On the relationship between spinal pain and temporomandibular disorders

Birgitta Wiesinger

Department of Odontology

Faculty of Medicine, Umeå University
Umeå 2010

ISSN: 0345-7532
ISBN: 978-91-7264-920-0
Cover photo: Birgitta Wiesinger, Layout: Vivan Rönnqvist
Printed by: Print & Media
Umeå, Sweden 2010

"Sometimes, if you stand on the bottom rail of a bridge
and lean over to watch the river slipping slowly away beneath you,
you will suddenly know everything
there is to be known."

A.A. Milne (Winnie the Pooh)

ABSTRACT

Both spinal pain and temporomandibular disorders (TMD) commonly occur in the general population. Previous studies demonstrate neurophysiologic and biomechanical couplings between the trigeminal and cervical regions. This investigation tested the null hypothesis of no relationship between spinal pain (neck, shoulder and/or low back) and TMD, by using questionnaires and clinical examinations of the jaw function.

In an age- and sex-matched case-control study, the specific aim was to compare the prevalence of signs and symptoms of TMD among cases with long-term spinal pain and controls without spinal pain. The results showed that subjects with spinal pain had signs and symptoms of TMD significantly more often than did controls. The associations remained after excluding all participants with jaw pain. Furthermore, the comorbidity pattern was similar, regardless of location of spinal pain.

In a cross-sectional study, the specific aim was to test whether there is a reciprocal cross-sectional dose-response-like relationship between spinal pain and TMD. Two different designs were used, one with frequency/severity of spinal pain as independent variable, and the other, with frequency/severity of TMD symptoms as independent variable. The analysis showed increasing odds for presence of TMD symptoms with increasing frequency/severity of spinal pain, and increasing odds for presence of spinal pain with increasing frequency/severity of TMD symptoms.

In a case-control study within a 2-year prospective cohort, the specific aim was to test whether there is a reciprocal temporal relationship between signs and symptoms in trigeminally, and symptoms in spinally, innervated areas. Incidence of symptoms in these areas was analyzed in relation to presence of spinal pain, headaches, and signs and symptoms of TMD at baseline. The main findings were that presence of signs of TMD at baseline increased the onset of spinal pain and symptoms in the trigeminal area, and that spinal pain increased the onset of symptoms in the trigeminal area. An augmentation effect between the significant baseline variables was observed for the incidence of headaches and jaw pain.

In conclusion, the investigation demonstrated a cross-sectional and temporal relationship between spinal pain and TMD; thus, the null hypothesis was rejected. The results indicate common pathophysiological mechanisms in the development of spinal pain and TMD. The comorbidity and reciprocal influence that were found call for an integrated and multidimensional approach in the management of individuals with long-term spinal pain and TMD.

Key words: back pain, comorbidity, cross-sectional, dose-response, headaches, matched case-control, musculoskeletal disorders, prospective cohort, spinal pain, temporomandibular disorders (TMD)

CONTENTS

DEFINITIONS AND ABBREVIATIONS

Comorbidity: presence of more than one disease or health condition in an individual at a given time.

Spinal pain: pain arising from the spinal column or its adjoining anatomical parts (International Association for the Study of Pain) (Merskey and Bogduk, 1994). In the present investigation spinal pain is defined as pain in the neck, shoulders, and/or low back.

Temporomandibular disorders (TMD) is a collective term for a group of musculoskeletal conditions characterized by pain and dysfunction in the jaw muscles, temporomandibular joint (TMJ) or both (Okeson, 1996; Okeson, 2008a).

ADL	activities of daily living
Ai	anamnestic dysfunction index (Helkimo, 1974)
CI	confidence interval
Di	clinical dysfunction index (Helkimo, 1974)
NRS	11-point numerical rating scale
OR	odds ratio
RDC/TMD	research diagnostic criteria for TMD (Dworkin and LeResche, 1992)
Sign	finding at clinical examination (Okeson, 2008d)
Symptom	reported complaint (Okeson, 2008d)
TMD	temporomandibular disorders
TMJ	temporomandibular joint

ORIGINAL PAPERS

This thesis is based on the following original papers, which will be referred to in the text by their Roman numerals:

I Wiesinger B, Malker H, Englund E, Wänman A. Back pain in relation to musculoskeletal disorders in the jaw-face: A matched case-control study. Pain 2007;131:311-319.

II Wiesinger B, Malker H, Englund E, Wänman A. Does a dose-response relation exist between spinal pain and temporomandibular disorders? BMC Musculoskelet Disord 2009;10:28.

III Marklund S, Wiesinger B, Wänman A. Reciprocal influence on the incidence of symptoms in trigeminally and spinally innervated areas. Eur J Pain 2009, doi:10.1016/j.ejpain.2009.06.004.

INTRODUCTION

Pain in the spinal region and temporomandibular disorders (TMD) are both musculoskeletal conditions commonly reported in the general population. They are each associated with impaired quality of life, sick leave, and increased use of health care (Kuttila et al., 1997; White et al., 2001; Picavet and Schouten, 2003; Breivik et al., 2006; Rubin, 2007), thus comprising serious public health problems. Spinal pain and its consequences constitute an extensive economic burden on those affected and on society (Hansson and Hansson, 2005; Dagenais et al., 2008; Wenig et al., 2009). Although there are numerous studies (De Kanter et al., 1993; SBU, 2000a; SBU, 2000b; Rubin, 2007; Clark, 2008) regarding prevalence, pathophysiology, and treatment of spinal pain and TMD, these disorders are still not well understood. This deficiency is reflected in the fact that a majority of patients with spinal pain do not have an identifiable diagnosis (Manek and MacGregor, 2005; Jull et al., 2008) and that treatments suggested for spinal pain and TMD, respectively, are often not evidence based (SBU, 2000b; Okeson, 2008b). Epidemiological research is important to explore the distribution and comorbidity of diseases and relate them to certain characteristics of the individuals or the environment. The comorbidity patterns between spinal pain and TMD have not been systematically evaluated; hence, there is a lack of knowledge in this field.

Prevalence and incidence of spinal pain and TMD

A large number of epidemiological studies on pain symptoms have been published; most of them are cross-sectional, and longitudinal studies are scarce. The comparison of prevalence and incidence estimates between different investigations is not straightforward, due to discrepancies in definitions and methods (De Kanter et al., 1993; Andersson, 1997; Carlsson, 1999; Hestbaek et al., 2003; Hogg-Johnson et al., 2008).

Spinal pain

Pain in the spinal area has mostly been studied with a single- or regional-area approach, that is, only low back or neck pain, whereas, neck pain and shoulder pain sometimes are merged. Specific results for thoracic spine pain are seldom reported. In the general population the estimated lifetime prevalence is 70-85% for low back pain (Andersson, 1997; Rubin, 2007) and 50-70% for neck pain (Côté et al., 1998; Fejer et al., 2006). In a recent Danish study among adult twins, 55% reported spinal pain in at least one of three spinal areas (neck, thoracic, or low back) in the previous year (Leboeuf-Yde et al., 2009). Low back pain for at least 30 days during a one-year period was reported by 12%, compared to 10% and 4%, respectively, for neck and thoracic pain (Leboeuf-Yde et al., 2009). A population-based study from the United States showed that the 3-month prevalence of low back and/or neck pain was 31% (Strine and Hootman, 2007), whereas, the corresponding 1-month prevalence in the United Kingdom was 29% (Webb et al., 2003). The estimated prevalence of long-term spinal pain among adults

was 15-30% in population-based surveys in Europe and the United States. (Brattberg et al., 1989; Andersson et al., 1993; Elliott et al., 1999; Webb et al., 2003; Von Korff et al., 2005).

Women are more likely than men to report musculoskeletal pain, including spinal pain (Elliott et al., 1999; Picavet and Schouten, 2003; Leboeuf-Yde et al., 2009). The prevalence of spinal pain increases with age, peaks in the middle years, and then declines (Andersson, 1999; Rubin, 2007; Hogg-Johnson et al., 2008). The annual incidence of neck pain in the adult general populations in Canada and the United Kindom was 15% and 18%, respectively (Croft et al., 2001; Côté et al., 2004). The corresponding rate for low back pain was 19% (Cassidy et al., 2005). A review concluded that 10-15% of the adult population has an annual incidence of low back pain of at least moderate intensity and duration (Andersson, 1999).

Temporomandibular disorders (TMD)

A meta-analysis of 51 TMD studies showed a prevalence of 30% (6-93%) for reported symptoms, and 44% (0-93%) for clinical signs (De Kanter et al., 1993). In a summary of 17 epidemiological studies 41% of the participants reported at least one symptom associated with TMD, and 56% showed at least one clinical sign (Okeson, 2008a). In a population-based study in Germany, 10% reported temporomandibular joint (TMJ) symptoms, and 50% had one or more clinical signs of TMD (Gesch et al., 2004). Pain in the temporomandibular region occurs in about 10% of the adult population (LeResche, 1997). Women have, in general, more prevalent and more severe signs and symptoms of TMD than men (LeResche, 1997; Carlsson, 1999). Moreover, women are less likely to recover from their symptoms (Wänman, 1996) and more likely to seek treatment (Carlsson, 1999). The prevalence of signs and symptoms of TMD increases with age, peaks in the middle years, and declines in later life (Carlsson, 1999; Okeson, 2008a), showing a similar pattern to spinal pain. A 10-year follow-up study reported a 6% incidence for TMD symptoms in both sexes (Wänman, 1996). A 4-year longitudinal study found an incidence of 6% for TMJ pain and 13% for TMJ sounds (Kamisaka et al., 2000).

Comorbidity between spinal pain and TMD

In the 1950s Schwartz noted the presence of tenderness in neck and shoulder muscles among patients with “temporomandibular joint pain-dysfunction syndrome” (Schwartz, 1956). More recent studies have demonstrated that patients with TMD report tenderness to palpation in the neck-shoulder area (Clark et al., 1987; De Laat et al., 1998; Stiesch-Scholz et al., 2003) and pain in different parts of the spinal region (neck, shoulders, thoracic back, and low back) (Hagberg, 1991; Visscher et al., 2001) more often than controls. Cervical segmental limitations are also more common in this patient group (De Laat et al., 1998; Stiesch-Scholz et al., 2003). Moreover, population-based studies have found a coexistence of signs and symptoms in the jaw region and the neck-shoulder area

(Wänman, 1995; Ciancaglini et al., 1999), and that prevalence of neck pain increased with increasing severity of TMD symptoms (Ciancaglini et al., 1999).

Clinical reports regarding presence of signs and symptoms of TMD among subjects with spinal pain are scarce. When patients with cervical disorders have been compared to previously reported population surveys, an Italian study found an increased prevalence of TMD in the patient sample (Carossa et al., 1993), whereas a Dutch study found a similar frequency of signs and symptoms of TMD in the patient and the population groups (de Wijer et al., 1996). The occurrence of TMD among individuals with low back or thoracic pain has not been investigated.

In a Norwegian study the frequency of headache had a dose-response-like association with the prevalence of musculoskeletal pain in the chest-abdomen, extremities, and spinal area (Hagen et al., 2002). A large cross-sectional study showed that adults with spinal pain reported significantly more headaches and jaw-face pain than subjects without spinal pain (Strine and Hootman, 2007). Taken together, several studies indicate comorbidity between spinal pain and TMD, but knowledge of the cross-sectional and temporal relationships is still lacking.

Pain–a predictor of new pain

In research on predictors for musculoskeletal pain, work-related factors have been one major area. The temporal relationship between different pain conditions has not been clarified, due to the scarcity of longitudinal studies in this field. In a study of the first onset rates of back pain, severe headache, chest pain, abdominal pain, and TMD pain, it was found that presence of one pain condition is associated with an increased risk of developing a new pain condition (Von Korff et al., 1993). It has also been demonstrated that pain in the neck and other musculoskeletal sites was a risk factor for subsequent low back pain (Papageorgiou et al., 1996). Moreover, low back pain (Croft et al., 2001) and headaches (Leclerc et al., 1999) in adults, and other musculoskeletal pain in schoolchildren (Ståhl et al., 2008) are associated with subsequent neck pain. Previous chronic pain, in the back or elsewhere, was the strongest predictor of “new” chronic back pain (Smith et al., 2004). The persistence of chronic widespread pain was predicted by the number of painful regions at baseline (Bergman et al., 2002). The widespread pattern of musculoskeletal pain and dysfunction has been interpreted as a tendency for symptoms to cluster in some individuals (Croft, 1996).

A prospective study based on patients with nonpainful TMD showed a dose-response relationship between the number of other pain sites at baseline (head, back, chest, stomach) and the risk of onset of dysfunctional TMD pain among women (John et al., 2003). The number of painful body sites at baseline was found to be associated with onset (LeResche et al., 2007) and persistence (Rammelsberg et al., 2003) of TMD pain.

Pathophysiological basis for comorbidity

The pathophysiological basis for the comorbidity of TMD and neck pain, previously reported in some populations, is not clear. Pain disorders generally have a multifactorial etiology reflected in current pain models. Diatchenko and colleagues (Diatchenko et al., 2006) suggest that genetic variability and exposure to environmental events may influence pain amplification and psychological profile, which in turn interactively contribute to the vulnerability of developing diverse pain conditions. In a biopsychosocial model, the interaction between biological, psychological, and social factors is emphasized to understand the etiology, assessment, and treatment of chronic pain conditions (Gatchel et al., 2007). The "Brussels model" for chronic work-related myalgia includes several possible mechanisms interacting on the neuromuscular system at different levels, resulting in various vicious circles that contribute to development of chronic pain (Johansson et al., 2003). In a proposed integrated pain adaptation model (Murray and Peck, 2007), motor behavior following pain represents the individual's integrated motor response to sensory, motivational, and cognitive components of pain, with the aim to minimize pain and maintain homeostasis. It has been proposed that "idiopathic pain disorders" are medically explicable in terms of central sensitization in combination with genetic predisposition, deficit in hypothalamic-pituitary-adrenal axis, psychological distress, sympathetic over-activity, and environmental stimuli (Yunus, 2008).

Central sensitization and deficits in endogenous pain modulating processes have been presented as possible explanations for amplification and spread of musculoskeletal pain (Coderre et al., 1993; Julien et al., 2005; DeSantana and Sluka, 2008). Experimentally induced pain in the masseter muscle produced a widespread mechanical allodynia in the hind paws in rats (Ambalavanar et al., 2006), implying that central pain modulating mechanisms are strongly activated by craniofacial nociception. Similarly, studies on patients with TMD have shown decreased distant pain thresholds (Maixner et al., 1998; Fernández-de-las-Peñas et al., 2009). Furthermore, experimental human studies have shown that spatial (increased pain perception caused by nociceptive input from large areas) and temporal (increased pain perception caused by repetitive noxious stimuli) summation influence the perceived muscle pain intensity and distribution (Graven-Nielsen et al., 1997), suggesting an increased central hyperexcitability. Vierck proposes that focal pain conditions like TMD, spinal pain, and headaches, in association with generalized hypersensitivity, contribute to development of pain at new locations (Vierck, 2006), thus supporting the view that generalized pain (i.e., fibromyalgia) represents one end of a continuum (Croft et al., 1996; Carli et al., 2002).

Intersegmental reflex connections between nociceptors in the temporomandibular region and the neck fusimotor system have been demonstrated in animal studies, indicating that the fusimotor system might be involved in the mechanisms for spread of muscle stiffness and pain from the trigeminal area to the neck (Hellström et al., 2000; Hellström et al., 2002). Experimental masseter muscle pain has been related to changes

in neuromuscular activity in the neck, for example, increased electromyographic (EMG) activity (Svensson et al., 2004) and facilitation of jaw stretch reflex recorded in human neck muscle (Wang et al., 2004). Inversely, experimental pain in the splenius muscle did not influence the EMG activity in masseter muscle (Svensson et al., 2004), but facilitated the jaw stretch effect (Wang et al., 2004).

