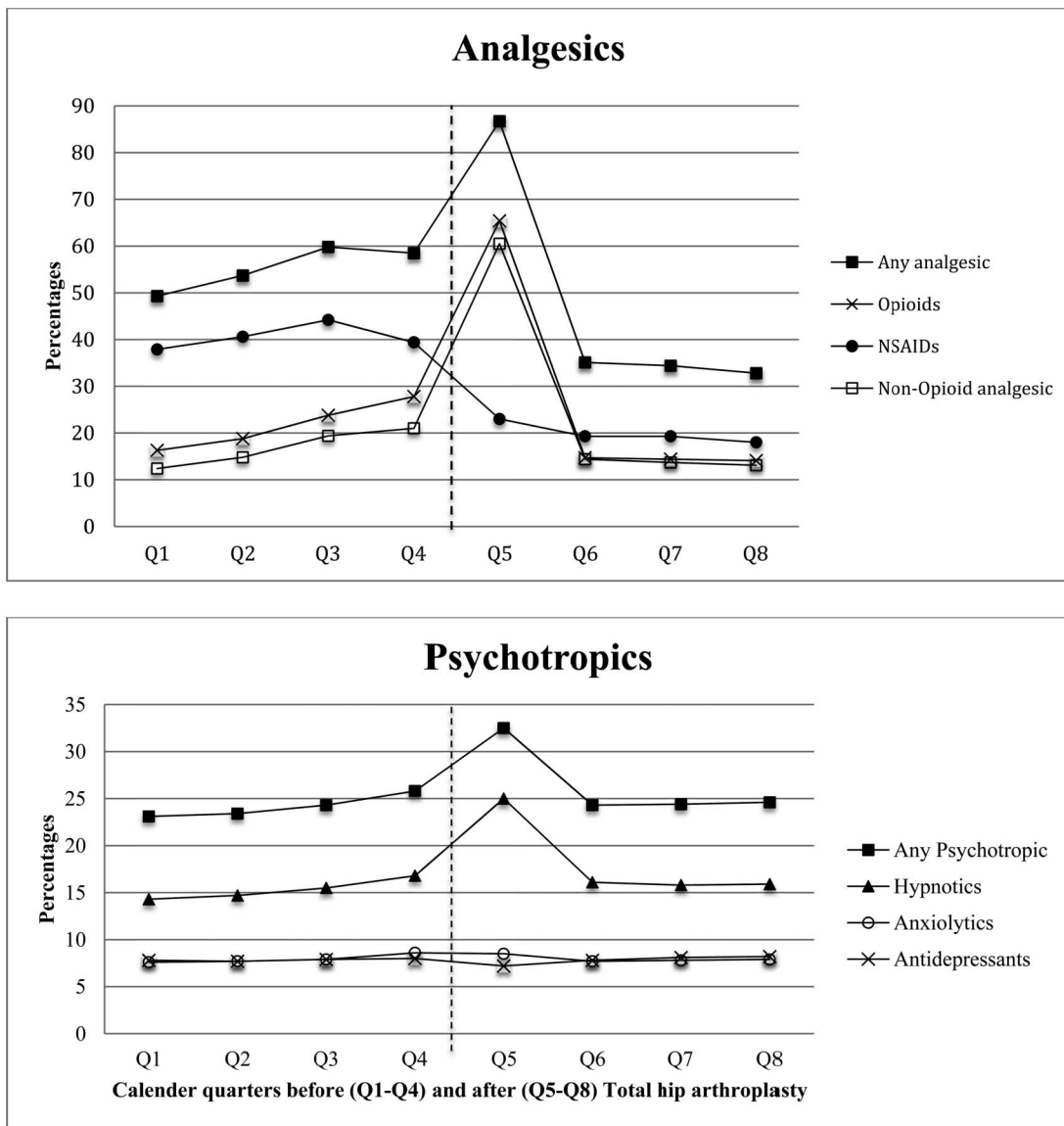


Figure 1. Prescription trajectories for user rates of redeemed prescriptions. NSAIDs, nonsteroid anti-inflammatory drugs.

might be encouraged to reduce their use of NSAIDs before surgery. Consequently, the observed increases in opioid and nonopioid use during the last quarter before surgery may be due to patients switching analgesic subgroup. Regardless, we conclude that hypothesis 1 was confirmed.

