

Department of Odontology, 2026

Chronic Pain Across Time and Generations:

A Longitudinal and Family Perspective

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ISBN: 978-91-8070-998-9 (print)
ISBN: 978-91-8070-999-6 (pdf)
ISSN: 0345-7532
Umeå University odontological dissertations no. 154
Illustrations: Marlene Lahti, Inhousebyrå Umeå University
Electronic version available at: <http://umu.diva-portal.org/>
Printed by: Scandinavian Print Group, Hågersten, 2026

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Abstract

Background

Pain is a complex and personal experience influenced by biological, psychological and social factors. Pain persisting beyond physical tissue healing is defined as chronic pain. Chronic pain is common among adults and has substantial consequences for both individuals and society. Although biological factors in relation to pain development have been widely studied, social and lifestyle factors have been given far less attention, particularly in longitudinal perspectives. Temporomandibular disorders (TMD) and widespread pain (WSP) represent two chronic pain conditions, both with substantial impact on the lives of those affected. Therefore, this thesis aims to improve our understanding of pain variation over time and generations, examining TMD pain and WSP in relation to gender, lifestyle, mental and physical well-being, and generational factors.

Methods

This thesis includes four studies. Studies I, II, and III utilized longitudinal data on TMD, collected during repeated dental visits at the individual level between 2010 to 2017. For studies II and III, the TMD data were linked to health survey data, independently collected at a health intervention. Studies I and III explored the onset and remission of TMD states and the associations with gender, physical and mental well-being, and sick leave. Study II explored associations between TMD and lifestyle factors and sick leave. Study IV utilized cross-sectional data from three databases. Together, these databases cover three generations, consisting of parents, children, and grandchildren, randomly sampled from the general population. The association between WSP and parental history of sick leave was explored among children and grandchildren.

Results

In Study I, women had higher rates of onset of all three symptomatic TMD states: TMD pain only, functional limitations only, and TMD pain and functional limitations. Moreover, women had a lower rate of remission from TMD pain. Study II showed that TMD was associated with increased sick leave and with lower health-related quality of life. Study III showed that better mental and physical well-being were associated with higher rates of TMD-pain remission, whereas sick leave was associated with lower rates. Better mental and physical well-being were associated with lower rates of TMD-pain onset, whereas sick leave was associated with higher rates. In Study IV, sick leave due to neck and shoulder pain in the parental generation was significantly associated with WSP in both subsequent generations.

Conclusions

The finding that not only was TMD pain more prevalent in women, but also that women had a worse TMD-pain prognosis than did men, highlights the importance of considering gender aspects in chronic pain assessment and management. The association between TMD pain and sick leave indicates a substantial burden for both individuals and society, whereas the role of mental and physical well-being in pain remission supports a holistic approach to care. In addition, the association between pain-related sick leave in an earlier generation and WSP in later generations suggests that WSP may be linked within families. Taken together, these findings attest to the burden of chronic pain beyond the purely biological and individual perspectives.

Abbreviations

3Q/TMD – three validated screening questions for temporomandibular disorders

CI – confidence interval

COPC – Chronic Overlapping Pain Conditions

DC/TMD – Diagnostic Criteria for Temporomandibular Disorders

HR – hazard ratio

HRQoL – health related quality of life

IASP – International Association for the Study of Pain

MCS – Mental Component Summary

MDC – Malmö Diet and Cancer Study

MNS – Malmö Neck and Shoulder Study

MOPS – Malmö Offspring Pain Study

MOS – Malmö Offspring Study

NICE – National Institute for Health and Care Excellence

PDHS – Public Dental Health Service

PCS – Physical Component Summary

SF-36 – Short Form 36 Health Survey

TMD – temporomandibular disorders

VIP – Västerbotten Intervention Programme

WSP – widespread pain

Enkel sammanfattning på svenska

Bakgrund

Smärta är en komplex och personlig upplevelse som påverkas av biologiska, psykologiska och sociala faktorer. Smärta som kvarstår mer än tre månader eller längre än den förväntade läkningstiden för vävnadsskada brukar beskrivas som kronisk smärta. Kronisk smärta är vanligt bland vuxna och har stora konsekvenser både för individen och för samhället.