Rationale for the investigation

The above-mentioned reciprocal interactions between the trigeminal and spinal sensory-motor systems indicate that a pathophysiological basis for comorbidity between jaw and neck pain may exist. Previous clinical and epidemiological studies indicate that neck pain and TMD are related, but a thorough assessment regarding the comorbidity patterns between spinal pain and TMD has not been conducted.

AIMS

The general aim of this thesis was to investigate the cross-sectional and temporal relationships between spinal pain and TMD, and thereby, contribute to the understanding of these disorders.

The specific aims were to study:

- the prevalence of signs and symptoms of TMD in subjects with long-term spinal pain, compared to matched subjects without spinal pain (Paper I)
- whether occurrence of TMD symptoms and headaches increase with increasing frequency/severity of spinal pain (Paper II)
- whether occurrence of spinal pain increases with increasing frequency/severity of TMD symptoms (Paper II)
- if the incidence of TMD symptoms and headaches is influenced by presence of spinal pain at baseline (Paper III)
- if the onset of spinal pain is influenced by headaches and TMD symptoms and signs at baseline (Paper III)

METHODS

Three observational studies with different designs were conducted. The participants were patients with long-term spinal pain referred to a vocational rehabilitation center (Papers I, II), employees at four companies (Papers I, II), students at two universities (Papers I, III), and members of a sports center (Paper I). An overview of study designs, research questions, modes of data collection, and population characteristics is presented in Table 1.

Table 1. Overview of designs, research questions, and study populations.

	Paper I	**Paper II**	**Paper III**
Study design	Age- and sex-matched case-control	Cross-sectional with 2 study designs	Case-control within a 2-year prospective cohort
Research question	Does a difference exist in prevalence of signs/symptoms of TMD between patients with spinal pain and subjects without spinal pain?	Does a reciprocal dose-response-like relationship exist between frequency/severity of spinal pain and TMD?	Do symptoms in trigeminally and spinally innervated areas reciprocally influence the onset of new symptoms?
Data collection	Questionnaire, clinical examination of jaw function	Questionnaire	Questionnaire, clinical examination of jaw function
Population characteristics	Cases with spinal pain, controls without spinal pain	Subjects with varying severity of spinal pain Subpopulation with varying severity of TMD symptoms	Dental students
Number (m/w)	96 cases (49/47) 192 controls (98/94)	616 (323/293)* Subpopulation 266 (159/107)	280 (98/182)
Mean age (range)	40 (22-62) years	40 (20-65) years	23 (18-43) years

*270 subjects from Paper I
m = men, w = women

The studies were approved by the Ethics Committee at Umeå University, and all subjects gave their informed consent to participate.

Study populations and study designs

Inclusion of participants (Papers I and II)

Consecutive patients (n = 112), referred to the Institute for Vocational Rehabilitation (Rygginstitutet), were invited to participate (see flowchart, Fig. 1). Rygginstitutet works with vocational rehabilitation of subjects with spinal pain. Inclusion criterion was reported spinal pain at a frequency of at least once a week. Ten people did not accept the invitation and two people did not meet the inclusion criterion. The original patient group thus consisted of 100 subjects.

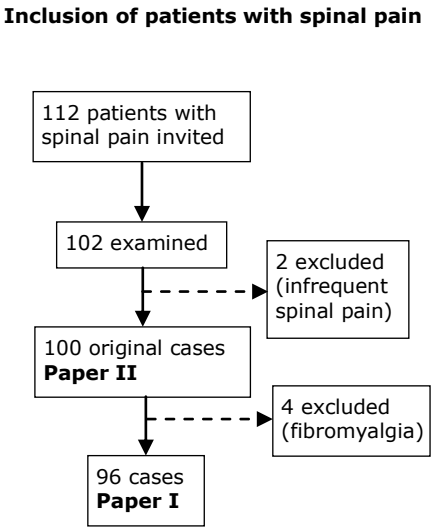

Figure 1. Flowchart showing how patients with spinal pain were included as participants in Papers I and II.

In total about 2,000 non-patients (i.e., subjects not referred to Rygginstitutet) were invited to participate (see flowchart, Fig. 2). The majority were employees at four companies, and the others were students or members of a sports center. Invitation of the participants was based on the requirements for age- and sex-matched subjects without spinal pain (Paper I), subjects for internal validity test (Paper I), and subjects with varying severity of spinal pain or no spinal pain (Paper II). At two of the companies and among the students and members of the sport-center, the primary interest was to identify subjects without spinal pain. At the two remaining companies, the employees participated regardless of presence or absence of spinal pain. In total, 884 subjects volunteered and answered either a screening form or a questionnaire. The screening procedure was implemented at some of the companies, where the volunteers answered

the following questions: “Have you had back or neck trouble during the previous year?” “Have you been on sick leave due to back or neck trouble during the previous year?” Students, members of a sports center, and employees at some companies did not go through the screening procedure, but answered the questionnaire directly. In total, 341 non-patients underwent the full study protocol (questionnaire and examination), and 250 subjects completed only the questionnaire. To keep the methods section comprehensible and within the scope of an article, the description of the screening procedure was simplified in Paper I. This did not have any consequence for the results or the interpretation.

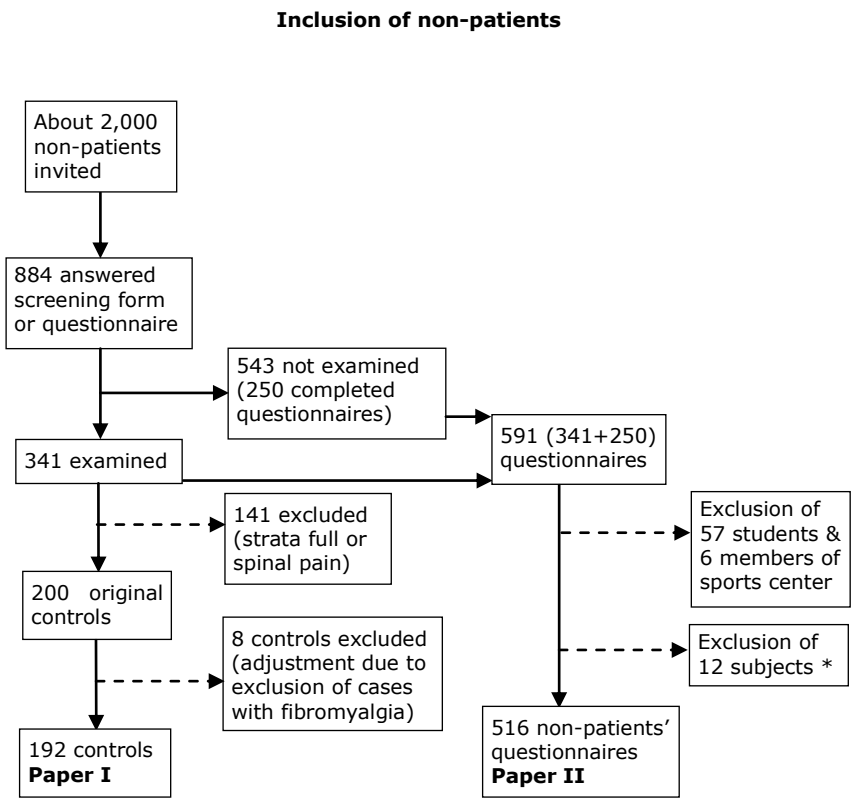

Figure 2. Flowchart showing how non-patients were included as participants in Papers I and II.
*Exclusion of 9 subjects due to current sick leave, and 3 subjects due to reported frequent spinal pain with duration less than one month.

Cases and controls (Paper I)

The study population comprised cases with spinal pain and matched controls without spinal pain. Four people were excluded from the original patient group due to reported fibromyalgia. The case group consequently consisted of 96 subjects with ongoing disabling spinal pain (Fig. 1). Subjects in the non-patient population who reported "never spinal pain" or "not now, but previously spinal pain" in the questionnaire and who fitted the matching criteria were included as controls. The matching was done by sex and age group in 5-year intervals, resulting in 16 strata. Two controls were included for each case, for a total of 200 original controls. Eight controls were randomly excluded to adjust for matching, after withdrawal of cases with fibromyalgia. The controls thus comprised 192 subjects without spinal pain (Fig. 2).

TMD in relation to location of spinal pain

To analyze whether the location of frequent spinal pain influenced the prevalence of signs and symptoms of TMD, the cases were grouped according to frequent pain in the neck, shoulders, low back, and/or combinations of these. Each spinal pain group was compared to the control group.

Subsample – participants without jaw pain

Since jaw pain may be considered a confounder to association between spinal pain and jaw dysfunction, separate analyses regarding signs and symptoms of jaw dysfunction were conducted on participants without frequent jaw pain. Seventy-eight cases and 190 controls were included in this test.

Internal validity test

To control for bias in the examination, a blind test was performed among employees at two of the companies. This procedure required extensive cooperation with the personnel managers, who randomly drew 52 screening cards from among the employees who reported neck/back trouble. The sampled subjects were examined, together with 76 people without neck/back trouble. The examiner was blinded to the presence or absence of neck/back trouble for these 128 subjects. In the questionnaire, 28 participants reported spinal pain once or twice a month, and these respondents were excluded from the internal validity test. Of the remaining participants, 63 reported no spinal pain and 37 reported frequent spinal pain. These 100 employees were used for the internal validity test. Subjects with frequent spinal pain were compared to those without spinal pain.

Participants (Paper II)

The total study population comprised 616 subjects with varying frequency/severity of spinal pain or no spinal pain. In total 591 questionnaires were eligible from the non-patient population (Fig. 2). The students (n = 57) and all members of the sports center (n = 6) were excluded, as well as nine subjects on sick leave, and three subjects reporting frequent spinal pain with a duration of less than one month. The resulting 516

subjects, together with 100 subjects from the original case group (Fig. 1), constituted the total study population. A subset of the population (n = 266) was sampled, regardless of reported presence or absence of spinal pain. Two different study designs were used, one with frequency/severity of spinal pain as independent variable, and the other with frequency/severity of TMD symptoms as independent variable.

Spinal pain as independent variable

The hypothesis tested was that occurrence of frequent TMD symptoms and headaches would increase with increasing frequency/severity of spinal pain. The 616 subjects were categorized into four groups (SP-0, SP-1, SP-2, or SP-3), according to the frequency/severity of reported spinal pain and related disability. SP-0 comprised subjects without spinal pain and was therefore designated as the control group. SP-1 included subjects with infrequent spinal pain, that is, spinal pain once or twice a month, at most. Subjects with frequent (weekly to daily) spinal pain that had been present for at least 1 month were included in SP-2. Subjects in the original patient group with long-term, disabling spinal pain constituted SP-3. These subjects had been on sick leave owing to spinal pain prior to rehabilitation. The prevalence of frequent symptoms of TMD and headaches were compared between the groups. Table 2 shows the characteristics of the study population, with spinal pain as independent variable.

Table 2. Characteristics of the study population, with spinal pain as independent variable. The table shows the number of subjects, sex, mean age, and age range in the study groups. Mean values (assessed on 11-point numerical rating scales) of pain intensity in the spinal region, and impact of pain on activities of daily living (ADL) are shown. Mean values are calculated among those who reported the specific pain location.

	SP-0	**SP-1**	**SP-2**	**SP-3**
Number, m/w	127/128	54/53	93/61	49/51
Mean age, m/w (years)	40.4/42.9	41.3/37.6	38.9/38.7	41.4/39.4
Age range, m/w (years)	20-64/23-62	25-65/26-60	20-59/23-59	25-56/24-61
Intensity of neck pain		3.4	5.2	6.5
Intensity of shoulder pain		3.2	5.2	6.6
Intensity of low back pain		3.7	5.3	6.6
Impact of neck/shoulder pain on ADL		2.1	3.7	6.0
Impact of low back pain on ADL		3.0	4.3	6.7

m = men, w = women
SP-0 = subjects without spinal pain; SP-1 = subjects with infrequent spinal pain; SP-2 = non-patients with frequent spinal pain; and SP-3 = patients with frequent spinal pain.

Symptoms of TMD as independent variable

The hypothesis tested was that occurrence of frequent spinal pain increases with increasing frequency/severity of TMD symptoms. For this purpose a subset of the population (n = 266) was used; these participants were sampled regardless of reported presence or absence of spinal pain. The subjects were classified into four groups (TMD-0, TMD-1, TMD-2 and TMD-3), according to frequency/severity of TMD symptoms. TMD-0 consisted of people without TMD symptoms and was considered the control group. TMD-1 comprised subjects with infrequently occurring (once or twice a month, at most) TMD symptoms. The inclusion criteria for TMD-2 were frequent (weekly to daily) and mild symptoms of TMD (TMJ sounds, tiredness/stiffness). Subjects with frequent and severe TMD symptoms (pain, impaired jaw opening, TMJ locking) were included in TMD-3. The prevalence of frequent spinal pain was compared between the groups. Table 3 shows the characteristics of the study population, with symptoms of TMD as independent variable.

Table 3. Characteristics of the study population, with symptoms of TMD as independent variable. The table shows the number of subjects, sex, mean age, and age range in the study groups. Mean values (assessed using the 11-point numerical rating scale) of the impact of TMD symptoms on activities of daily living (ADL) are shown.

	TMD-0	TMD-1	TMD-2	TMD-3
Number, m/w	89/48	23/21	35/28	12/10
Mean age, m/w (years)	38.5/36.0	37.1/32.3	35.3/35.4	36.7/34.4
Age range, m/w (years)	20-65/23-58	26-58/26-43	20-59/23-56	29-58/31-52
Impact of TMD symptoms on ADL		0.7	1.1	3.0

m = men, w = women
TMD-0 = subjects without symptoms of TMD; TMD-1 = subjects with infrequent symptoms of TMD; TMD-2 = subjects with frequent, mild symptoms of TMD; and TMD-3 = subjects with frequent, severe symptoms of TMD.

Inclusion of participants (Paper III)

The study population comprised a cohort of 280 dental students followed for two years. In total 372 students at the beginning of their education were invited to participate in the study, of whom 371 accepted. During the observation period 91 subjects dropped out, due to interruption of their education. There were proportionally more men among the dropouts than in the study population. No significant differences were found between the dropouts and the study population regarding prevalence of baseline variables.

Allocation of participants

The subjects answered a questionnaire and their jaw function was evaluated in a clinical examination at baseline, and at 1 year and 2 years following baseline. At 2 years following baseline each subject was classified into five different case-control groups with regard to onset of nonpain TMD symptoms, jaw pain, headaches, spinal pain, and TMD pain (RDC/TMD). Subjects with an onset of a specific condition were considered cases in that case-control group, and subjects without the specific condition during the total study period were considered controls. Subjects with a specific condition at baseline were excluded from the corresponding case-control group. Each participant could belong to five different case-control groups. The number of cases, controls, and excluded participants for each group is presented in Table 4. The incidence of nonpain TMD symptoms, jaw pain, headaches, spinal pain, and TMD pain was studied with respect to presence or absence of the following baseline factors: symptoms of TMD, signs of TMD, headaches, and spinal pain, as well as age and sex. If more than one baseline factor appeared as significant for a specific incidence, a possible augmentation effect on the incidence rate between these factors was tested.

Table 4. Distribution of cases, controls, and excluded subjects for each incidence variable. Cases are subjects without a specific symptom at baseline, who did report onset of the symptom during a following 2-year period. Controls are those without the mentioned symptom. Excluded are those who presented the indicated symptom at baseline. The total study population comprised 280 dental students.