Total hip arthroplasty patients in their 3-month postoperative phase (Q5) doubled their use of opioid and nonopioid analgesics from Q4, corresponding with clinical pain trajectories previously reported.³³ It should be noted that in many patients, postoperative pain decreases earlier than 3 months after surgery,^{19,33} and studies are warranted to investigate more accurately when the corresponding decrease in analgesics occurs. Interestingly, hypnotic use follows the same prescription trajectory as analgesics, supporting the link between pain and sleep. Although analgesics might be prescribed preemptively at discharge from hospital regardless of actual pain levels, patients normally have to ask their general practitioner specifically for new or repeat prescriptions of hypnotics. Hence, our finding may reflect an actual increase in sleep problems in the recovery phase after surgery. Interestingly, disturbed sleep

leads to hyperalgesia and impaired endogenous pain modulation.^{27,59} Furthermore, sleep disruptions postsurgically have been found to partially mediate the relationship between pain 1 month after surgery and functional limitations 3 months after surgery,¹⁷ underscoring the importance of adequate sleep during postsurgical recovery. In that respect, increased short-term use of hypnotics may be positive, especially if non-pharmacological sleep interventions are not available. Improved sleep has both short-term and long-term effects on chronic pain⁶⁰ and may be ancillary to a positive cycle of reduced pain and improved sleep after THA. Narcotics have been found to disrupt sleep architecture and the increased need for hypnotics postsurgically found in this study may be due to adverse side effects of narcotic use.⁵⁵ The occurrence of such narcotic-induced sleep disturbance has to be taken into account to optimize the choice of analgesic and sedative medication in the treatment of THA patients. Regardless, our results warrant attention to the increased risk of adverse medication effects occurring with the use of both opioids and hypnotics increase in the recovery phase.