Den här avhandlingen undersöker två kroniska smärttillstånd: temporomandibulär smärta (TMD-smärta), och utbredd smärta. Syftet är att öka förståelsen för hur smärta varierar över tid och mellan generationer, samt hur detta relaterar till kön, livsstil, psykiskt och fysiskt välbefinnande, sjukskrivning och familjerelaterade faktorer.

Metod

Avhandlingen består av fyra delarbeten. I tre av dessa delarbeten användes upprepade data på TMD-smärta från tandvårdsbesök mellan 2010 och 2017. I två av dessa delarbeten kopplades TMD-data till hälsodata från hälsoundersökningar. Dessa delarbeten undersökte insjuknande och tillfrisknande i TMD-smärta, samt samband mellan kön, välbefinnande, livsstilsfaktorer och sjukskrivning. Det fjärde delarbetet använde data från tre databaser som tillsammans omfattade tre generationer: föräldrar, barn och barnbarn. Där undersöktes om utbredd smärta i senare generationer hade samband med tidigare generationers smärta och sjukskrivning.

Resultat

Kvinnor rapporterade i högre grad insjuknande i TMD-smärta och lägre grad av tillfrisknande jämfört med män. Individer med bättre psykiskt och fysiskt välbefinnande rapporterade lägre grad av insjuknande i TMD-smärta och högre grad av tillfrisknande från TMD-smärta. För sjukskrivning var sambandet det motsatta, det vill säga högre grad av insjuknande och lägre grad av tillfrisknande. Dessutom fanns ett samband mellan TMD-smärta och mer sjukskrivning samt mellan TMD-smärta och lägre livskvalitet. I generationsstudien sågs ett samband mellan sjukskrivning på grund av nack- och skuldersmärta i föräldragenerationen och utbredd smärta i de två efterföljande generationerna.

Slutsats

Sammanfattningsvis visar avhandlingen att TMD-smärta inte bara är vanligare bland kvinnor utan att kvinnor också verkar ha en sämre prognos jämfört med män. Resultaten belyser dessutom betydelsen av psykiskt och fysiskt välbefinnande, sjukskrivning och sociala eller familjerelaterade faktorer som viktiga i relation till smärta.

Sammantaget understryker avhandlingen att kronisk smärta behöver betraktas och värderas i ett bredare perspektiv, där biologiska, individuella, sociala och familjerelaterade faktorer vägs in. I det perspektivet bör bredare sociala faktorer, såsom levnadsförhållanden inklusive familjeförhållanden, beaktas i framtida studier.

List of original paper

This thesis is based on the four original papers listed below.

- I.** Lövgren A, Vallin S, Häggman-Henrikson B, Kapos FP, Peck CC, Visscher CM, et al. Women are worse off in developing and recovering from temporomandibular disorder symptoms. *Scientific Reports*. 2025;15(1):4732.
- II.** Vallin S, Liv P, Häggman-Henrikson B, Visscher CM, Lobbezoo F, Lövgren A. Temporomandibular disorder pain is associated with increased sick leave and reduced health related quality of life. *Eur J Pain*. 2024;28(10):1827-40.
- III.** Vallin S, Liv P, Häggman-Henrikson B, Visscher CM, Lobbezoo F, Lövgren A. Mental well-being is associated with temporomandibular disorder pain onset and remission. Submitted.
- IV.** Stanisic N, Vallin S, Sharma S, Nilsson PM, Östergren PO, Liv P, et al. Painful Relations – The echoes of pain-related sick leaves in next generations. Manuscript in preparation.

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Introduction

As pain is inherently unpleasant, we naturally seek to avoid it, yet the ability to feel pain is imperative for our survival. Pain is supposed to direct attention to a threatened area, and as such it is an important part of our protective system keeping us safe from potential or ongoing harm. However, for some individuals, the pain persists after the threat has been removed and the tissue has healed; this is referred to as chronic pain.

Understanding of pain

Nociception refers to the physiological process of encoding potentially tissue-damaging stimuli via nociceptors (1). However, the pain experience is not shaped by nociception alone. The pain experience is shaped by how the nociceptive stimuli are interpreted and integrated with cognitive, social, and contextual factors (2-4).