Incidence variable	Cases	Controls	Excluded
	N (m/w)	N (m/w)	N (m/w)
Nonpain TMD symptoms	48 (11/37)	131 (60/71)	101* (27/74)
Jaw pain	49 (10/39)	213 (83/130)	18 (5/13)
Headaches	53 (11/42)	198 (81/117)	29 (6/23)
Spinal pain	63 (17/46)	124 (59/65)	93 (22/71)
TMD pain	33 (3/30)	229 (92/137)	18 (3/15)

*70 subjects were excluded due to any TMD symptoms at baseline, 31 were excluded due to jaw pain at 1 year and/or 2 years following baseline.
N = number, m = men, w = women

Data collection

Questionnaires

Papers I and II

The questionnaire is presented in Appendix 1. The following symptoms were assessed:

- symptoms of TMD: tiredness/stiffness; pain during rest, jaw opening, or chewing; clicking or crepitation during jaw opening or chewing; locking of jaws; impaired jaw opening
- tinnitus
- headaches
- pain in the neck
- pain in the shoulders
- pain in the low back

Presence of each symptom was marked according to:

- frequency: never; not now, but previously; once or twice a month; once or twice a week; several times a week; daily
- duration: less than 1 month, 1 month to 1 year, 1 year to 5 years, more than 5 years
- intensity: 11-point numerical rating scale (NRS) (Jensen and Karoly, 2001)

Impact on activities of daily living (ADL) was marked (NRS) for pooled symptoms in the jaw, pooled neck and shoulder pain, and for headaches, tinnitus, and low back pain, respectively.

Presence of clenching, grinding, and tongue pressing as well as lip, nail, cheek or tongue biting was marked for each alternative separately, with yes/no/don't know.

Health care utilization (dentist, health-care center, physiotherapist, pain clinic, psychologist, chiropractor/naprapath, other) due to jaw symptoms, headaches, and spinal pain was marked, for each alternative separately, with yes/no.

Paper III

The baseline questionnaire (Appendix 2) concerned symptoms during the previous month. The follow-up questionnaires (Appendix 3) concerned symptoms during the previous year. Symptoms were marked according to frequency (never, occasionally, once a week, several times a week, daily). The following symptoms were examined:

- symptoms of TMD: tiredness in the jaw muscles, stiffness in the jaw muscles, pain in the jaw muscles, clicking in left/right TMJ, locking of left/right TMJ, pain in/around left/right TMJ during chewing or jaw opening, impaired jaw opening
- headaches in right/left temple and/or forehead

- pain in the neck
- pain in the shoulders
- pain in the back

Clinical examinations (Papers I and III)

The jaw function was evaluated during a standardized clinical examination. The examination was performed by one dentist (Paper I) or by two TMD/orofacial pain specialists (Paper III). The protocol was extensively described in Paper I. The examination included registration of:

- TMJ signs: sounds during jaw opening/closing movements, pain/tenderness to palpation, pain on movement or joint loading for 30 sec, locking
- jaw muscle signs: pain/tenderness to palpation (16 sites), pain on muscle loading for 30 sec
- mandibular range of motion
- mandibular movement pattern
- muscle pain/tenderness to palpation of sternocleidomastoid muscles, trapezius muscles, and neck muscles in the region of linea nuchae

Variable definitions

Symptoms of TMD comprised one or more of the following reported symptoms: jaw stiffness or tiredness, jaw pain (pain in muscles or TMJ), TMJ sounds, TMJ locking, and impaired jaw opening. These symptoms were summarized in Papers I and II by Helkimo's anamnestic dysfunction index (Ai) (Helkimo, 1974). This classification system grades the severity of reported symptoms into Ai0, absence of symptoms; AiI, mild symptoms (tiredness/stiffness, TMJ sounds); and AiII, severe symptoms (jaw pain, TMJ locking, impaired jaw opening). In the classification of Ai, symptoms occurring at least once a week (frequent symptoms) were categorized into AiI or AiII, whereas infrequent symptoms (once or twice a month, at most), were classified into Ai0. Frequency of TMD symptoms was used as classification variable in Paper II (symptoms of TMD as independent variable).

Clinically registered signs of TMD were summarized in Papers I and III by Helkimo's clinical dysfunction index (Di) (Helkimo, 1974). The severity of signs (Di) is graded into Di0, no signs; DiI, mild signs; DiII, moderate signs; and DiIII, severe signs. The following signs are included in the protocol: reduced mandibular movement capacity, TMJ dysfunction (mandibular movement pattern, TMJ sounds, and TMJ locking), palpation tenderness/pain over muscles and TMJ joint, and pain during mandibular movement. Each of the signs is given a score, established in the protocol, and the sums of these scores are used to form the clinical dysfunction index.

In Paper I, the following clinical signs were used in the analyses:

- TMJ disk displacement denotes clinical signs of a symptomatic TMJ disk displacement with reduction.
- Clicking or crepitation denotes the presence of these TMJ sounds during jaw opening and closing.
- TMJ dysfunction denotes TMJ sounds and/or deviation >2mm on jaw opening.
- TMJ pain denotes the presence of TMJ pain/tenderness to palpation and/or pain elicited during a load test and/or pain during jaw opening and closing.
- Clench symptoms denotes elicited pain during a 30-second jaw clenching task.
- Jaw muscle tenderness denotes presence of pain/tenderness to palpation at one or more of 16 jaw muscle sites.
- Neck and jaw muscle tenderness denotes presence of pain/tenderness to palpation at one or more sites over 16 jaw muscle sites and one or more sites over 6 neck muscle sites.

The term nonpain TMD symptoms was used in Paper III. It included reported frequent jaw stiffness/tiredness, TMJ sounds, TMJ locking, and/or impaired jaw opening.

The research diagnostic criteria (RDC/TMD) (Dworkin and LeResche, 1992) Axis I was used for classification of myofascial pain (Papers I and III) and arthralgia (Paper III). In the analysis, the subcategories myofascial pain and arthralgia were merged (Paper III), and the variable was named TMD pain.

Headaches and spinal pain were dichotomized into those occurring at least once a week (frequent symptoms) and those occurring less often.

Statistics

Statistical analyses were performed using Epi Info version 3.3 and SPSS versions 14.0 and 15.0. Frequency distribution, mean, standard deviation, and range were used for descriptive statistics.

Paper I

Comparison between cases and matched controls was conducted on the 16 strata with Mantel-Haenszel estimates of matched odds ratio (OR) and 95% confidence interval (CI). Statistical significance was assessed by the Corrected Mantel-Haenszel χ^2 test (Selvin, 1996a). The Benjamini-Hochberg correction was used to control for multiple tests (Benjamini and Hochberg, 1995). In the sub-analyses, that is, TMD among subjects without jaw pain, TMD in relation to location of spinal pain, and internal validity test, the Mantel-Haenszel estimates of unmatched OR and 95% CI was calculated. Differences between mean scores were measured with Independent Samples t-Test (jaw movement capacity) and Mann-Whitney *U* test (intensities of spinal pain

and impact of pain on ADL) (Altman, 1991a). Statistical tests were considered statistically significant if the *P*-value was <0.05.

Paper II

Case groups SP-1, SP-2, and SP-3 were each compared with the control group SP-0, and TMD-1, TMD-2, and TMD-3 were compared with TMD-0. OR and 95% CI were calculated with binary logistic regression analysis (Altman, 1991b), controlling for age and sex. Results were considered statistically significant if the 95% CI did not include 1. To test the trends for dose-response associations Cochran-Armitage Test for Trend (Agresti, 2002) with syntax for SPSS was used (Garcia-Granero, M): http://www.listserv.uga.edu/cgi-bin/wa?A2=ind0605&L=spssx-l&P=R24952&D=0.

Paper III

The analyses were conducted with binary logistic regression in a backward stepwise likelihood ratio procedure. The baseline factors (signs of TMD, symptoms of TMD, headaches, and spinal pain) constituted the independent variables, which were removed from the model with 5% significance level. Age and sex were not removed from the model, thus controlling for these variables at all stages. Cases and controls in the respective groups were used as dependent variables. For the incidence of TMD pain, only spinal pain was included as independent factor in the model, since signs and symptoms of TMD, as well as headache, are included in this diagnosis. For the incidence of nonpain TMD symptoms and incidence of jaw pain, symptoms of TMD were not included in the regression model. The condition for which each incidence was calculated was excluded as an independent factor in the model. Augmentation of significant baseline factors was calculated with the Mantel-Haenszel estimates of OR and 95% CI. Results were considered statistically significant if the 95% CI did not include 1. Differences between mean ages were measured with Mann-Whitney *U* test, which was considered statistically significant if the *P*-value <0.05.

RESULTS

TMD in patients with long-term spinal pain (Paper I)

Symptoms of TMD

Statistically significant associations between long-term spinal pain and frequent symptoms of TMD were found. The overall prevalence of TMD symptoms (Helkimo's AiI–II) was 47% among cases and 12% among controls ($P < 0.0001$). Among the cases, 55% reported headaches and 19% reported jaw pain, in comparison to 8% and 1% among the controls ($P < 0.0001$ for each comparison). Jaw tiredness/stiffness, TMJ sounds, and impaired jaw opening were significantly more common among cases than among controls. OR and 95% CI for symptoms of TMD, headaches, and tinnitus are presented in Figure 3.

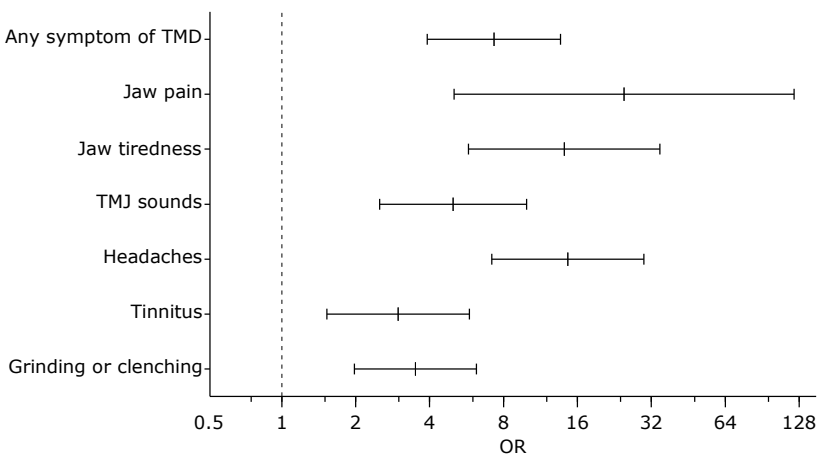

Figure 3. OR and 95% CI for reported frequent symptoms of TMD, headaches and tinnitus, and reported grinding or clenching among subjects with long-term spinal pain compared to matched controls.

Signs of TMD

One or more clinical signs of TMD (DiI–III), in accordance with Helkimo, were registered significantly more often among cases (91%) than among controls (52%) ($P < 0.0001$). Moderate to severe signs (DiII–III) were present in 49% of cases and 17% of controls ($P < 0.0001$). TMJ dysfunction occurred among 34% of cases and among 19% of controls ($P < 0.01$). TMJ clicking and crepitation, palpation tenderness at both

jaw muscle and neck muscle sites, and symptoms elicited by tooth clenching were also significantly more common among cases than among controls. The maximal jaw opening and protrusive capacities were significantly lower among patients with spinal pain ($P < 0.0001$). The criteria for myofascial pain, according to RDC/TMD were met by 34% of patients with spinal pain, in comparison to 1% among the controls ($P < 0.0001$). OR and 95% CI for clinically registered signs are presented in Figure 4.

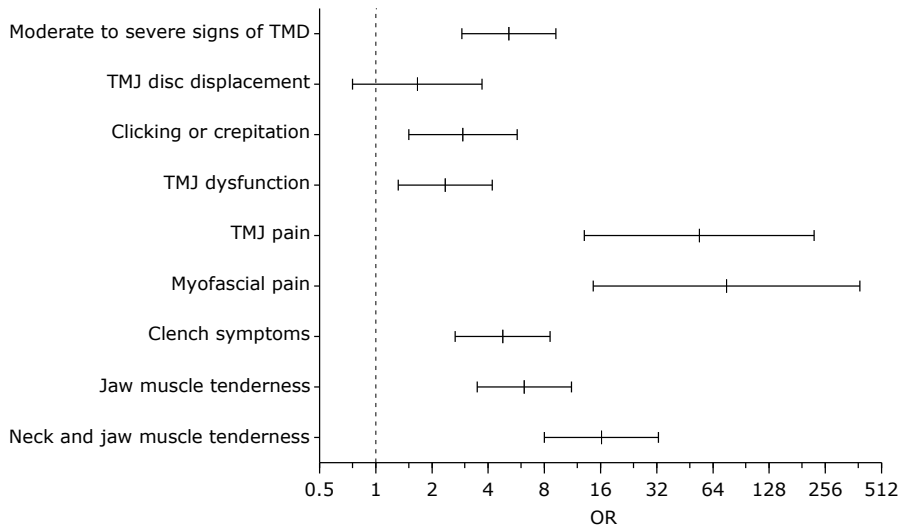

Figure 4. OR and 95% CI for clinically registered signs of TMD among subjects with spinal pain compared to matched controls.

Oral parafunctions

Patients with spinal pain were significantly more often aware of tooth grinding, tooth clenching, tongue pressing, and lip/cheek/tongue biting than were controls. OR and 95% CI for pooled grinding and clenching are presented in Figure 3.

Controlling for multiple tests

The results were also significant after controlling for multiple tests.

TMD in relation to location of spinal pain

Different locations of spinal pain showed similar OR patterns for signs (DiII–III) and symptoms (AiI–II) of TMD. OR and 95% CI for pooled signs and symptoms of TMD among subjects with different locations of spinal pain compared to the controls are shown in Figure 5.

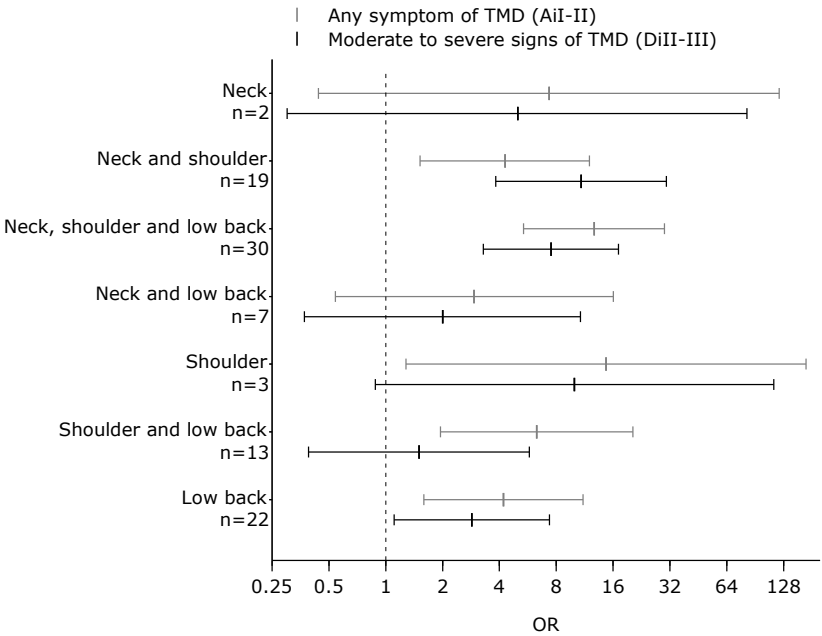

Figure 5. OR and 95% CI for symptoms and signs of TMD with regard to spinal pain location.

Subsample–participants without jaw pain

Comparison of cases and controls without frequent jaw pain showed a comorbidity pattern between spinal pain and TMD similar to that of the total study population, but with generally lower OR. Cases with spinal pain, but without jaw pain, reported TMJ sounds ($P < 0.0001$), impaired jaw opening ($P < 0.05$), and tiredness in the jaws ($P < 0.0001$) significantly more often than their controls. These cases had also lower maximal jaw opening capacity ($P < 0.05$) and lower ability to protrude the mandible ($P < 0.0001$) than their controls. Furthermore, TMJ sounds ($P < 0.05$), pain/tenderness to palpation of the jaw muscles ($P < 0.0001$), and moderate to severe signs (DiII-III) of jaw dysfunction ($P < 0.0001$) were recorded significantly more often among these cases than among their controls.