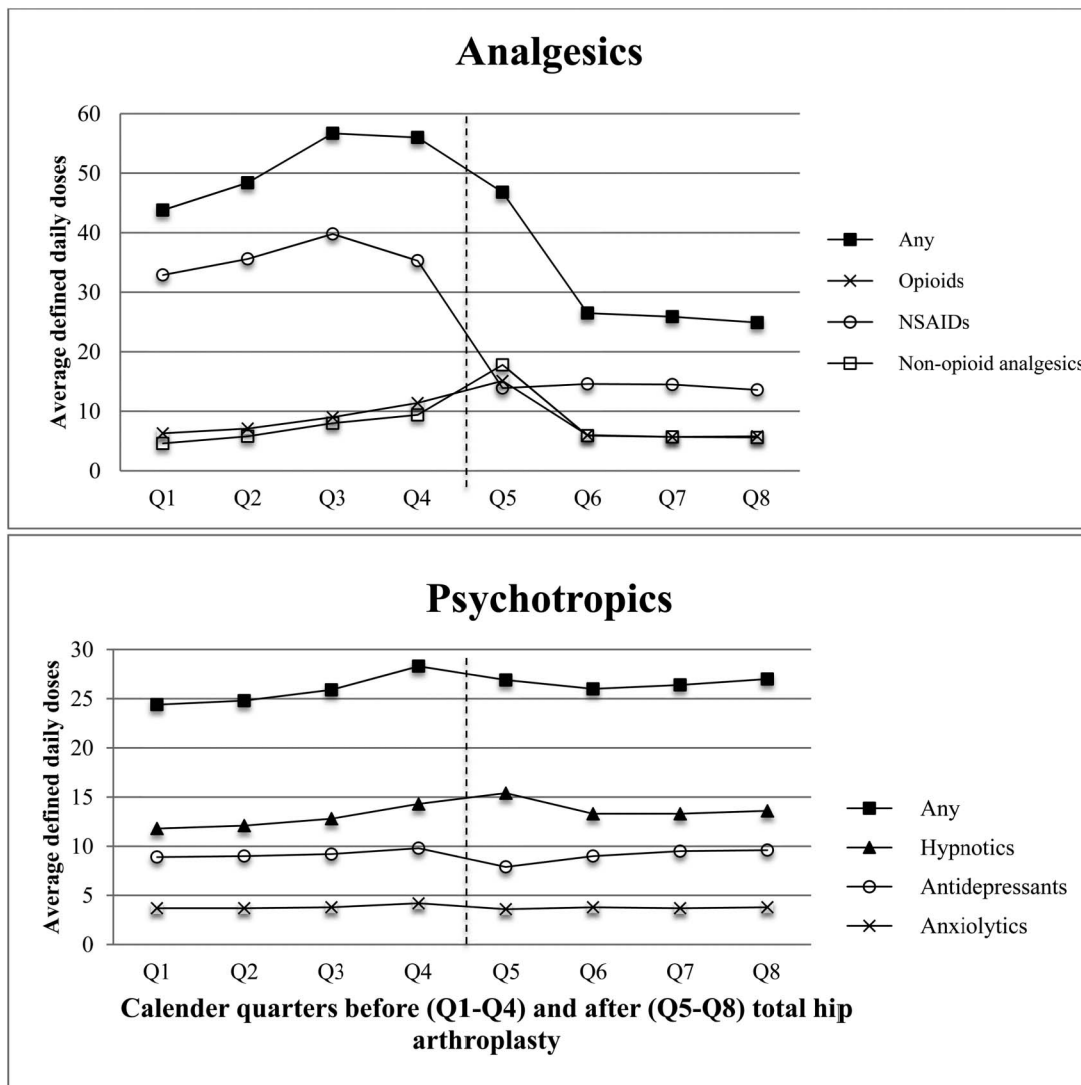


Figure 2. Prescription trajectories for drug volume DDDs. DDDs, defined daily doses; NSAIDs, nonsteroid anti-inflammatory drugs.

At odds with our expectations, user rates and drug volumes of antidepressants and drug volumes of anxiolytics decreased significantly from Q4 to Q5. This might reflect that anxiety and corresponding depression related to a forthcoming major surgical procedure declined rapidly after the surgery.¹⁴ Still it should be noted that an increase in use of these drugs was observed after Q5, which might suggest that the anxiolytic and antidepressant effect of THA is not long-lasting. We conclude that hypothesis 2 was supported regarding analgesics and hypnotics, although not for antidepressants and anxiolytics.

Comparing preoperative levels (Q4) with long-term postoperative levels (Q8), THA was associated with decreased use of analgesics, hypnotics, and anxiolytics, but not antidepressants. The effect of THA has been thoroughly studied, with consistent findings of reduced pain after surgery,^{33,39,52} and our results extend the effect to the use of analgesics. Nonsteroid anti-inflammatory drugs showed the most profound reduction, in accordance with 1 previous report.¹³ Nonsteroid anti-inflammatory drugs are found to be superior to nonopioid analgesics, such as paracetamol (acetaminophen), when used to alleviate pain caused by inflammation. However, NSAIDs are not recommended for older patients and for long-term use in general because of increased risks of gastrointestinal bleeding,

renal failure, and congestive heart failure.^{56,41} Opioids can be an appropriate option for patients with osteoarthritis not responding to acetaminophen therapy and who have a contraindication for use of NSAIDs.^{8,20,42} However, opioids also have potentially severe adverse side effects, such as cognitive impairment and falls, and risk of tolerance, dependence, and overdose.^{6,8,23} In light of this, this study extends the positive effect of THA to include reduced use of all subgroups of analgesics.