Nociceptive signalling may influence the affective system, which in turn may spark negative emotions such as fear, anxiety, sadness, and shame (5). These emotional factors along with cognitive factors such as catastrophic thinking, self-criticism, and prior experiences can amplify the emotional response and thereby influence the pain experience.

The perception and reporting of pain is therefore a complex and personal experience that includes several components, such as physical, biological, psychological, and social dimensions. This multidimensional nature is reflected in the current definition of pain of the International Association for the Study of Pain (IASP): “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” (6).

This definition emphasizes that pain is not just a physical response to biological damage but also a personal and emotional experience.

This understanding is reflected in the biopsychosocial model (Figure 1), commonly used to understand pain development and maintenance. Moreover, this model also provides a framework for the assessment and prognosis of pain (7). The model is based on the understanding that pain develops and is maintained through a process in which biological factors interact with psychological, social, and contextual factors to shape the pain experience (2, 3).

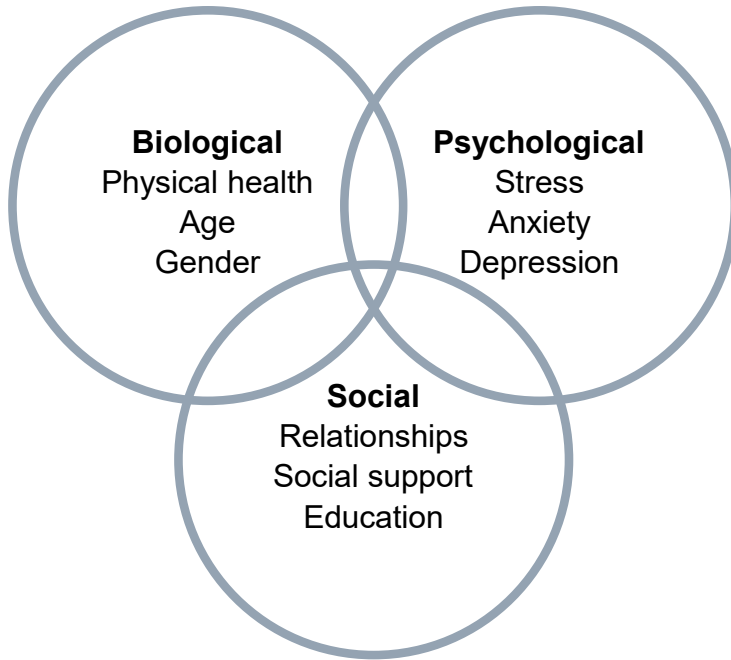


Figure 1. The biopsychosocial model of pain, illustrating biological, psychological, and social factors involved in the development and maintenance of pain.

Types of pain

Pain can be classified in different ways depending on its mechanisms and duration.

In terms of mechanisms, pain can be classified as nociceptive, neuropathic, and nociplastic. Nociceptive pain refers to pain that is caused by the activation of nociceptors because of actual or threatened tissue damage (6). Neuropathic pain arises from a lesion or disease of the somatosensory nervous system (6). This type of pain can, for example, be observed in individuals with nerve injury, herpes zoster, or autoimmune diseases such as multiple sclerosis (6, 8). In contrast, nociplastic pain refers to pain arising from altered pain nociception and persistent pain without evidence of any tissue damage. Nociplastic pain is an umbrella term, initially proposed by the international research community in 2017 (6, 9), that has since been accepted by the IASP. The mechanism of nociplastic pain is different from those of nociceptive pain and neuropathic pain (9, 10). However, this mechanism is not entirely understood, although it is thought to involve altered pain processing within the central nervous system, including both central excitability and decreased central inhibition (9-11). Symptoms of nociplastic pain often include generalized or widespread pain and may also be accompanied with other non-painful symptoms such as cognitive problems, sleep disturbances, and fatigue. In addition, increased sensitivity to both painful and non-painful stimuli may also occur. Altogether, this supports the view that nociplastic pain likely reflects altered pain processing rather than ongoing nerve or tissue damage (10).

In terms of duration, pain can be described as acute or chronic in nature. In contrast to acute pain, which commonly reflects nociception, chronic pain, with a duration of three or more months after tissue healing, may

become a pathological condition in its own right (9, 12). Chronic pain is often associated with profound emotional distress, functional disability, or both, and cannot be better explained by another condition (13).