Internal validity test

Employees with frequent spinal pain (n = 37) had a higher prevalence of signs and symptoms of TMD compared to employees without spinal pain (n = 63). The difference was significant for symptoms, and non-significant for moderate to severe signs, of TMD. The ORs were generally lower than in the true case-control analysis. Compared to the true cases in this study (n = 96), the employees with spinal pain had a

significantly lower degree of neck and low back pain intensity, and spinal pain had a significantly lower impact on their activities of daily living.

Reciprocal dose-response-like relationship between spinal pain and TMD (Paper II)

Spinal pain as independent variable

The prevalence of jaw tiredness/stiffness, jaw pain, impaired jaw opening, and headaches, as well as the overall prevalence of any TMD symptoms and severe TMD symptoms increased with increasing frequency/severity of spinal pain (Fig. 6). The ORs increased in a similar pattern (Fig. 7). The test for trends showed significant ($P < 0.001$) dose-response-like relationships between spinal pain and all TMD variables, except TMJ locking, as well as between spinal pain and headaches.

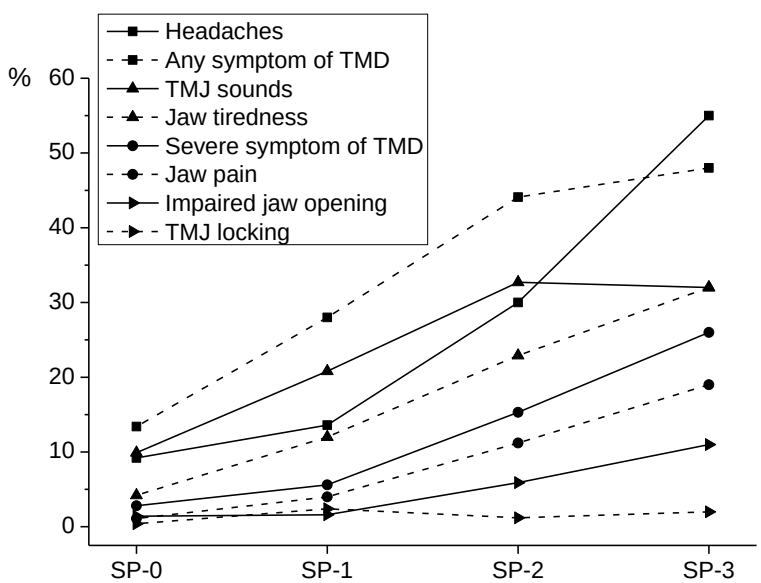

Figure 6. Prevalence of frequent symptoms of TMD and headaches among subjects with varying frequency/severity of spinal pain. SP-0 = subjects without spinal pain, SP-1 = subjects with infrequent spinal pain, SP-2 = non-patients with frequent spinal pain, SP-3 = subjects with frequent, disabling spinal pain.

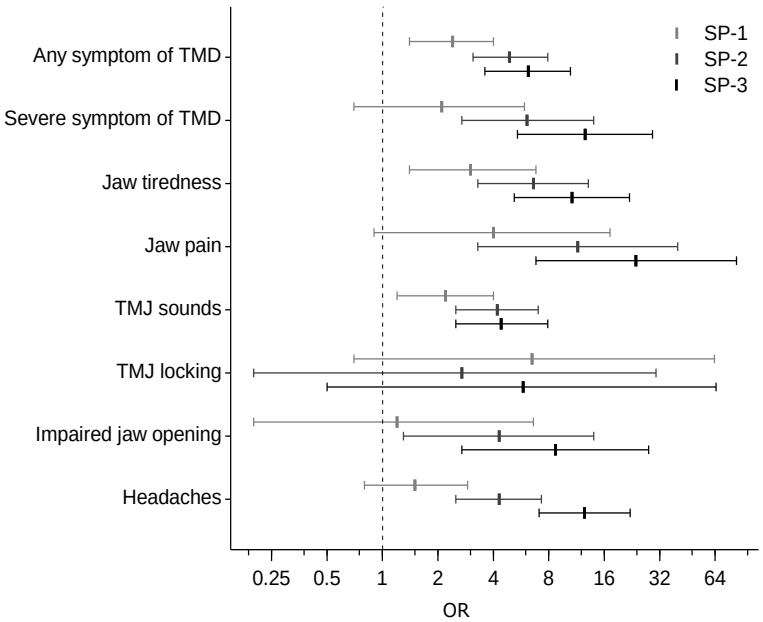

Figure 7. OR and 95% CI for presence of frequent symptoms of TMD and headaches among subjects with varying frequency/severity of spinal pain compared to controls (SP-0). SP-1 = subjects with infrequent spinal pain, SP-2 = non-patients with frequent spinal pain, SP-3 = patients with frequent spinal pain attending a rehabilitation program.

Symptoms of TMD as independent variable

The prevalence of frequent spinal pain increased with increasing frequency/severity of symptoms of TMD, from 30% in TMD-0 to 68% in TMD-3 (Fig. 8). The OR for frequent spinal pain increased from 2.8 (95% CI: 1.4-5.7) among subjects with infrequent TMD symptoms to 3.3 (95% CI: 1.8-6.2) among those with frequent, mild symptoms, and 5.1 (95% CI: 1.9-13.4) among those with frequent, severe TMD symptoms, compared with the controls. The test for trends demonstrated a significant ($P < 0.001$) dose-response-like relationship between symptoms of TMD and spinal pain.

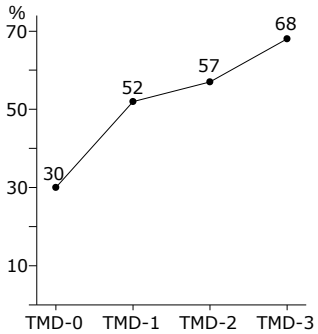

Figure 8. Prevalence of frequent spinal pain among subjects with increasing frequency/ severity of TMD symptoms.
TMD-1 = infrequent symptoms of TMD
TMD-2 = frequent, mild symptoms of TMD
TMD-3 = frequent, severe symptoms of TMD

Reciprocal influence between spinally and trigeminally innervated areas (Paper III)

The 2-year incidence of frequent nonpain TMD symptoms, jaw pain, headaches, spinal pain, and TMD pain rated between 13% and 34% (Table 5). Cases with incidence of nonpain TMD symptoms and cases with incidence of spinal pain significantly more often presented with signs of TMD at baseline compared to controls. Incidence cases of TMD pain reported spinal pain at baseline significantly more often than the controls, and were mostly women. Incidence cases of jaw pain and headaches had signs of TMD and reported spinal pain at baseline significantly more often than controls. Table 5 shows the 2-year incidence and significant baseline factors with OR and 95% CI for each incidence variable.

Table 5. Baseline factors of statistical significance for the 2-year incidence of respective symptoms as well as 2-year incidence, are shown. Independent variables were spinal pain, headaches, symptoms of TMD, and signs of TMD. For the incidence of TMD pain, only spinal pain was used in the model. For the incidence of nonpain TMD symptoms and jaw pain, symptoms of TMD were not included in the regression model.

Incidence Variable	2-year incidence (%)	Baseline factors of significance	OR (95% CI)
Nonpain TMD symptoms	27	Signs of TMD	6.3 (3.0-13.2)
Jaw pain	19	Signs of TMD Spinal pain	2.4 (1.2-4.7) 2.4 (1.2-4.6)
Headaches	21	Signs of TMD Spinal pain	2.2 (1.1-4.2) 2.0 (1.03-3.9)
Spinal pain	34	Signs of TMD	2.6 (1.4-5.0)
TMD pain	13	Female sex Spinal pain	5.6 (1.6-19.7) 2.9 (1.3-6.2)

Augmentation effect between significant baseline variables

The odds of developing headaches or jaw pain was amplified among subjects with signs of TMD or spinal pain at baseline, compared to subjects without these baseline variables. Further increased odds were found when both signs of TMD and spinal pain were present at baseline (Fig. 9A–B). The odds of meeting the criteria for incidence of TMD pain were highest among women with spinal pain at baseline (Fig. 9C).

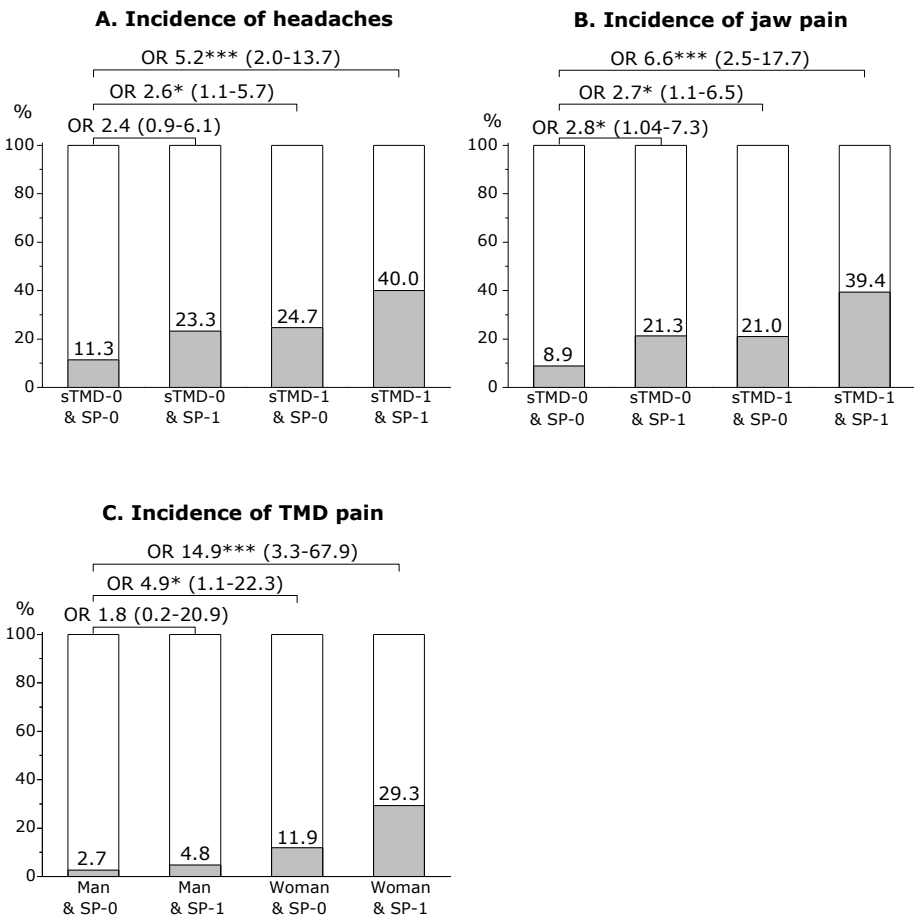

Figure 9. Distribution of prevalence, OR, and 95% CI among subjects at risk for onset of (**A**) frequent headaches (n = 251), (**B**) frequent jaw pain (n = 262) and (**C**) TMD pain (n = 262). Occurrence of the significant baseline variables in different combinations was compared in relation to the incidence, and ORs were calculated. Filled columns indicate the proportion of cases; unfilled columns indicate the proportion of controls. SP-0 = absence of spinal pain at baseline; SP-1 = presence of spinal pain at baseline; sTMD-0 = absence of signs of TMD at baseline; sTMD-1 = presence of signs of TMD at baseline. Statistically significant differences between conditions are denoted in the figure (*P < 0.05; ***P < 0.001).

DISCUSSION

Main findings

This thesis provides new knowledge on the cross-sectional and temporal relationship between spinal pain and TMD. The overall results demonstrate a close relationship between spinal pain and TMD, and additionally, underline the associations of headaches to both spinal pain and TMD. First, it was shown that patients with long-term spinal pain had significantly more pain and dysfunction in the jaw-face area compared to matched controls (Paper I). Second, in a cross-sectional study design a reciprocal dose-response-like relationship between frequency/severity of spinal pain and TMD symptoms was found (Paper II). Finally, in a prospective study, spinal pain and TMD reciprocally influenced the incidence of each other (Paper III). In relation to the neuroanatomic and biomechanical couplings between the jaw-face and cervical regions, the demonstrated comorbidity and the mutual interaction between disorders in these areas seem reasonable.

Results in relation to previous studies

Concurrent symptoms

The associations in the matched case-control study followed the same pattern regardless of location of spinal pain. Previous studies have shown that patients with TMD have more pain and dysfunction in the spinal area, compared to controls without TMD (Hagberg, 1991; De Laat et al., 1998; Visscher et al., 2001). Opposite to this, cases with facial pain reported more pain areas outside the face, with the exception of shoulders and lower back (Sipila et al., 2005). Concurrent pain in other body areas has also been reported, for example, low back pain has been associated with neck pain, upper back pain, and headaches (Mäkela et al., 1991; Côté et al., 2000; Webb et al., 2003; Hestbaek et al., 2004; Hagen et al., 2006; Kääriä et al., 2009), and headache co-occurred with pain in the jaw (Ciancaglini and Radaelli, 2001). Nevertheless, up till now, presence of long-term spinal pain has not been associated with both pain and dysfunction in the jaw-face area. For the first time it was demonstrated that subjects with long-term spinal pain localized to the lower back have significantly more signs and symptoms of TMD compared to controls (Paper I).

Reciprocal relationship

The finding that the associations between spinal pain and TMD became stronger as the severity of either condition increased suggests a reciprocal coupling between the trigeminal and spinal areas. Similar results were obtained in a population-based study, where increasing odds of neck pain were found with increasing severity of TMD symptoms (Ciancaglini et al., 1999). In a sample of patients with neuromuscular disorders a correlation between severity of TMD and perceived intensity of bodily pain

has been reported (Fischer et al., 2009b). The present results demonstrated the strength of this association, in that, not only long-term, frequent spinal pain was associated with an increased risk of TMD, but also infrequent spinal pain was related to a higher prevalence of TMD symptoms. Inversely, subjects with infrequent TMD symptoms had a significantly higher prevalence of frequent spinal pain, compared to subjects without TMD symptoms. The suggestion of a reciprocal relationship between spinally and trigeminally innervated areas in the cross-sectional population study was further strengthened in the prospective study. Clinically registered mild to severe signs of TMD at baseline increased the onset of spinal pain, headaches, jaw pain, and nonpain TMD symptoms. Equally, spinal pain at baseline increased the onset of jaw pain, headaches, and TMD pain. This finding of a mutual influence between symptoms in the spinal and the jaw-face areas expands previous results showing that headache, back, chest, or stomach pain was not differentially associated with the risk of onset of dysfunctional TMD pain, but that the cumulative effect of the different pain conditions increased the risk for developing dysfunctional TMD pain, as shown among women (John et al., 2003). Onset and duration is difficult to measure since symptoms often fluctuate and recur (Ghaffari et al., 2006; Marklund, 2009). Accordingly, incidence of symptoms (Paper III) should not be interpreted as first onset.

Alanen and Kirveskari (Alanen and Kirveskari, 1984) have suggested that TMJ dysfunction may be a predisposing factor for symptoms in the upper spine, but to our knowledge, the present investigation is the first to show that signs of jaw dysfunction increase the risk for onset of pain in the spinal area.