Nocturnal pain is a key indication for THA,⁴⁴ and improvements in sleep have been found after surgery.^{12,26,61} Accordingly, we expected user rates and drug volumes of hypnotics to be reduced after surgery, and to the best of our knowledge, this study is the first documentation of this outcome. Our findings support and extend decades of research establishing the bidirectional relationship between pain and sleep.⁴⁸ The reduction in hypnotics may indicate that many patients experience improved sleep after surgery, which may be an underrecognized benefit of THA that contributes to lower levels of pain and improved quality of life.^{18,24,54} It should be noted that although pharmacological treatment is effective for short-term sleep problems, research-based guidelines do not recommend long-term use of hypnotics because of risks of dependence and tolerance.¹ Despite this, hypnotics are frequently prescribed long-term, especially in the

Table 3

Changes in medication use measured in user rates (prevalence) and drug volume (DDDs) preoperatively (Q1 vs Q4), immediately after surgery (Q4 vs Q5) and from preoperative to follow-up (Q4 vs Q8) in a population undergoing total hip replacement (N = 39,688).

	Preoperative trends (Q1 vs Q4)		Immediate postoperative change (Q4 vs Q5)			Changes from preoperative to follow-up (Q4 vs Q8)			
	χ^2	<i>d</i>	χ^2	<i>d</i>	95% CI	χ^2	<i>d</i>	95% CI	
User rates									
Analgesics									
Any	1016.2*	0.2	7756.0*	0.7	8.5 to 10.0	6722.3*	0.6	30.4 to 31.9	
Opioids	2309.5*	0.4	10,881.5*	0.8	-4.0 to -3.5	3199.8*	0.4	5.3 to 5.8	
NSAIDs	27.5*	0.0	3103.1*	0.4	20.9 to 22.0	5396.7*	0.5	21.2 to 22.3	
Nonopioids	1580.7*	0.3	12,088.0*	0.9	-8.8 to -8.2	1250.4*	0.3	3.6 to 4.0	
Psychotropics									
Any	208.1*	0.1	889.8*	0.2	0.8 to 1.9	39.9*	0.0	0.7 to 1.8	
Hypnotics	228.9*	0.1	1464.6*	0.3	-1.4 to -0.8	24.2*	0.0	0.4 to 1.0	
Antidepressants	4.7	0.0	60.7*	0.1	1.5 to 2.2	3.5	0.0	-0.2 to 0.5	
Anxiolytics	61.7*	0.1	0.6	0.0	0.5 to 0.8	27.5*	0.0	0.3 to 0.6	
Drug volume									
Analgesics									
Any	-32.4*	0.2	-13.0 to -11.5	24.8*	0.1	8.5 to 10.0	85.3*	0.4	30.4 to 31.9
Opioids	-43.6*	0.2	-5.4 to -4.9	-28.0*	0.1	-4.0 to -3.5	41.9*	0.2	5.3 to 5.8
NSAIDs	-7.5*	0.0	-3.0 to -1.8	72.7*	0.4	20.9 to 22.0	74.4*	0.4	21.2 to 22.3
Nonopioids	-42.5*	0.2	-4.9 to -4.5	-61.2*	0.3	-8.8 to -8.2	32.0*	0.2	3.6 to 4.0
Psychotropics									
Any	15.3*	0.1	-4.4 to -3.4	5.0*	0.0	0.8 to 1.9	4.6*	0.0	0.7 to 1.8
Hypnotics	-16.0*	0.1	-2.8 to -2.2	-6.3*	0.0	-1.4 to -0.8	4.1*	0.0	0.4 to 1.0
Antidepressants	-4.8*	0.0	-1.2 to -0.5	10.2*	0.1	1.5 to 2.2	1.0	0.0	-0.2 to 0.5
Anxiolytics	-7.1*	0.0	-0.7 to -0.4	8.7*	0.0	0.5 to 0.8	5.0*	0.0	0.3 to 0.6

* Indicates $P < 0.001$ (Bonferroni-corrected).

CI, confidence interval for the difference; *d*, Cohen D for effect size; DDDs, defined daily doses; NSAIDs, nonsteroid anti-inflammatory drugs; *t*, *t* test for paired samples (degrees of freedom for all variables: 1.39687); χ^2 , McNemar chi-square test for related samples (continuity corrected).

elderly.⁴⁰ Sleep in chronic users of hypnotics has been found to be no better than in drug-free insomniacs,⁵⁸ further suggesting that the adverse risk associated with chronic hypnotic use outweighs the benefits in older patients.