The most common chronic pain locations are reported to be the back and neck, followed by the orofacial area (14). However, in individuals with more generalized pain conditions caused by nociplastic pain, there is often a lack of correlation between the pain location and any actual tissue damage. Many chronic musculoskeletal pain conditions, such as fibromyalgia, may have nociplastic components (10).

Chronic pain

Approximately 20% of the world's population report some kind of chronic pain (14-16). The prevalence of chronic pain is higher in women than men (16-18). In addition, higher prevalence has also been observed among older individuals and those with lower socioeconomic status (19, 20). Moreover, there is evidence that the prevalence of pain is increasing over time (21-23), although the reason for this increase is unknown.

Chronic pain often has a profound impact on the lives of those affected and is associated with lower quality of life (14, 24, 25). Chronic pain is also associated with psychological comorbidities, such as depression, stress, and anxiety (26). In addition, sleep disturbance is common in individuals with chronic pain (27, 28). There is evidence suggesting that chronic pain has a familial component, as studies have shown that chronic pain in parents is associated with chronic pain in their children (29-31). However, the mechanism for this link is currently poorly understood.

The impact of pain extends beyond individual suffering, driving both substantial healthcare costs and productivity loss (32, 33). Consistent

with this, pain is among the most common reasons for adults to seek health care (34-36). Chronic pain often reduces work ability and is associated with increased sick leave (37-39), potentially constituting a burden extending beyond the individual level to encompass the family and societal levels as well.

Chronic pain is often accompanied by a fear of movement (kinesiophobia) or catastrophizing. This in turn can lead to avoidance of activities or movements that are perceived as likely to provoke pain or to an exaggerated negative interpretation of pain and its consequences, which may contribute to the maintenance of symptoms of pain and add to the overall pain disability (40).

To enable evidence-based medicine in line with the biopsychosocial model of pain and to ensure a holistic approach, a combination of different treatment modalities, provided by interdisciplinary teams or multiprofessional settings, is often recommended for chronic pain management (41). The complex nature of chronic pain assessment is reflected in the Swedish national system for knowledge-driven management (42) and in the National Institute for Health and Care Excellence (NICE) guidelines, NG193 (43), both emphasizing person-centred and multimodal approaches. In line with these guidelines, management of chronic pain primarily aims to reduce pain intensity, improve function, and support coping strategies. For some chronic pain conditions, antidepressants can provide some relief (44). However, non-pharmacological approaches are generally suggested, such as physical activity and psychological interventions that promote acceptance and coping (43, 45). In this context, there is some evidence that cognitive behavioural therapy, acceptance, and commitment therapy can lead to an increased sense of control and reduced anxiety (46, 47).

Chronic pain conditions

Widespread pain

Widespread pain (WSP) is of special interest in pain research because it affects multiple regions of the body simultaneously, and with an approximate prevalence of 10%, a substantial proportion of people is affected (48). Although reduced quality of life and functional limitations are not unique to WSP, these consequences may be particularly pronounced when the pain affects multiple regions simultaneously (49).

WSP is typically assessed using self-reported pain locations during anamnesis, commonly using standardized paper-based body manikins or pain drawings (50, 51). Several approaches to defining WSP have been proposed over the years. Most commonly, WSP is assessed based on either pain in multiple body regions or a specific number of pain sites (50). One commonly used measure is the Widespread Pain Index, a count-based measure encompassing 19 body areas and scored from 0 to 19 (50, 52, 53). The index is included in the diagnostic criteria for fibromyalgia and can also be used to research WSP (54).

WSP is associated with several comorbidities, such as irritable bowel syndrome, migraines, back pain, and temporomandibular disorders (TMD) (55). This pattern suggests that WSP may reflect a broader pain condition instead of an isolated pain condition. This interpretation is further supported by the overlap between WSP and fibromyalgia, with many individuals with WSP also fulfilling the criteria for fibromyalgia (56). This highlights that central processes in the nervous system can lead to multiple manifestations of chronic pain, with disrupted pain modulation being the common denominator of all these conditions.

This pattern of overlapping pain conditions has given rise to the concept of Chronic Overlapping Pain Conditions (COPC), with TMD being one of several conditions without an established single pathophysiology that often appear together with WSP (55). Moreover, it has been recently shown that even in a general population sample with TMD pain, there was a large overlap with WSP (57).