Possible explanatory components in relation to the results

Sensory amplification

Several mechanisms may be involved in the observed patterns between spinal pain and TMD. The pathophysiological mechanisms underlying the two conditions are poorly understood, but the close relationship between these disorders indicates a common pathophysiology. One possible explanation is based on the *convergence theory*. The trigeminal (V) brainstem complex, and particularly, subnucleus caudalis, is strongly involved in sensory transmission from the jaw-head region, receiving converging inputs from deep and superficial trigeminal, facial, and upper cervical nerves, as shown in several experimental animal studies (Kerr, 1962; Sessle et al., 1986). According to most reports in mammals, the V brainstem complex extends caudally to the upper spinal cord (Sessle, 2000; Shankland, 2000), whereas, other studies have found that fibers may be conveyed throughout the entire length of the spinal cord (Matsushita et al., 1981; Ruggiero et al., 1981). Extensive convergent input from cutaneous and deep craniofacial and cervical tissues has been found also in the upper cervical dorsal horn (Chudler et al., 1991; Hu et al., 2005; Mørch et al., 2007). Hence, subnucleus caudalis and the upper cervical dorsal horn are functionally integrated in processing sensory

information from craniofacial and spinal afferent inputs (Piovesan et al., 2003; Hu et al., 2005; Mørch et al., 2007).

The convergence patterns of afferent inputs are considered to be the physiological basis for referred pain (Arendt-Nielsen and Svensson, 2001), as well as a possible explanation for the poorly localized nature of muscle pain (Sessle, 2000; Mense et al., 2001). In fact, experimental (Svensson et al., 2005; Schmidt-Hansen et al., 2006) and clinical (Fricton et al., 1985; Simons et al., 1999) studies have shown a referral of musculoskeletal pain in the neck-shoulder area to the jaw-head area.

Central sensitization is another mechanism extensively involved in pain referral and concerns the capacity of dorsal horn and brainstem neurons to change their function, chemical profile, or structure (i.e., neural plasticity) (Woolf and Salter, 2000), resulting in an increased excitability. This is manifested in disinhibition and opening up of formerly ineffective synaptic connections, and increased efficacy of the convergent afferent inputs (Sessle, 1999; Mense et al., 2001). Central sensitization has been associated with jaw-face pain (Svensson et al., 2001; Sarlani and Greenspan, 2003; Fernández-de-las-Peñas et al., 2009), headaches (Fernández-de-las-Peñas et al., 2007; Schmidt-Hansen et al., 2007), shoulder pain (Leffler et al., 2002), and low back pain (Giesecke et al., 2004; O'Neill et al., 2007). Central sensitization may thus, in part, account for the observed findings in the present investigation.

The indication of an amplification effect found between signs of TMD and spinal pain (Paper III) imply that afferent inputs from diverse regions might contribute to an increased risk for onset of jaw pain and headaches, which may be understood as a consequence of spatial summation (Graven-Nielsen et al., 1997; Staud et al., 2007). Temporal and spatial summation may also be involved in the found reciprocal dose-response-like pattern (Paper II), which may be interpreted in terms of sensitization mechanisms.

The reason for the finding that signs of TMD increased the risk for incidence of spinal pain and headaches is unclear (Paper III). It could be speculated that palpation tenderness (one of the main variables of signs of TMD) over jaw muscles is a sign for generalized lowered pain thresholds, which could be a risk indicator for development of pain at other sites.

Pain and motor dysfunction

The concepts of muscle pain and related dysfunction have been a topic of much research (Johansson and Sojka, 1991; Stohler, 1999; Graven-Nielsen et al., 2003). It is well known that experimental and clinical jaw muscle pain modulates jaw motor behavior (Stohler, 1999; Svensson and Graven-Nielsen, 2001; Lobbezoo et al., 2006b). In the present investigation subjects with long-term spinal pain, but without jaw pain, showed sensory-motor disturbances of the jaw (e.g., reported impaired jaw opening, registered reduced maximal jaw movement capacity) more often than controls (Paper I). The emerging question is whether remote pain can modulate jaw motor function.

Normal maximal jaw movements involve simultaneous activation of jaw and neck muscles, such that jaw opening is paralleled by craniocervical extension and jaw closing coincides with craniocervical flexion (Eriksson et al., 2000). A high degree of temporal coordination between concomitant mandibular and head-neck movements was found during single (Zafar et al., 2000), as well as rhythmic (Eriksson et al., 2000), jaw opening-closing tasks. Patients with whiplash-associated disorders have reduced speed and amplitude and impaired temporal coordination of jaw-head movements, presumably related to pain (Häggman-Henrikson et al., 2002).

It is known that afferent neurons converging in the V brainstem complex project, via cranial nerve motor nuclei in the brainstem, to trigeminal motoneurons innervating the jaw muscles (Sessle, 2000). This convergence of various afferent inputs may contribute to the regulation of trigeminal motor function (Romaniello et al., 2000), implying that remote pain might have modulatory effects on oral motor control. Experimental human studies in this topic have shown diverging results. Induced splenius muscle pain did not yield an increase in EMG activity in the masseter muscle at different head positions (Svensson et al., 2004), nor did noxious stimulation of the tibialis muscle influence the reflex response of jaw closing muscles (Wang et al., 1999). However, induced trapezius and splenius myalgia resulted in reduced jaw opening (Komiyama et al., 2005) and facilitation of the jaw stretch reflex (Wang et al., 2004), respectively. Thus, it could be speculated that spinal pain induced the disturbed jaw motor function found among patients with spinal pain, but without jaw pain. Inversely, experimental jaw muscle pain increased the EMG activity (Svensson et al., 2004) and facilitated the stretch reflex in neck muscles (Wang et al., 2004). In line with this, higher EMG resting activities of sternocleidomastoid and trapezius muscles were found in patients with myogenous TMD, compared with control subjects (Pallegama et al., 2004).

Injection of bradykinin in the TMJ or masseter muscle in the cat influenced the activity of muscle spindle afferent discharge in neck muscles (Hellström et al., 2000; Hellström et al., 2002), indicating intersegmental reflex connections between nociceptors in the temporomandibular region and the neck fusimotor–muscle spindle system. The authors suggest that these reflex connections could be involved in the spread of muscle stiffness and pain, as well as motor control disturbances.

The interpretation of the finding that patients with spinal pain were likely to report bruxism (Paper I) is not straightforward. The relationship between bruxism and jaw muscle pain has been much debated (Svensson et al., 2008; Lobbezoo et al., 2006b). Evidence for a cause-effect relationship is lacking, but a central etiology has been suggested (Lobbezoo et al., 2006a; Lavigne et al., 2008; Svensson et al., 2008). It has been speculated that interaction between converging sensory neurons, including sensitization mechanisms, and the jaw motor system could play a role in bruxism (Svensson et al., 2008), but there are no human studies to confirm this theory. However, experimental nociception in animal TMJ regions has shown a co-contraction of jaw-opening and jaw-closing muscles (Sessle, 2000).

Individual vulnerability

Subjects exposed to the same stressor will exhibit different responses. This sign of individual vulnerability represents a wide concept with interacting components.

Human pain genetics is a growing research field. Recent studies have identified a number of genetic polymorphisms implicated in modulation of both pain processing and psychological distress (Lötsch and Geisslinger, 2007; Maixner, 2008). One of these is the polymorphism of the gene encoding for catechol-0-methyltransferase (COMT) (Zubieta et al., 2003). COMT is an enzyme that inactivates catecholamines, including the neurotransmitters noradrenaline, adrenaline, and dopamine (Andersen and Skorpen, 2009), and therefore serves as a key regulator of pain perception, cognitive function and affective mood (Nackley et al., 2006). Genetic variants of lower COMT activity have been associated with enhanced experimental pain sensitivity and amplified risk of developing TMD (Zubieta et al., 2003; Diatchenko et al., 2005). It seems reasonable to assume that genetic variants may modulate the susceptibility to other pain conditions, as well. Indeed, genetic components have been shown to influence reporting on back and neck pain (MacGregor et al., 2004). Thus, pain genetics might partly explain the individual vulnerability to pain perception and development of various pain conditions.

Subjects with mood disorders may have an increased vulnerability to pain (Bair et al., 2003; Katona et al., 2005). The causal relationship between pain and psychological factors is largely unsolved (Dersh et al., 2002; Angst et al., 2008), but a bidirectional relationship has been suggested (Magni et al., 1994; Gureje, 2007).

The hypothalamic-pituitary-adrenal (HPA) axis is involved in the individual's response to physical or psychological stress (Habib et al., 2001). A prospective study has suggested that dysfunction of the HPA stress-response system is associated with an increased risk of onset of chronic widespread pain (McBeth et al., 2007). The complexity of the pain-modulating components is further emphasized in results indicating that genetic variation in the HPA axis may influence vulnerability to developing musculoskeletal pain (Holliday et al., 2009).

Concluding remarks and interpretation of results

Both spinal pain and TMD have a multifactorial etiology with factors that predispose, initiate, and perpetuate their course. It has been suggested that multiple interacting individual components are involved in musculoskeletal disorders, and that much work is needed to unveil the details of these processes (Johansson et al., 2003). One such presumed component is stress. Cassel suggested that psychosocial factors do not act as direct etiological factors for specific diseases, but rather alter the endocrine balance in the body and thus enhance susceptibility to disease in general (Cassel, 1976).

The observed reciprocal dose-response-like relationship and mutual influence between spinal pain and TMD indicate comorbidity, but they cannot be interpreted as evidence of cause and effect. Based on the convergence theory and sensitization mechanisms, it

could be speculated that sensory afference in one of the systems may affect the other system. However, it is not possible to conclude that one condition caused the other, or whether there are other factors beyond the study design that affected the outcome. The results show that spinal pain and TMD have a partial and significant overlap, even at low severity and frequency levels, and that they mutually constitute risk factors for each other. Due to this relationship between the disorders, it seems reasonable to assume that they have common pathophysiological mechanisms. This conclusion would not exclude the existence of separate mechanisms for onset and development of spinal pain and TMD, such as local injury and inflammatory diseases, but shows that occurrence of one condition increases the risk for onset of the other. The relationship between spinal pain and TMD may not be unique. Analogous results might be found in relation to other regional pain conditions, as well.

More research is needed for a better understanding of mechanisms of the found comorbidity and interaction between the investigated conditions, and also on the pathophysiological processes behind spinal pain and TMD, for each one separately.

Methodological considerations

Study populations

Results must always be considered in relation to the performed measurements and the population from which the subjects were drawn. The patients included in Papers I and II worked in various occupations, from which they were on part-time or full-time sick leave, prior to participation in the rehabilitation program. The motive for including these patients in the study, apart from accessibility, was that all had long-term spinal pain and related disability. Their mean scores for intensity of pain and impact on ADL were high, as shown in Table 2. The participation rate was high (91%), and the reason for not participating is unknown.

In the process of identifying non-patients (Papers I and II), cooperation was established primarily with companies within different sectors like manufacturing, health care, engineering, and information technology. Hence, patients and non-patients had a background in working life. A standardized inclusion procedure for non-patients was not feasible, because the method required extensive cooperation with the management at each company. The screening procedure was implemented at some companies mainly to obtain a rough selection of participants, regarding age, sex, and spinal status. The classification of participants was based solely on the answers in the questionnaires.

To minimize the risk of examiner bias, a blinded procedure would have been preferable. It was not possible to examine the patients and non-patients at the same place, and thus, the examiner was not blinded to the study group affiliation. To test the internal validity (Paper I) a subsample was included, from which the examiner was blinded to the spinal status. This test showed the same pattern of association as the case-control analysis, in spite of the fact that subjects with spinal pain from the blinded sample had a

significantly lower degree of reported spinal pain intensity and impact on ADL than cases from the rehabilitation center. Hence, the non-blinded design did not cause any obvious bias.

The strength of a case-control study is the possibility to achieve enough statistical power with fairly limited resources. In Paper I, each case was matched for sex and age with two controls, thereby reducing the confounding, and improving the estimation precision of analysis (Selvin, 1996b). The drawback of matching is that variables matched for are not available in the analyses. Since spinal pain (Sternbach, 1986; Mäkela et al., 1991; Andersson et al., 1993; Webb et al., 2003) and TMD (De Kanter et al., 1993; Wänman, 1996; Carlsson, 1999) may be related to age and sex, these factors were controlled for. Accordingly, these variables were also controlled for in the regression models in Papers II and III.

In Paper II, the classification of subjects into different spinal pain groups was based on the most frequent spinal pain location. For example, a combination of daily shoulder pain and infrequent low back pain resulted in classification according to the shoulder pain. Patients referred to the rehabilitation program who were on sick leave were considered to have more severe and disabling spinal pain than subjects with frequent pain who were not on sick leave. An increasing frequency/severity of spinal pain in the different groups was reflected in increasing mean values for pain intensity and impact on ADL (Table 2). Correspondingly, the increasing frequency/severity of TMD symptoms was mirrored by the impact of TMD symptoms on ADL in the different TMD groups (Table 3). The construction of spinal pain and TMD groups, aiming at discrete severity categories (dose), therefore seems valid with respect to the mean intensity level and the impact on ADL.

In Paper III, dental students were included at the beginning of their education and followed for 2 years. As students, they were easily accessed and represented a rather homogeneous group, following the syllabus. Furthermore, they were exposed to similar ergonomic and psychosocial factors during their working day. It could be argued that dental students constitute a sample with an increased risk of reporting musculoskeletal symptoms. Previous studies have demonstrated a high prevalence of body pain among dental students (Rising et al., 2005), and that their work behaviors, upon entering the clinical part of education, constitute a risk for development of musculoskeletal symptoms (Thornton et al., 2008). In the present study, the data collection was finished before the students entered the clinical part of their education. Another study showed that compared to psychology students, dental students significantly more often reported low back pain, but no difference was found in the prevalence of headache, neck pain, upper back pain, or arm symptoms (Melis et al., 2004). Therefore, it is unclear whether dental students, at the beginning of their education, are more vulnerable to musculoskeletal symptoms than other students.

During the study period 25% of the participating students decided to interrupt their education, which is a normal magnitude for dental education at Umeå University.

Reasons for interruption, that could have influenced the results would be those related to increased or decreased presence of symptoms in the jaw-face, head, and spinal area. The first possibility is that some of the students had an onset of musculoskeletal symptoms and for that reason decided to interrupt their studies. The second possibility is that the subjects dropped out because of fewer symptoms after the first year, which seems extremely unlikely. However, the most likely motive for dropping out was a wish to change education or university. The dropouts were proportionately more often men, but did not differ from the study population regarding measured baseline variables. Hence, the dropout probably had a random effect on the results.

Data collection

The measurements were based on questionnaires and clinical examinations of the jaw function. The examiners were always blinded to the questionnaires during the examinations, in order to avoid bias (Papers I and III). Pain is a subjective experience, and self-report measures are the "gold standard" in assessing pain (Dworkin et al., 2005). The questions included in the questionnaires are commonly used in the clinical praxis and in research. In Papers I and II, the symptoms were reported according to location, frequency, duration, intensity, and impact on activities of daily life, and in Paper III, only location and frequency were used. A schematic representation of the targeted area might have improved the precision of pain location. To improve reliability, a cutoff value of symptoms reported once a week or more often was used (Wahlund et al., 1998); these were defined as frequent symptoms. Pain intensity was measured with an 11-point numerical rating scale, which is a recommended standard (Jensen and Karoly, 2001; Dworkin et al., 2005) and has high reliability also for TMD symptoms (Magnusson et al., 1995). The RDC/TMD Axis I (Dworkin and LeResche, 1992) was used for classification of myofascial pain (Papers I and III) and arthralgia (Paper III). This is a widely used diagnostic tool for classifying subtypes of TMD. The indices by Helkimo (Helkimo, 1974) differentiate the severity of TMD signs and symptoms, independent of etiology. The questionnaires covered five well-known and established symptoms of TMD, which are also used in the Helkimo anamnestic index. The reliability of signs and symptoms related to TMD has been evaluated in a number of studies with reliability values ranging from modest to excellent (Dworkin et al., 1990; Wahlund et al., 1998; John and Zwijnenburg, 2001; Nilsson et al., 2006). High validity has been found for self-reported questions of TMD pain (Nilsson et al., 2006), as well as jaw pain and function (Gerstner et al., 1994).