Symptoms of depression and anxiety are prevalent among persons with chronic pain conditions such as osteoarthritis,^{9,7} hence, patients with chronic pain are often prescribed both analgesics and psychotropics.^{28,46} Total hip arthroplasty is shown to improve anxiety and depressive symptoms after surgery,²² however this study only found corresponding reductions in the use of anxiolytics. The fact that no long-term effect of THA was observed regarding antidepressants might suggest that pain and depression are dissociated in these patients. Another explanation for the lack of association between THA and antidepressant use is that factors not assessed in this study influence level of depression. Still, most previous studies do support a causal link between pain and depression.²⁹ One-third of the patients in our study continue to use some form of prescription analgesic after 1 year, which may indicate persistent pain, comorbid pain conditions, or comorbid joint pain.^{36,62} These patients have been found to report more depressive symptoms than those without.^{32,36} Both clinical studies and studies on prescription data are needed to clarify the relationship between pain, depression, and medication use. We conclude that hypothesis 3 was supported regarding analgesics, hypnotics, and anxiolytics, but not for antidepressants.

The connection between a complete population of patients undergoing THA and a national prescription database comprises a major and unique asset of this study ensuring high ecologic validity. Furthermore, the large sample of participants should be

considered a major strength of the study as it provided high statistical power to the analyses.

Still, our results should be considered in light of some limitations. First, redeemed drugs may not be used by the recipients or may be used for other indications. Inferences should therefore be made cautiously concerning pain, sleep, and mental symptoms. Second, information is limited to prescription drugs dispensed by retail pharmacies; hence, there is no information about purchases of over-the-counter products. Lower-dose, over-the-counter NSAIDs and non-opioid analgesics are to a nondetermined extent used to treat osteoarthritis in addition to prescription medications,²¹ and we may therefore have underestimated the real extent of pharmacotherapy in this study. Additionally, in studies like this one with a very large number of participants, statistical significance should be separated from clinical relevance. We specifically added effect size estimations to overcome this limitation. Another confounder is individual differences in terms of initiatives and attitudes of treating MDs regarding drug prescriptions.⁵⁷ Some MDs may motivate patients to get their pills on a routine basis even if the patient does not want them, whereas others may adhere to a much more restrictive prescription practice. Regardless, in light of the inappropriate use of medication at the group level, the reduction in medication use may be highly valuable at the individual level.

In conclusion, THA is found to be associated with a reduction in the use of analgesics, hypnotics, and anxiolytics and extends the positive effects of this surgery to include medication use. Furthermore, the increase in the use of medication preoperatively suggests increasing symptom load in the waiting period. Last, analgesics and hypnotics showed a marked increase in the

postoperative phase. This warrants special attention from prescribers because one might reasonably assume that adverse effects (such as falls) can increase during this phase.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Supplemental media

Video content associated with this article can be found online as Supplemental Digital Content at <http://links.lww.com/PAIN/A233>.