Temporomandibular disorders

The most common reason for acute pain in the orofacial area is toothache, whereas chronic orofacial pain is commonly related to temporomandibular disorders (TMD). TMD is the umbrella term used to describe pain and disorders of the jaw muscles, the temporomandibular joint, and associated structures. The aetiology of TMD is multifactorial, and several factors are likely to increase susceptibility, trigger onset, and contribute to chronification (58-60). As with other chronic pain conditions, TMD is best understood within a biopsychosocial framework (61) and its pathophysiology is not fully understood. However, TMD is not always painful: TMD also encompasses non-painful functional limitations, such as restricted jaw movement and joint noises. TMD is broadly grouped into painful TMD, including myalgia, arthralgia, and headache attributed to TMD, and intraarticular conditions, including disc displacement with reduction, disc displacement without reduction, and degenerative joint disease (62).

TMD is often described as a condition that fluctuates over time, although this view is supported by only a limited number of longitudinal studies (63, 64). As a result, there is little information about how TMD develops over time. At the individual level, TMD onset and remission can vary considerably among individuals. The focus in this thesis is mainly on the painful aspect, referred to as TMD pain.

Few studies have reported the incidence of TMD pain; however, the Orofacial Pain Prospective Evaluation and Risk Assessment cohort (age 18–44 years) reported an incidence of TMD pain of 3.9% (65). Approximately 10% of the adult population is affected by TMD (66). The prevalence is higher in working ages and is more common in women than men (67). TMD is also associated with numerous psychological comorbidities, such as anxiety, poor sleep quality, and depression (68). Because of these frequent comorbidities in addition to interference with daily functions such as chewing and talking, TMD is associated with reduced quality of life (69). As mentioned previously, TMD is related to COPC, meaning that TMD often coexists with other chronic pain conditions such as primary headaches, fibromyalgia, and irritable bowel syndrome (55). Studies aiming to identify factors associated with the transition from acute TMD pain to a more chronic condition have been published. However, these studies often have a limited sample size with relatively short follow-up periods, which is reflected in the studies included in the critical review by Sabsoob et al. (70). Additionally, despite the burden of TMD pain at the individual level, population-based studies of the associations between TMD pain and lifestyle factors remain limited. Finally, a previous Swedish register-based study found that individuals with TMD are more dependent on sickness benefits and disability pension (71). However, little is known about how sick leave relates to the course of TMD pain over time.

To screen for possible TMD, three validated questions were introduced in 2010 in large parts of the Swedish Public Dental Health Service (PDHS). Since their implementation, these screening questions (3Q/TMD) have been validated (72). The three questions are designed to identify individuals who may require a more comprehensive clinical TMD examination. The questions are phrased as follows:

Q1: Do you have pain in the temple, jaw, or jaw joint once a week or more?

Q2: Do you have pain when you open your mouth or chew, once a week or more?

Q3: Does your jaw lock, or become stuck, once a week or more?

The first two questions show high sensitivity and specificity for identifying individuals with TMD pain (72), whereas the third question is useful for ruling out functional jaw limitations (72, 73).

TMD is diagnosed using the Diagnostic Criteria for TMD (DC/TMD), which is a standardized instrument for the clinical examination and classification of TMD. It was first published in 2014 and developed from an earlier instrument, the Research Diagnostic Criteria for TMD (62). The DC/TMD instrument retains the dual-axis approach, incorporating a physical assessment (Axis I) and psychosocial status (Axis II).

Rationale

The associations with chronic pain conditions have been well studied (26, 74). Despite current knowledge of the necessity of a biopsychosocial perspective in pain assessment, most studies still focus on the biological and, to a lesser extent, the psychological factors. In contrast, studies of social and lifestyle factors in relation to pain development are especially rare. As early identification and early intervention are regarded as key to improving the long-term prognosis, it is important to identify factors contributing to chronic pain (75). This type of understanding needs to consider the individual's lifestyle as well as social, biological, and psychological factors. In addition, large study samples are needed to allow stratifications and to enable the study of interactions between these factors.

Finally, few studies have explored pain onset and remission in relation to lifestyle and social factors. Even fewer studies have explored the interplay between pain and social factors across generations.