In order to maintain conformity between questions regarding spinal pain and TMD, these were uniformly constructed (see Appendices). The participants reported absence or presence of spinal pain in three different locations. In Papers I and II, the subjects were asked about pain in the neck, shoulders, and low back, and in Paper III, the wording was correspondingly neck, shoulders, and back. Site-specific analyses were performed only in Paper I; in the other analyses the different locations were merged into one spinal unit. The construct variable frequent spinal pain comprised seven possible

combinations of pain location. These separate pain locations and combinations were analyzed with regard to signs and symptoms of TMD in Paper I. The implementation of the same procedure in Papers II and III would have meant numerous analyses, each of weak statistical power. The cervical spine, upper thoracic spine, and shoulder girdle are considered to represent a functional unit (Mannheimer and Dunn, 1991). Therefore, one option was to group occurrence of spinal pain into upper back, lower back, and whole back pain. With this alternative, all subjects with pain in the neck/low back and shoulders/low back would have been excluded. The whole spine with its neural and muscular parts has also been viewed as a functional system (Panjabi, 1992). Thus, within the frames of this investigation, the choice was to consider the spine as one unit.

The clinical examination of the jaw function followed a standardized routine procedure used at the Department of Clinical Oral Physiology at Umeå University and in line with recommended guidelines (Okeson, 2008c, Dworkin and LeResche, 1992). All participants in Paper I were examined by the same examiner. In Paper III, the two examiners were calibrated prior to the start, to improve inter-examiner reliability (Dworkin et al., 1990; List et al., 2006). In assessment of the jaw function, intra-examiner consistency has been shown to be higher than inter-examiner consistency (Carlsson et al., 1980). Each subject was thus followed by the same examiner.

Presence of spinal pain was not validated by a clinical examination. A pathoanatomical diagnosis is not identifiable in the majority of patients with spinal pain (Manek and MacGregor, 2005; Jull et al., 2008), and most cases are therefore designated as nonspecific or idiopathic. The rationale for epidemiologic studies of pain symptoms, without diagnostic differentiation, is that symptoms in different locations are believed to share common pathophysiological mechanisms (Von Korff et al., 1993). Hence, a mechanism-based approach in pain research has been advocated (Woolf et al., 1998; Baron, 2006; Croft et al., 2007).

Generalizability

Generalizability is mainly determined by the characteristics of the study populations. The external validity of observational studies (i.e., case-control and cohort studies) is usually not considered as robust as in randomized clinical trials. Several confounders, of which some are difficult to foresee, may complicate the interpretations of results. In this thesis the two most obvious confounders were controlled for, but others may have been incorporated in the study populations. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Initiative has published guidelines for observational studies with the aim to improve methodology and transparency in reports (von Elm et al., 2007). The items proposed by STROBE were essentially fulfilled in this thesis.

The study populations comprised participants with presence or absence of spinal pain, and with different levels of severity of spinal pain and related disability, in this sense representing a broad variety of individuals. The main strength of this thesis is that the

different study designs, with mostly different populations, all indicate similar patterns of a reciprocal relationship between spinal pain and TMD. Furthermore, the results are in line with some previous studies and concur with current research on pathophysiological mechanisms. The results should be verified in larger randomized studies.

SUMMARY OF RESULTS

- Signs and symptoms of TMD were more common in individuals with long-term spinal pain, compared to matched controls without spinal pain. The association remained after exclusion of participants with jaw pain.
- The pattern of association between spinal pain and TMD was similar, regardless of location of long-term spinal pain.
- Subjects with infrequent spinal pain reported TMD symptoms more often than controls without spinal pain.
- Subjects with infrequent TMD symptoms reported spinal pain more often than controls.
- The prevalence of TMD symptoms and headaches increased in a dose-response-like pattern, with increasing frequency/severity of spinal pain.
- The prevalence of spinal pain increased in a dose-response-like pattern, with increasing frequency/severity of TMD symptoms.
- Presence of spinal pain at baseline increased the 2-year incidence of jaw pain, headaches, and TMD pain.
- Presence of TMD signs at baseline increased the 2-year incidence of spinal pain, jaw pain, headaches, and nonpain TMD symptoms.
- Concomitant presence of spinal pain and TMD signs had a stronger influence on the incidence of jaw pain and headaches than separately present factors.
- Women with spinal pain at baseline had the highest probability of TMD pain incidence.

CLINICAL IMPLICATIONS

Pain is one of the most common reasons for patients to consult healthcare professionals. There is a potential risk that each profession will focus only on the site-specific musculoskeletal symptom presented by the patient. The same patient may discuss pain in the low back with the physician, pain in the jaw with the dentist, and pain in the shoulders with the physiotherapist. In view of the fact that multi-site musculoskeletal pain is common, a wider perspective is justified and treatment providers should routinely ensure that patients with pain and dysfunction report the actual and complete distribution of pain and disability.

Since presence of one pain condition is associated with an increased risk of developing a new pain condition, early detection and management of pain are essential to stop further spread and to prevent the transition from acute to chronic pain. Pain should thus be targeted on the peripheral, spinal, and cortical level with the aim to reduce its effect on sensitization mechanisms. Due to the connections between spinal and trigeminal neural networks, it can be hypothesized that treatment targeted to the spinal area may also have an effect on patients with TMD, and inversely, treatment of TMD may reduce spinal pain. In fact, patients with neck/shoulder pain or headaches who received both physical therapy and occlusal adjustment had a better long-term response to therapy, compared to patients who underwent only physical therapy (Karppinen et al., 1999). In patients with chronic regional pain syndrome (CRPS) an increased hip abduction was observed after TMJ treatment, and a decreased hip abduction was found after jaw clenching (Fischer et al., 2009a). The authors thus suggested an involvement of the temporomandibular system with hip range of movement. In contrast to this, a pilot study showed that occlusal splints had no short-term effect on pain related to CRPS (Fischer et al., 2008). It has also been advocated that manual therapy and exercise directed at cervical spine might reduce orofacial pain and increase the pressure pain thresholds of jaw muscles in patients with TMD (La Touche et al., 2009).

A general pattern of chronic pain comorbidity was recently shown in a community sample, where multi-site chronic pain was more common than single-site chronic pain (Carnes et al., 2007). In line with this, it has been suggested that generalized pain is at one end of a continuum of pain and tender points (Croft et al., 1996; Wolfe, 1997; Carli et al., 2002) that starts with localized musculoskeletal pain (Arendt-Nielsen and Henriksson, 2007), for example, in the temporomandibular region (Vierck, 2006). The local nociceptive input may thus contribute to development of generalized hypersensitivity (Vierck, 2006), a key feature of fibromyalgia (Arendt-Nielsen and Henriksson, 2007). The mouth, jaws, and face have rich sensory innervations and extensive projections on the sensory cortex. Several studies, including this thesis, indicate that pain from the trigeminally innervated region may affect the pathophysiology of pain perception in a wider perspective. Hence, it could be speculated that pain in the jaw-face area may be of higher significance for the spread and development of musculoskeletal pain than is currently known and recognized.

Dentists should observe the increased risk of jaw pain onset among patients with spinal pain, since it may be important in the clinical judging process. In countries where dentists regularly conduct check-ups among the general population, an examination of the jaw system, including range of mobility and pain to palpation, may have a part in health promotion and pain prevention. Further studies are warranted based on this perspective.

In the management of patients with several pain sites, a multiprofessional and integrated approach should be implemented. Specifically, jaw function and pain should be evaluated in patients with long-term spinal pain, and spinal function and pain should be evaluated in patients with persistent TMD.

CONCLUSIONS

The results presented in this thesis show comorbidity, and indicate a reciprocal influence, between spinal pain and TMD. The results call for enhanced knowledge of the pathophysiological mechanisms underlying the found relationship. It is advocated that symptoms and signs in the jaw-face-head should be considered in patients with long-term spinal pain, and spinal pain should be considered in patients with persistent TMD. Until mechanism-based treatments are available, a multidisciplinary and integrated approach should be implemented in the management of individuals with spinal pain and TMD.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Huvudsyftet med avhandlingen var att undersöka om det finns samband mellan ryggvärk (nacke, skuldra, ländrygg) och käkfunktionsstörning (eng. TemporoMandibular Disorders, TMD). TMD kännetecknas av smärta och ömhet i käkmuskler och käkled, samt käkledsljud och nedsatt käkrörlighet.

Värk och funktionsnedsättning i rörelseorganen, såsom ryggvärk och TMD, är omfattande folkhälsoproblem. Bägge dessa tillstånd medför försämrad livskvalitet samt ökad sjukfrånvaro och sjukvårdskonsumtion. Tidigare studier har visat att käkens och nackens nervbanor är sammankopplade, samt att käkens och nackens rörelser är koordinerade.

Avhandlingens delarbeten fokuserade på följande frågeställningar: Är käkfunktionsstörning vanligare bland individer med långvarig ryggvärk än bland personer utan ryggvärk? Har svårighetsgraden av ryggvärk respektive käkfunktionsstörning betydelse för hur vanligt det andra tillståndet är? Kan förekomsten av ryggvärk eller käkfunktionsstörning påverka uppkomsten av varandra? Totalt deltog 914 personer i en enkätundersökning och drygt hälften av dessa genomgick också en undersökning av käksystemets funktion. Resultaten visade att personer med långvarig ryggvärk, oavsett var i ryggen den upplevdes, hade en högre förekomst av TMD än personer utan ryggvärk. Fynden visade också att med stigande svårighetsgrad av ryggvärk eller TMD, så ökade förekomsten av det andra tillståndet. Vidare påvisade undersökningen att ryggvärk och TMD ömsesidigt påverkade varandras uppkomst under en 2-årsperiod.

Sammantaget visar undersökningen att det finns en tydlig samsjuklighet mellan ryggvärk och TMD, och att de två tillstånden påverkar varandra. Detta tyder på gemensamma uppkomstmekanismer för utvecklingen av dessa tillstånd. Därför bör symtom och funktion i käksystemet utvärderas hos patienter med långvarig ryggvärk, liksom ryggfunktion och ryggvärk bör bedömas hos patienter med långvarig käkfunktionsstörning. Resultaten understryker betydelsen av god kommunikation och välutvecklat samarbete mellan vårdpersonal som utreder och behandlar individer med ryggvärk och TMD. Uppkomstmekanismer för ryggvärk och TMD är ett viktigt forskningsområde för att på sikt kunna utveckla bättre behandlingsmetoder för dessa tillstånd.

ACKNOWLEDGMENTS

I wish to express my sincere gratitude to all of you who have helped, encouraged and supported me in the work of this thesis. In particular, I want to thank

Anders Wänman, my supervisor, who guided me into the fields of science and clinical oral physiology. Thank you for your encouragement and constructive discussions, and for patiently supporting and believing in me.

Hans Malker, co-supervisor, for sharing your deep knowledge in the field of epidemiology, answering my never-ending questions, and always being such an incurable optimist.

Erling Englund, co-author and friendliest statistician on earth, for always trying to explain unexplainable "stuff," preparing endless numbers of figures, and performing analyses.

Susanna Marklund, co-author and former fellow Ph.D. student, for generously sharing your data, fruitful discussions, and spirit-boosting talks.

Staff at the Research and Development Center (FoU-Centrum), for great company, support, good laughs, and help in practical and methodological matters. In particular, Mats Sjöling, Jeanette Sundberg Granlund, and Per-Arne Lyrén.

Birgitta Häggman Henrikson for superb advice, help, support, and pep talks.

Per-Olof Eriksson, for excellent guidance. Thanks to you, I realized that a dentist's field extends beyond the mouth and teeth.

Christina Storm Mienna, Catharina Österlund, Ewa Lampa, Susanne Eriksson, and Agneta Lundström. I appreciate your company, our discussions, and good laughs.

Ann-Sofie Strandberg for help with practical matters.

Vivan Rönnqvist for help with layout and posters, and Ove, Marika, Lennart, K-G, Per, Ingela, and Göran for encouragement and congenial lunch company.

Fredrik Hellström for valuable and constructive comments.

K-G Westberg for valuable advice.

Helmut Kerschbaumer for smooth cooperation and help with endurance test.

Special thanks to Pentti Kirveskari for letting me visit you in Åbo, and for inspiring discussions.

The staff of the Medical Library, Sundsvall Hospital, for excellent service.

All participants in the studies: Management, employees, and patients at Rygginstitutet Sundsvall; management and employees at County Council Västernorrland, Emhart Glass, Metso Paper and Metso Panelboard, Swedish Social Insurance Agency

Development Division; students at Mid Sweden University; dental students at Umeå University; and members of Friskis&Svettis, Sundsvall. Thank you for your contribution!

Friends, relatives, and acquaintances for just being there.

Mina föräldrar Margareta och Karl-Erik för er kärlek och omtanke.

My wonderful family, Hans, Jakob, and Tobias. You are the best!

This work was supported by grants from:

Dept. of Research and Development Center, Västernorrland County Council

Dept. of Odontology, Umeå University

Västerbotten County Council

The Swedish Dental Society

Stiftelsen Goljes Minne

Anna Cederbergs stiftelse

REFERENCES

Agresti A. Logistic regression. Categorical data analysis. Hoboken, New Jersey: Wiley-Interscience; 2002. p. 165-211.

Alanen PJ, Kirveskari PK. Occupational cervicobrachial disorder and temporomandibular joint dysfunction. Cranio 1984;3:69-72.

Altman DG. Comparing groups - continous data. Practical statistics for medical research. London: Chapman and Hall; 1991a. p. 179-228.

Altman DG. Relation between several variables. Practical statistics for medical research. London: Chapman and Hall; 1991b. p. 325-364.

Ambalavanar R, Moutanni A, Dessem D. Inflammation of craniofacial muscle induces widespread mechanical allodynia. Neurosci Lett 2006;399:249-254.

Andersen S, Skorpen F. Variation in the COMT gene: implications for pain perception and pain treatment. Pharmacogenomics 2009;10:669-684.

Andersson GB. Epidemiological features of chronic low-back pain. Lancet 1999;354:581-585.

Andersson GBJ. The epidemiology of spinal disorders. In: Frymoyer JW, editor. The adult spine: principles and practice, Vol. 1. Philadelphia: Lippincott-Raven; 1997. p. 93-141.

Andersson HI, Ejlertsson G, Leden I, Rosenberg C. Chronic pain in a geographically defined general population: studies of differences in age, gender, social class, and pain localization. Clin J Pain 1993;9:174-182.

Angst F, Verra ML, Lehmann S, Aeschlimann A, Angst J. Refined insights into the pain-depression association in chronic pain patients. Clin J Pain 2008;24:808-816.

Arendt-Nielsen L, Henriksson KG. Pathophysiological mechanisms in chronic musculoskeletal pain (fibromyalgia): the role of central and peripheral sensitization and pain disinhibition. Best Pract Res Clin Rheumatol 2007;21:465-480.

Arendt-Nielsen L, Svensson P. Referred muscle pain: basic and clinical findings. Clin J Pain 2001;17:11-19.

Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Arch Intern Med 2003;163:2433-2445.

Baron R. Mechanisms of disease: neuropathic pain—a clinical perspective. Nat Clin Pract Neurol 2006;2:95-106.

Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B 1995;57:289-300.

Bergman S, Herrström P, Jacobsson LT, Petersson IF. Chronic widespread pain: a three year followup of pain distribution and risk factors. J Rheumatol 2002;29:818-825.

Brattberg G, Thorslund M, Wikman A. The prevalence of pain in a general population. The results of a postal survey in a county of Sweden. Pain 1989;37:215-222.

Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain 2006;10:287-333.

Carli G, Suman AL, Biasi G, Marcolongo R. Reactivity to superficial and deep stimuli in patients with chronic musculoskeletal pain. Pain 2002;100:259-269.