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References

- National Institutes of Health State of the Science Conference statement on manifestations and management of chronic insomnia in adults, June 13–15, 2005. *Sleep* 2005;28:1049–57.
- Ackerman IN, Bennell KL, Osborne RH. Decline in Health-Related Quality of Life reported by more than half of those waiting for joint replacement surgery: a prospective cohort study. *BMC Musculoskelet Disord* 2011;12:108.
- American Society of Anesthesiologists. ASA physical status classification system. Book *ASA Physical Status Classification System*, Vol. 2013. City, 2013.
- Ashton H. Guidelines for the rational use of benzodiazepines. When and what to use. *Drugs* 1994;48:25–40.
- Askildsen JE, Holmas TH, Kaarboe O. Monitoring prioritisation in the public health-care sector by use of medical guidelines. The case of Norway. *Health Econ* 2011;20:958–70.
- Avouac J, Gossec L, Dougados M. Efficacy and safety of opioids for osteoarthritis: a meta-analysis of randomized controlled trials. *Osteoarthritis Cartilage* 2007;15:957–65.
- Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity—A literature review. *Arch Intern Med* 2003;163:2433–45.
- Ballantyne JC, LaForge KS. Opioid dependence and addiction during opioid treatment of chronic pain. *PAIN* 2007;129:235–55.
- Benjamin S, Morris S, McBeth J, Macfarlane GJ, Silman AJ. The association between chronic widespread pain and mental disorder: a population-based study. *Arthritis Rheum* 2000;43:561–7.
- Berger A, Bozic K, Stacey B, Edelsberg J, Sadosky A, Oster G. Patterns of pharmacotherapy and health care utilization and costs prior to total hip or total knee replacement in patients with osteoarthritis. *Arthritis Rheum* 2011;63:2268–75.
- Blagestad T, Pallesen S, Lunde LH, Sivertsen B, Nordhus IH, Gronli J. Sleep in older chronic pain patients: a comparative polysomnographic study. *Clin J Pain* 2012;28:277–83.
- Bogoch ER, Olschewski E, Zangger P, Henke ML, Smythe HA. Increased tender point counts before and after total hip arthroplasty are associated with poorer outcomes but are not individually predictive. *J Arthroplasty* 2010;25:945–50.
- Bolland BJ, Culliford DJ, Maskell J, Latham JM, Dunlop DG, Arden NK. The effect of hip and knee arthroplasty on oral anti-inflammatory use and the relationship to body mass index: results from the UK general practice research database. *Osteoarthritis Cartilage* 2011;19:29–36.
- Caumo W, Schmidt AP, Schneider CN, Bergmann J, Iwamoto CW, Bandeira D, Ferreira MB. Risk factors for preoperative anxiety in adults. *Acta Anaesthesiol Scand* 2001;45:298–307.
- Chiu Y, Silman A, Macfarlane G, Ray D, Gupta A, Dickens C, Morriss R, McBeth J. Poor sleep and depression are independently associated with a reduced pain threshold. Results of a population based study. *PAIN* 2005;115:316–21.
- Cohen J. *Statistical power analysis for the behavioral sciences*. Hillsdale: Lawrence Erlbaum Associates, 1988.
- Creameans-Smith JK, Millington K, Sledjeski E, Greene K, Delahanty DL. Sleep disruptions mediate the relationship between early postoperative pain and later functioning following total knee replacement surgery. *J Behav Med* 2006;29:215–22.
- Davies KA, Macfarlane GJ, Nicholl BI, Dickens C, Morriss R, Ray D, McBeth J. Restorative sleep predicts the resolution of chronic widespread pain: results from the EPiFUND study. *Rheumatology (Oxford)* 2008;47:1809–13.
- Davis AM, Perruccio AV, Ibrahim S, Hogg-Johnson S, Wong R, Streiner DL, Beaton DE, Cote P, Gignac MA, Flannery J, Schemitsch E, Mahomed NN, Badley EM. The trajectory of recovery and the inter-relationships of symptoms, activity and participation in the first year following total hip and knee replacement. *Osteoarthritis Cartilage* 2011;19:1413–21.
- de Leon-Casasola OA. Opioids for chronic pain: new evidence, new strategies, safe prescribing. *Am J Med* 2013;126:S3–11.