Carlsson GE. Epidemiology and treatment need for temporomandibular disorders. J Orofac Pain 1999;13:232-237.

Carlsson GE, Egermark-Eriksson I, Magnusson T. Intra- and inter-observer variation in functional examination of the masticatory system. Swed Dent J 1980;4:187-194.

Carnes D, Parsons S, Ashby D, Breen A, Foster NE, Pincus T, Vogel S, Underwood M. Chronic musculoskeletal pain rarely presents in a single body site: results from a UK population study. Rheumatology (Oxford) 2007;46:1168-1170.

Carossa S, Catapano S, Previgliano V, Preti G. [The incidence of craniomandibular disorders in patients with cervical dysfunctions. A clinico-statistical assessment]. Minerva Stomatol 1993;42:229-233.

Cassel J. The contribution of the social environment to host resistance: the Fourth Wade Hampton Frost Lecture. Am J Epidemiol 1976;104:107-123.

Cassidy JD, Côté P, Carroll LJ, Kristman V. Incidence and course of low back pain episodes in the general population. Spine 2005;30:2817-2823.

Chudler EH, Foote WE, Poletti CE. Responses of cat C1 spinal cord dorsal and ventral horn neurons to noxious and non-noxious stimulation of the head and face. Brain Res 1991;555:181-192.

Ciancaglini R, Radaelli G. The relationship between headache and symptoms of temporomandibular disorder in the general population. J Dent 2001;29:93-98.

Ciancaglini R, Testa M, Radaelli G. Association of neck pain with symptoms of temporomandibular dysfunction in the general adult population. Scand J Rehabil Med 1999;31:17-22.

Clark GT. Classification, causation and treatment of masticatory myogenous pain and dysfunction. Oral Maxillofac Surg Clin North Am 2008;20:145-157.

Clark GT, Green EM, Dornan MR, Flack VF. Craniocervical dysfunction levels in a patient sample from a temporomandibular joint clinic. J Am Dent Assoc 1987;115:251-256.

Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. Pain 1993;52:259-285.

Côté P, Cassidy JD, Carroll L. The Saskatchewan Health and Back Pain Survey. The prevalence of neck pain and related disability in Saskatchewan adults. Spine 1998;23:1689-1698.

Côté P, Cassidy JD, Carroll L. The factors associated with neck pain and its related disability in the Saskatchewan population. Spine 2000;25:1109-1117.

Côté P, Cassidy JD, Carroll LJ, Kristman V. The annual incidence and course of neck pain in the general population: a population-based cohort study. Pain 2004;112:267-273.

Croft P. The epidemiology of pain: the more you have, the more you get. Ann Rheum Dis 1996;55:859-860.

Croft P, Burt J, Schollum J, Thomas E, Macfarlane G, Silman A. More pain, more tender points: is fibromyalgia just one end of a continuous spectrum? Ann Rheum Dis 1996;55:482-485.

Croft P, Dunn KM, Von Korff M. Chronic pain syndromes: you can't have one without another. Pain 2007;131:237-238.

Croft PR, Lewis M, Papageorgiou AC, Thomas E, Jayson MI, Macfarlane GJ, Silman AJ. Risk factors for neck pain: a longitudinal study in the general population. Pain 2001;93:317-325.

Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. Spine J 2008;8:8-20.

De Kanter RJ, Truin GJ, Burgersdijk RC, Van 't Hof MA, Battistuzzi PG, Kalsbeek H, Käyser AF. Prevalence in the Dutch adult population and a meta-analysis of signs and symptoms of temporomandibular disorder. J Dent Res 1993;72:1509-1518.

De Laat A, Meuleman H, Stevens A, Verbeke G. Correlation between cervical spine and temporomandibular disorders. Clin Oral Investig 1998;2:54-57.

de Wijer A, Steenks MH, Bosman F, Helders PJ, Faber J. Symptoms of the stomatognathic system in temporomandibular and cervical spine disorders. J Oral Rehabil 1996;23:733-741.

Dersh J, Polatin PB, Gatchel RJ. Chronic pain and psychopathology: research findings and theoretical considerations. Psychosom Med 2002;64:773-786.

DeSantana JM, Sluka KA. Central mechanisms in the maintenance of chronic widespread noninflammatory muscle pain. Curr Pain Headache Rep 2008;12:338-343.

Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W. Idiopathic pain disorders—pathways of vulnerability. Pain 2006;123:226-230.

Diatchenko L, Slade GD, Nackley AG, Bhalang K, Sigurdsson A, Belfer I, Goldman D, Xu K, Shabalina SA, Shagin D, Max MB, Makarov SS, Maixner W. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mol Genet 2005;14:135-143.

Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9-19.

Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6:301-355.

Dworkin SF, LeResche L, DeRouen T, Von Korff M. Assessing clinical signs of temporomandibular disorders: reliability of clinical examiners. J Prosthet Dent 1990;63:574-579.

Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. Lancet 1999;354:1248-1252.

Eriksson PO, Häggman-Henrikson B, Nordh E, Zafar H. Co-ordinated mandibular and head-neck movements during rhythmic jaw activities in man. J Dent Res 2000;79:1378-1384.

Fejer R, Kyvik KO, Hartvigsen J. The prevalence of neck pain in the world population: a systematic critical review of the literature. Eur Spine J 2006;15:834-848.

Fernández-de-las-Peñas C, Cuadrado M, Arendt-Nielsen L, Simons D, Pareja J. Myofascial trigger points and sensitization: an updated pain model for tension-type headache. Cephalalgia 2007;27:383–393.

Fernández-de-las-Peñas C, Gálan-del-Río F, Fernández -Carnero J, Pesquera J, Arendt-Nielsen L, Svensson P. Bilateral widespread mechanical pain sensitivity in women with myofascial temporomandibular disorder: evidence of impairment in central nociceptive processing. J Pain 2009;10:1170-1178.

Fischer MJ, Reiners A, Kohnen R, Bernateck M, Gutenbrunner C, Fink M, Svensson P. Do occlusal splints have an effect on complex regional pain syndrome? A randomized, controlled proof-of-concept trial. Clin J Pain 2008;24:776-783.

Fischer MJ, Riedlinger K, Gutenbrunner C, Bernateck M. Influence of the temporomandibular joint on range of motion of the hip joint in patients with complex regional pain syndrome. J Manipulative Physiol Ther 2009a;32:364-371.

Fischer MJ, Riedlinger K, Schoser B, Bernateck M. Perceived pain and temporomandibular disorders in neuromuscular diseases. Muscle Nerve 2009b;40:595-602.

Fricton JR, Kroening R, Haley D, Siegert R. Myofascial pain syndrome of the head and neck: a review of clinical characteristics of 164 patients. Oral Surg Oral Med Oral Pathol 1985;60:615-623.

Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull 2007;133:581-624.

Gerstner GE, Clark GT, Goulet JP. Validity of a brief questionnaire in screening asymptomatic subjects from subjects with tension-type headaches or temporomandibular disorders. Community Dent Oral Epidemiol 1994;22:235-242.

Gesch D, Bernhardt O, Alte D, Schwahn C, Kocher T, John U, Hensel E. Prevalence of signs and symptoms of temporomandibular disorders in an urban and rural German population: results of a population-based Study of Health in Pomerania. Quintessence Int 2004;35:143-150.

Ghaffari M, Alipour A, Farshad AA, Yensen I, Vingard E. Incidence and recurrence of disabling low back pain and neck-shoulder pain. Spine 2006;31:2500-2506.

Giesecke T, Gracely RH, Grant MA, Nachemson A, Petzke F, Williams DA, Clauw DJ. Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis Rheum 2004;50:613-623.

Graven-Nielsen T, Arendt-Nielsen L, Svensson P, Jensen TS. Quantification of local and referred muscle pain in humans after sequential i.m. injections of hypertonic saline. Pain 1997;69:111-117.

Graven-Nielsen T, Svensson P, Arendt-Nielsen L. Interaction between muscle pain and motor control. In: Johansson H, Windhorst U, Djupsjöbacka M, Passatore M, editors. Chronic work-related myalgia: neuromuscular mechanisms behind work-related chronic muscle pain syndromes. Gävle, Sweden: Gävle University Press; 2003. p. 141-154.

Gureje O. Psychiatric aspects of pain. Curr Opin Psychiatry 2007;20:42-46.

Habib KE, Gold PW, Chrousos GP. Neuroendocrinology of stress. Endocrinol Metab Clin North Am 2001;30:695-728; vii-viii.

Hagberg C. General musculoskeletal complaints in a group of patients with craniomandibular disorders (CMD). A case control study. Swed Dent J 1991;15:179-185.

Hagen EM, Svensen E, Eriksen HR, Ihlebaek CM, Ursin H. Comorbid subjective health complaints in low back pain. Spine 2006;31:1491-1495.

Hagen K, Einarsen C, Zwart JA, Svebak S, Bovim G. The co-occurrence of headache and musculoskeletal symptoms amongst 51 050 adults in Norway. Eur J Neurol 2002;9:527-533.

Häggman-Henrikson B, Zafar H, Eriksson PO. Disturbed jaw behavior in whiplash-associated disorders during rhythmic jaw movements. J Dent Res 2002;81:747-751.

Hansson EK, Hansson TH. The costs for persons sick-listed more than one month because of low back or neck problems. A two-year prospective study of Swedish patients. Eur Spine J 2005;14:337-345.

Helkimo M. Studies on function and dysfunction of the masticatory system. II. Index for anamnestic and clinical dysfunction and occlusal state. Sven Tandlak Tidskr 1974;67:101-121.

Hellström F, Thunberg J, Bergenheim M, Sjölander P, Pedersen J, Johansson H. Elevated intramuscular concentration of bradykinin in jaw muscle increases the fusimotor drive to neck muscles in the cat. J Dent Res 2000;79:1815-1822.

Hellström F, Thunberg J, Bergenheim M, Sjölander P, Djupsjöbacka M, Johansson H. Increased intra-articular concentration of bradykinin in the temporomandibular joint changes the sensitivity of muscle spindles in dorsal neck muscles in the cat. Neurosci Res 2002;42:91-99.

Hestbaek L, Leboeuf-Yde C, Kyvik KO, Vach W, Russell MB, Skadhauge L, Svendsen A, Manniche C. Comorbidity with low back pain: a cross-sectional population-based survey of 12- to 22-year-olds. Spine 2004;29:1483-1491.

Hestbaek L, Leboeuf-Yde C, Manniche C. Low back pain: what is the long-term course? A review of studies of general patient populations. Eur Spine J 2003;12:149-165.

Hogg-Johnson S, van der Velde G, Carroll LJ, Holm LW, Cassidy JD, Guzman J, Côté P, Haldeman S, Ammendolia C, Carragee E, Hurwitz E, Nordin M, Peloso P. The burden and determinants of neck pain in the general population: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine 2008;33:39-51.

Holliday KL, Nicholl BI, Macfarlane GJ, Thomson W, Davies KA, McBeth J. Genetic variation in the hypothalamic-pituitary-adrenal stress axis influences susceptibility to musculoskeletal pain: Results from the EPIFUND study. Ann Rheum Dis 2009 [Epub ahead of print]. doi: 10.1136/ard.2009.116137.

Hu JW, Sun KQ, Vernon H, Sessle BJ. Craniofacial inputs to upper cervical dorsal horn: implications for somatosensory information processing. Brain Res 2005;1044:93-106.

Jensen MP, Karoly P. Self-report scales and procedures for assessing pain in adults. In: Turk DC, Melzack R, editors. Handbook of pain assessment. New York: Guilford Press, 2001. p. 15-34.

Johansson H, Arendt-Nielsen L, Bergenheim M, Blair S, van Dieen J, Djupsjöbacka M, Fallentin N, Gold J, Hägg G, Kalezic N, Larsson S-E, Ljubisavljevic M, Lyskov E, Mano T, Magnusson M, Passatore M, Pedrosa-Domellöf F, Punnett L, Roatta S, Thornell LE, Windhorst U, Zukowska Z. Epilogue: an integrated

model for chronic work-related myalgia, "Brussels Model." In: Johansson H, Windhorst U, Djupsjöbacka M, Passatore M, editors. Chronic work-related myalgia: neuromuscular mechanisms behind work-related chronic muscle pain syndromes. Gävle, Sweden: Gävle University Press; 2003. p. 291-300.

Johansson H, Sojka P. Pathophysiological mechanisms involved in genesis and spread of muscular tension in occupational muscle pain and in chronic musculoskeletal pain syndromes: a hypothesis. Med Hypotheses 1991;35:196-203.

John MT, Miglioretti DL, LeResche L, Von Korff M, Critchlow CW. Widespread pain as a risk factor for dysfunctional temporomandibular disorder pain. Pain 2003;102:257-263.

John MT, Zwijnenburg AJ. Interobserver variability in assessment of signs of TMD. Int J Prosthodont 2001;14:265-270.

Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain 2005;114:295-302.

Jull GA, Sterling M, Falla D, Treleaven J, O'Leary S. Whiplash, headache, and neck pain: research-based directions for physical therapies. Edinburgh and New York: Churchill Livingstone; 2008. p. 5-20.

Kääria S, Solovieva S, Leino-Arjas P. Associations of low back pain with neck pain: a study of industrial employees with 5-, 10-, and 28-year follow-ups. Eur J Pain 2009;13:406-411.

Kamisaka M, Yatani H, Kuboki T, Matsuka Y, Minakuchi H. Four-year longitudinal course of TMD symptoms in an adult population and the estimation of risk factors in relation to symptoms. J Orofac Pain 2000;14:224-232.

Karppinen K, Eklund S, Suoninen E, Eskelin M, Kirveskari P. Adjustment of dental occlusion in treatment of chronic cervicobrachial pain and headache. J Oral Rehabil 1999;26:715-721.

Katona C, Peveler R, Dowrick C, Wessely S, Feinmann C, Gask L, Lloyd H, Williams AC, Wager E. Pain symptoms in depression: definition and clinical significance. Clin Med 2005;5:390-395.

Kerr FW. Facial, vagal and glossopharyngeal nerves in the cat. Afferent connections. Arch Neurol 1962;6:264-281.

Komiyama O, Arai M, Kawara M, Kobayashi K, De Laat A. Pain patterns and mandibular dysfunction following experimental trapezius muscle pain. J Orofac Pain 2005;19:119-126.

Kuttila M, Kuttila S, Le Bell Y, Alanen P. Association between TMD treatment need, sick leaves, and use of health care services for adults. J Orofac Pain 1997;11:242-248.

La Touche R, Fernández-de-las-Peñas C, Fernandez-Carnero J, Escalante K, Angulo-Díaz-Parreño S, Paris-Alemany A, Cleland JA. The effects of manual therapy

and exercise directed at the cervical spine on pain and pressure pain sensitivity in patients with myofascial temporomandibular disorders. J Oral Rehabil 2009;36:644-652.

Lavigne GJ, Khoury S, Abe S, Yamaguchi T, Raphael K. Bruxism physiology and pathology: an overview for clinicians. J Oral Rehabil 2008;35:476-494.

Leboeuf-Yde C, Nielsen J, Kyvik KO, Fejer R, Hartvigsen J. Pain in the lumbar, thoracic or cervical regions: do age and gender matter? A population-based study of 34,902 Danish twins 20-71 years of age. BMC Musculoskelet Disord 2009;10:39.

Leclerc A, Niedhammer I, Landre MF, Ozguler A, Etore P, Pietri-Taleb F. One-year predictive factors for various aspects of neck disorders. Spine 1999;24:1455-1462.

Leffler AS, Hansson P, Kosek E. Somatosensory perception in a remote pain-free area and function of diffuse noxious inhibitory controls (DNIC) in patients suffering from long-term trapezius myalgia. Eur J Pain 2002;6:149-159.