- Driban JB, Boehret SA, Balasubramanian E, Cattano NM, Glutting J, Sittler MR. Medication and supplement use for managing joint symptoms among patients with knee and hip osteoarthritis: a cross-sectional study. *BMC Musculoskelet Disord* 2012;13.
- Duivenvoorden T, Vissers MM, Verhaar JA, Busschbach JJ, Gosens T, Bloem RM, Bierma-Zeinstra SM, Reijman M. Anxiety and depressive symptoms before and after total hip and knee arthroplasty: a prospective multicentre study. *Osteoarthritis Cartilage* 2013;21:1834–40.
- Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, Weisner CM, Silverberg MJ, Campbell CI, Psaty BM, Von Korff M. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med* 2010;152:85–92.
- Edwards RR, Almeida DM, Klick B, Haythornthwaite JA, Smith MT. Duration of sleep contributes to next-day pain report in the general population. *PAIN* 2008;137:202–7.
- Espehaug B, Furnes O, Havelin LI, Engesaeter LB, Vollset SE, Kindseth O. Registration completeness in the Norwegian Arthroplasty Register. *Acta Orthop* 2006;77:49–56.
- Fielden JM, Gander PH, Horne JG, Lewer BM, Green RM, Devane PA. An assessment of sleep disturbance in patients before and after total hip arthroplasty. *J Arthroplasty* 2003;18:371–6.
- Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. *J Pain* 2013;14:1539–52.
- Fishbain DA. Polypharmacy treatment approaches to the psychiatric and somatic comorbidities found in patients with chronic pain. *Am J Phys Med Rehabil* 2005;84:S56–63.
- Fishbain DA, Cole B, Lewis JE, Gao J. Does pain interfere with antidepressant depression treatment response and remission in patients with depression and pain? An evidence-based structured review. *Pain Med* 2014;15:1522–39.
- Furu K. Establishment of the nationwide Norwegian Prescription Database. *Nor J Epidemiol* 2008;18:129–36.
- Gandhi R, Davey JR, Mahomed NN. Predicting patient dissatisfaction following joint replacement surgery. *J Rheumatol* 2008;35:2415–18.
- Gureje O, Von Korff M, Kola L, Demyttenaere K, He Y, Posada-Villa J, Lepine JP, Angermeyer MC, Levinson D, de Girolamo G, Iwata N, Karam A, Guimaraes Borges GL, de Graaf R, Browne MO, Stein DJ, Haro JM, Bromet EJ, Kessler RC, Alonso J. The relation between multiple pains and mental disorders: results from the World Mental Health Surveys. *PAIN* 2008;135:82–91.
- Hamel MB, Toth M, Legedza A, Rosen MP. Joint replacement surgery in elderly patients with severe osteoarthritis of the hip or knee: decision making, postoperative recovery, and clinical outcomes. *Arch Intern Med* 2008;168:1430–40.
- He Y, Zhang M, Lin EH, Bruffaerts R, Posada-Villa J, Angermeyer MC, Levinson D, de Girolamo G, Uda H, Mneimneh Z, Benjet C, de Graaf R, Scott KM, Gureje O, Seedat S, Haro JM, Bromet EJ, Alonso J, von Korff M, Kessler R. Mental disorders among persons with arthritis: results from the World Mental Health Surveys. *Psychol Med* 2008;38:1639–50.
- Health NLP. Norwegian prescription database. Book *Norwegian prescription database*. City, 2013.
- Hoogeboom TJ, den Broeder AA, Swierstra BA, de Bie RA, van den Ende CH. Joint-pain comorbidity, health status, and medication use in hip and knee osteoarthritis: a cross-sectional study. *Arthritis Care Res (Hoboken)* 2012;64:54–8.
- Hoogeboom TJ, van den Ende CH, van der Sluis G, Elings J, Dronkers JJ, Aiken AB, van Meeteren NL. The impact of waiting for total joint replacement on pain and functional status: a systematic review. *Osteoarthritis Cartilage* 2009;17:1420–7.
- Hossain M, Parfitt DJ, Beard DJ, Darrach C, Nolan J, Murray DW, Andrew G. Does pre-operative psychological distress affect patient satisfaction after primary total hip arthroplasty? *BMC Musculoskelet Disord* 2011;12:122.
- Jones CA, Voaklander DC, Johnston DW, Suarez-Almazor ME. The effect of age on pain, function, and quality of life after total hip and knee arthroplasty. *Arch Intern Med* 2001;161:454–60.
- Kjosavik SR, Ruths S, Hunskaar S. Use of addictive anxiolytics and hypnotics in a national cohort of incident users in Norway. *Eur J Clin Pharmacol* 2012;68:311–19.