LeResche L. Epidemiology of temporomandibular disorders: implications for the investigation of etiologic factors. Crit Rev Oral Biol Med 1997;8:291-305.

LeResche L, Mancl LA, Drangsholt MT, Huang G, Von Korff M. Predictors of onset of facial pain and temporomandibular disorders in early adolescence. Pain 2007;129:269-278.

List T, John MT, Dworkin SF, Svensson P. Recalibration improves inter-examiner reliability of TMD examination. Acta Odontol Scand 2006;64:146-152.

Lobbezoo F, Van Der Zaag J, Naeije M. Bruxism: its multiple causes and its effects on dental implants—an updated review. J Oral Rehabil 2006a;33:293-300.

Lobbezoo F, van Selms MK, Naeije M. Masticatory muscle pain and disordered jaw motor behaviour: Literature review over the past decade. Arch Oral Biol 2006b;51:713-720.

Lötsch J, Geisslinger G. Current evidence for a modulation of nociception by human genetic polymorphisms. Pain 2007;132:18-22.

MacGregor AJ, Andrew T, Sambrook PN, Spector TD. Structural, psychological, and genetic influences on low back and neck pain: a study of adult female twins. Arthritis Rheum 2004;51:160-167.

Magni G, Moreschi C, Rigatti-Luchini S, Merskey H. Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain. Pain 1994;56:289-297.

Magnusson T, List T, Helkimo M. Self-assessment of pain and discomfort in patients with temporomandibular disorders: a comparison of five different scales with respect to their precision and sensitivity as well as their capacity to register memory of pain and discomfort. J Oral Rehabil 1995;22:549-556.

Maixner W. Biopsychosocial and genetic risk factors for temporomandibular joint disorders and related conditions. In: Graven-Nielsen T, Arendt-Nielsen L, Mense S, editors. Fundamentals of musculoskeletal pain. Seattle: IASP Press; 2008. p. 263-279.

Maixner W, Fillingim R, Sigurdsson A, Kincaid S, Silva S. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain: evidence for altered temporal summation of pain. Pain 1998;76:71-81.

Mäkela M, Heliovaara M, Sievers K, Impivaara O, Knekt P, Aromaa A. Prevalence, determinants, and consequences of chronic neck pain in Finland. Am J Epidemiol 1991;134:1356-1367.

Manek NJ, MacGregor AJ. Epidemiology of back disorders: prevalence, risk factors, and prognosis. Curr Opin Rheumatol 2005;17:134-140.

Mannheimer JS, Dunn J. Cervical spine. Evaluation and relation to temporomandibular disorders. In: Kaplan A, Assael L, editors. Temporomandibular disorders: diagnosis and treatment. Philadelphia: Saunders; 1991. p. 50-94.

Marklund S. Temporomandibular disorders: incidence, course, and risk factors. Thesis. Umeå: Umeå university; 2009.

Matsushita M, Okado N, Ikeda M, Hosoya Y. Descending projections from the spinal and mesencephalic nuclei of the trigeminal nerve to the spinal cord in the cat. A study with the horseradish peroxidase technique. J Comp Neurol 1981;196:173-187.

McBeth J, Silman AJ, Gupta A, Chiu YH, Ray D, Morriss R, Dickens C, King Y, Macfarlane GJ. Moderation of psychosocial risk factors through dysfunction of the hypothalamic-pituitary-adrenal stress axis in the onset of chronic widespread musculoskeletal pain: findings of a population-based prospective cohort study. Arthritis Rheum 2007;56:360-371.

Melis M, Abou-Atme YS, Cottogno L, Pittau R. Upper body musculoskeletal symptoms in Sardinian dental students. J Can Dent Assoc 2004;70:306-310.

Mense S, Simons DG, Russell IJ. Central pain and centrally modified pain. Muscle pain: understanding its nature, diagnosis, and treatment. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 158-204.

Merskey H, Bogduk N. International Association for the Study of Pain. Task Force on Taxonomy. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. Seattle: IASP Press; 1994.

Mørch CD, Hu JW, Arendt-Nielsen L, Sessle BJ. Convergence of cutaneous, musculoskeletal, dural and visceral afferents onto nociceptive neurons in the first cervical dorsal horn. Eur J Neurosci 2007;26:142-154.

Murray GM, Peck CC. Orofacial pain and jaw muscle activity: a new model. J Orofac Pain 2007;21:263-278.

Nackley A, Diatchenko L, Maixner W. Perspectives on the genetic basis of opioid-induced hyperalgesia. Anesthesiology 2006;104:909-910.

Nilsson IM, List T, Drangsholt M. The reliability and validity of self-reported temporomandibular disorder pain in adolescents. J Orofac Pain 2006;20:138-144.

Okeson JP. Differential diagnosis and management considerations of temporomandibular disorders. In: Okeson JP, American Academy of Orofacial Pain, editor. Orofacial pain: guidelines for assessment, classification, and management. Chicago: Quintessence; 1996. p. 113-184.

Okeson JP. Etiology of functional disturbances in the masticatory system. Management of temporomandibular disorders and occlusion. St. Louis, MO; London: Mosby; 2008a. p. 130-163.

Okeson JP. General considerations in the treatment of temporomandibular disorders. Management of temporomandibular disorders and occlusion. St. Louis, MO; London: Mosby; 2008b. p. 334-376.

Okeson JP. History of and examination for temporomandibular disorders. Management of temporomandibular disorders and occlusion. St. Louis, MO; London: Mosby; 2008c. p. 216-284.

Okeson JP. Signs and symptoms of temporomandibular disorders. Management of temporomandibular disorders and occlusion. St. Louis, MO; London: Mosby; 2008d. p. 164-215.

O'Neill S, Manniche C, Graven-Nielsen T, Arendt-Nielsen L. Generalized deep-tissue hyperalgesia in patients with chronic low-back pain. Eur J Pain 2007;11:415-420.

Pallegama RW, Ranasinghe AW, Weerasinghe VS, Sitheeque MA. Influence of masticatory muscle pain on electromyographic activities of cervical muscles in patients with myogenous temporomandibular disorders. J Oral Rehabil 2004;31:423-429.

Panjabi MM. The stabilizing system of the spine. Part I. Function, dysfunction, adaptation, and enhancement. J Spinal Disord 1992;5:383-389; discussion 397.

Papageorgiou AC, Croft PR, Thomas E, Ferry S, Jayson MI, Silman AJ. Influence of previous pain experience on the episode incidence of low back pain: results from the South Manchester Back Pain Study. Pain 1996;66:181-185.

Picavet HS, Schouten JS. Musculoskeletal pain in the Netherlands: prevalences, consequences and risk groups, the DMC(3)-study. Pain 2003;102:167-178.

Piovesan EJ, Kowacs PA, Oshinsky ML. Convergence of cervical and trigeminal sensory afferents. Curr Pain Headache Rep 2003;7:377-383.

Rammelsberg P, LeResche L, Dworkin S, Mancl L. Longitudinal outcome of temporomandibular disorders: a 5-year epidemiologic study of muscle

disorders defined by research diagnostic criteria for temporomandibular disorders. J Orofac Pain 2003;17:9-20.

Rising DW, Bennett BC, Hursh K, Plesh O. Reports of body pain in a dental student population. J Am Dent Assoc 2005;136:81-86.

Romaniello A, Svensson P, Cruccu G, Arendt-Nielsen L. Modulation of exteroceptive suppression periods in human jaw-closing muscles induced by summation of nociceptive and non-nociceptive inputs. Exp Brain Res 2000;132:306-313.

Rubin DI. Epidemiology and risk factors for spine pain. Neurol Clin 2007;25:353-371.

Ruggiero DA, Ross CA, Reis DJ. Projections from the spinal trigeminal nucleus to the entire length of the spinal cord in the rat. Brain Res 1981;225:225-233.

Sarlani E, Greenspan JD. Evidence for generalized hyperalgesia in temporomandibular disorders patients. Pain 2003;102:221-226.

SBU Statens beredning för medicinsk utvärdering. Ont i ryggen, ont i nacken: en evidensbaserad kunskapssammanställning. [The Swedish Council on Technology Assessment in Health Care. Back pain and neck pain]. Vol. 1. Stockholm: 2000a.

SBU Statens beredning för medicinsk utvärdering. Ont i ryggen, ont i nacken: en evidensbaserad kunskapssammanställning. [The Swedish Council on Technology Assessment in Health Care. Back pain and neck pain]. Vol. 2. Stockholm: 2000b.

Schmidt-Hansen PT, Svensson P, Bendtsen L, Graven-Nielsen T, Bach FW. Increased muscle pain sensitivity in patients with tension-type headache. Pain 2007;129:113-121.

Schmidt-Hansen PT, Svensson P, Jensen TS, Graven-Nielsen T, Bach FW. Patterns of experimentally induced pain in pericranial muscles. Cephalalgia 2006;26:568-577.

Schwartz LL. A temporomandibular joint pain-dysfunction syndrome. J Chronic Dis 1956;3:284-293.

Selvin S. The analysis of contingency table data: logistic model I. Statistical analysis of epidemiologic data. New York: Oxford University Press; 1996a. p. 197-242.

Selvin S. The analysis of matched data. Statistical analysis of epidemiologic data. New York: Oxford University Press; 1996b. p. 271-310.

Sessle BJ. The neural basis of temporomandibular joint and masticatory muscle pain. J Orofac Pain 1999;13:238-245.

Sessle BJ. Acute and chronic craniofacial pain: brainstem mechanisms of nociceptive transmission and neuroplasticity, and their clinical correlates. Crit Rev Oral Biol Med 2000;11:57-91.

Sessle BJ, Hu JW, Amano N, Zhong G. Convergence of cutaneous, tooth pulp, visceral, neck and muscle afferents onto nociceptive and non-nociceptive neurones in

trigeminal subnucleus caudalis (medullary dorsal horn) and its implications for referred pain. Pain 1986;27:219-235.

Shankland WE, 2nd. The trigeminal nerve. Part I: An over-view. Cranio 2000;18:238-248.

Simons DG, Travell JG, Simons LS. Travell & Simons' myofascial pain and dysfunction. The trigger point manual. Vol 1. Baltimore: Williams & Wilkins; 1999.

Sipilä K, Zitting P, Siira P, Niinimaa A, Raustia AM. Generalized pain and pain sensitivity in community subjects with facial pain: a case-control study. J Orofac Pain 2005;19:127-132.

Smith BH, Elliott AM, Hannaford PC, Chambers WA, Smith WC. Factors related to the onset and persistence of chronic back pain in the community: results from a general population follow-up study. Spine 2004;29:1032-1040.

Ståhl M, Kautiainen H, El-Metwally A, Hakkinen A, Ylinen J, Salminen JJ, Mikkelsson M. Non-specific neck pain in schoolchildren: prognosis and risk factors for occurrence and persistence. A 4-year follow-up study. Pain 2008;137:316-322.

Staud R, Koo E, Robinson ME, Price DD. Spatial summation of mechanically evoked muscle pain and painful aftersensations in normal subjects and fibromyalgia patients. Pain 2007;130:177-187.

Sternbach RA. Survey of pain in the United States: the Nuprin Pain Report. Clin J Pain 1986:49-53.

Stiesch-Scholz M, Fink M, Tschernitschek H. Comorbidity of internal derangement of the temporomandibular joint and silent dysfunction of the cervical spine. J Oral Rehabil 2003;30:386-391.

Stohler CS. Craniofacial pain and motor function: pathogenesis, clinical correlates, and implications. Crit Rev Oral Biol Med 1999;10:504-518.

Strine TW, Hootman JM. US national prevalence and correlates of low back and neck pain among adults. Arthritis Rheum 2007;57:656-665.

Svensson P, Graven-Nielsen T. Craniofacial muscle pain: review of mechanisms and clinical manifestations. J Orofac Pain 2001;15:117-145.

Svensson P, Jadidi F, Arima T, Baad-Hansen L, Sessle BJ. Relationships between craniofacial pain and bruxism. J Oral Rehabil 2008;35:524-547.

Svensson P, List T, Hector G. Analysis of stimulus-evoked pain in patients with myofascial temporomandibular pain disorders. Pain 2001;92:399-409.

Svensson P, Wang K, Arendt-Nielsen L, Cairns BE, Sessle BJ. Pain effects of glutamate injections into human jaw or neck muscles. J Orofac Pain 2005;19:109-118.

Svensson P, Wang K, Sessle BJ, Arendt-Nielsen L. Associations between pain and neuromuscular activity in the human jaw and neck muscles. Pain 2004;109:225-232.

Thornton LJ, Barr AE, Stuart-Buttle C, Gaughan JP, Wilson ER, Jackson AD, Wyszynski TC, Smarkola C. Perceived musculoskeletal symptoms among dental students in the clinic work environment. Ergonomics 2008;51:573-586.

Vierck CJ, Jr. Mechanisms underlying development of spatially distributed chronic pain (fibromyalgia). Pain 2006;124:242-263.

Visscher CM, Lobbezoo F, de Boer W, van der Zaag J, Naeije M. Prevalence of cervical spinal pain in craniomandibular pain patients. Eur J Oral Sci 2001;109:76-80.

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Bull World Health Organ 2007;85:867-872.

Von Korff M, Crane P, Lane M, Miglioretti DL, Simon G, Saunders K, Stang P, Brandenburg N, Kessler R. Chronic spinal pain and physical-mental comorbidity in the United States: results from the national comorbidity survey replication. Pain 2005;113:331-339.

Von Korff M, Le Resche L, Dworkin SF. First onset of common pain symptoms: a prospective study of depression as a risk factor. Pain 1993;55:251-258.

Wahlund K, List T, Dworkin SF. Temporomandibular disorders in children and adolescents: reliability of a questionnaire, clinical examination, and diagnosis. J Orofac Pain 1998;12:42-51.

Wang K, Sessle BJ, Svensson P, Arendt-Nielsen L. Glutamate evoked neck and jaw muscle pain facilitate the human jaw stretch reflex. Clin Neurophysiol 2004;115:1288-1295.

Wang K, Svensson P, Arendt-Nielsen L. Modulation of exteroceptive suppression periods in human jaw-closing muscles by local and remote experimental muscle pain. Pain 1999;82:253-262.

Wänman A. The relationship between muscle tenderness and craniomandibular disorders: a study of 35-year-olds from the general population. J Orofac Pain 1995;9:235-243.

Wänman A. Longitudinal course of symptoms of craniomandibular disorders in men and women. A 10-year follow-up study of an epidemiologic sample. Acta Odontol Scand 1996;54:337-342.

Webb R, Brammah T, Lunt M, Urwin M, Allison T, Symmons D. Prevalence and predictors of intense, chronic, and disabling neck and back pain in the UK general population. Spine 2003;28:1195-1202.

Wenig CM, Schmidt CO, Kohlmann T, Schweikert B. Costs of back pain in Germany. Eur J Pain 2009;13:280-286.

White BA, Williams LA, Leben JR. Health care utilization and cost among health maintenance organization members with temporomandibular disorders. J Orofac Pain 2001;15:158-169.

Wolfe F. The relation between tender points and fibromyalgia symptom variables: evidence that fibromyalgia is not a discrete disorder in the clinic. Ann Rheum Dis 1997;56:268-271.

Woolf CJ, Bennett GJ, Doherty M, Dubner R, Kidd B, Koltzenburg M, Lipton R, Loeser JD, Payne R, Torebjork E. Towards a mechanism-based classification of pain? Pain 1998;77:227-229.

Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science 2000;288:1765-1769.

Yunus MB. Central sensitivity syndromes: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. Semin Arthritis Rheum 2008;37:339-352.

Zafar H, Nordh E, Eriksson PO. Temporal coordination between mandibular and head-neck movements during jaw opening-closing tasks in man. Arch Oral Biol 2000;45:675-682.

Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, Koeppe RA, Stohler CS, Goldman D. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. Science 2003;299:1240-1243.