- [41] Lanas A, Ferrandez A. Inappropriate prevention of NSAID-induced gastrointestinal events among long-term users in the elderly. *Drug Aging* 2007;24:121–31.
- [42] McCracken L, Hoskins J, Eccelston C. Concerns about medication and medication use in chronic pain. *J Pain* 2006;10:726–34.
- [43] McHugh GA, Campbell M, Luker KA. GP referral of patients with osteoarthritis for consideration of total joint replacement: a longitudinal study. *Br J Gen Pract* 2011;61:e459–468.
- [44] McHugh GA, Luker KA, Campbell M, Kay PR, Silman AJ. A longitudinal study exploring pain control, treatment and service provision for individuals with end-stage lower limb osteoarthritis. *Rheumatology (Oxford)* 2007;46:631–7.
- [45] McHugh GA, Luker KA, Campbell M, Kay PR, Silman AJ. Pain, physical functioning and quality of life of individuals awaiting total joint replacement: a longitudinal study. *J Eval Clin Pract* 2008;14:19–26.
- [46] Mellbye A, Svendsen K, Borchgrevink PC, Skurtveit S, Fredheim OMS. Concomitant medication among persistent opioid users with chronic non-malignant pain. *Acta Anaesthesiologica Scand* 2012;56:1267–76.
- [47] Methodology WCCfDS. ATC classification index with DDDs, Vol. 2014. Oslo: Norwegian Institute of Public Health, 2012.
- [48] Moldofsky H. Sleep and pain. *Sleep Med Rev* 2001;5:385–96.
- [49] Monstad K, Engesaeter LB, Espehaug B. Waiting time and socioeconomic status—an individual-level analysis. *Health Econ* 2014;23:446–61.
- [50] Morris SB, DeShon RP. Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. *Psychol Methods* 2002;7:105–25.
- [51] Murphy SL, Lyden AK, Phillips K, Clauw DJ, Williams DA. Subgroups of older adults with osteoarthritis based upon differing comorbid symptom presentations and potential underlying pain mechanisms. *Arthritis Res Ther* 2011;13:R135.
- [52] Nilsson AK, Isaksson F. Patient relevant outcome 7 years after total hip replacement for OA—a prospective study. *BMC Musculoskelet Disord* 2010;11:47.
- [53] Nilsson AK, Lohmander LS. Age and waiting time as predictors of outcome after total hip replacement for osteoarthritis. *Rheumatology (Oxford)* 2002;41:1261–7.
- [54] Onen SH, Alloui A, Gross A, Eschallier A, Dubray C. The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. *J Sleep Res* 2001;10:35–42.
- [55] Onen SH, Onen F, Courpron P, Dubray C. How pain and analgesics disturb sleep. *Clin J Pain* 2005;21:422–31.
- [56] Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem. *Arch Intern Med* 2000;160:777–84.
- [57] Sivertsen B, Nordhus IH, Bjorvatn B, Pallesen S. Sleep problems in general practice: a national survey of assessment and treatment routines of general practitioners in Norway. *J Sleep Res* 2010;19:36–41.
- [58] Sivertsen B, Omvik S, Pallesen S, Nordhus IH, Bjorvatn B. Sleep and sleep disorders in chronic users of zopiclone and drug-free insomniacs. *J Clin Sleep Med* 2009;5:349–54.
- [59] Smith MT, Quartana PJ, Okonkwo RM, Nasir A. Mechanisms by which sleep disturbance contributes to osteoarthritis pain: a conceptual model. *Curr Pain Headache Rep* 2009;13:447–54.
- [60] Vitiello MV, McCurry SM, Shortreed SM, Baker LD, Rybarczyk BD, Keefe FJ, Von Korff M. Short-term improvement in insomnia symptoms predicts long-term improvements in sleep, pain, and fatigue in older adults with comorbid osteoarthritis and insomnia. *PAIN* 2014;155:1547–54.
- [61] Wiklund I, Romanus B. A comparison of quality of life before and after arthroplasty in patients who had arthrosis of the hip joint. *J Bone Joint Surg Am* 1991;73:765–9.
- [62] Wylde V, Hewlett S, Learmonth ID, Dieppe P. Persistent pain after joint replacement: prevalence, sensory qualities, and postoperative determinants. *PAIN* 2011;152:566–72.