Taken together, there are several identified knowledge gaps concerning pain development. This thesis accordingly deepens our knowledge by exploring lifestyle, social, biological, and psychological factors. Identifying factors associated with chronic pain may improve our understanding of the underlying mechanisms and help inform preventative strategies.

Objective

Overall aim

The overall aim of this thesis is to improve our understanding of pain variations by exploring how lifestyle and biopsychosocial factors relate to pain, including its onset and remission.

Specific aims

- Study I** To explore variations over time in TMD symptoms, including possible gender and age differences

- Study II** To estimate TMD prevalence and evaluate the association between TMD and lifestyle factors, sick leave, and health-related quality of life

- Study III** To assess whether a history of sick leave and health-related quality of life, respectively, are associated with TMD-pain onset and remission

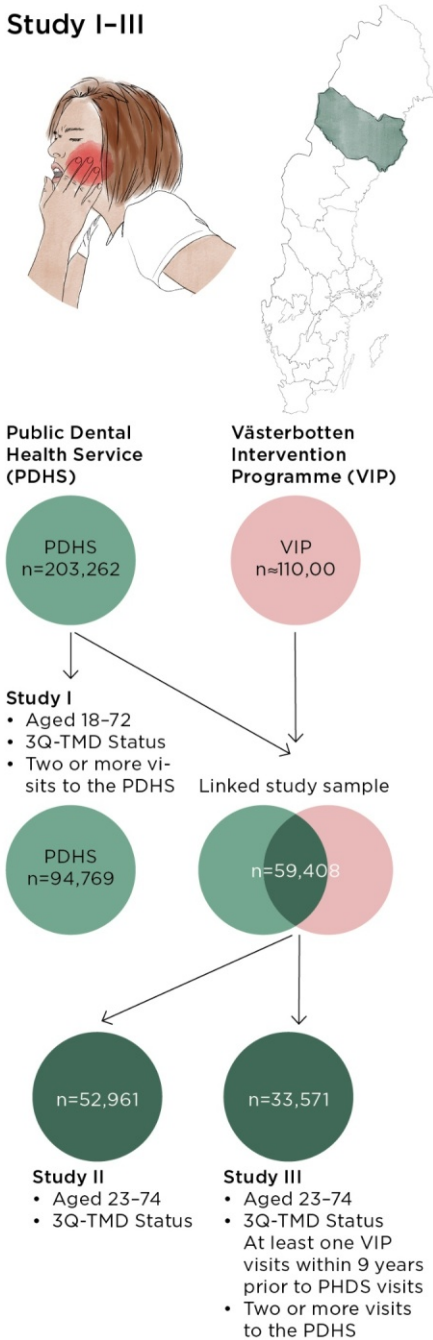
- Study IV** To explore whether substantial sick leave within a parental generation is associated with widespread pain in first- and second-generation offspring

Overview

Table 1: Overview of studies I–IV.

	Study I	Study II	Study III	Study IV
Aim	Variations over time in TMD symptoms	TMD prevalence and association with lifestyle, sick leave, and health-related quality of life	Sick leave and health-related quality of life, TMD-pain onset, and TMD-pain remission	Sick leave in parents and widespread pain in the first and second generations
Design	Cohort	Cohort	Cohort	Cross-sectional
Participants	Individuals from the Public Dental Health Service in the Region of Västerbotten, 2010–2017	Individuals from the Public Dental Health Service in the Region of Västerbotten, 2010–2017, linked to health survey data from VIP	Individuals from the Public Dental Health Service in the Region of Västerbotten, 2010–2017, linked to health survey data from VIP	Individuals in Malmö Neck and Shoulder with least one child or grandchild in Malmö Offspring Study and Malmö Offspring Pain Study
Data	- 3Q/TMD - Age - Gender	- 3Q/TMD - Age - Gender - SF-36 - Sick leave - Physical activity - Education	- 3Q/TMD - Age - Gender - SF-36 - Sick leave - Physical activity - Education	- Pain drawings - Age - Gender - GHQ-30 - PSS-4 - Sick leave (only parents)
Methods	- Markov multi-state model	- Poisson regression - Inverse probability weighting	- Markov multi-state model	- Poisson regression

Study I-III



Study IV

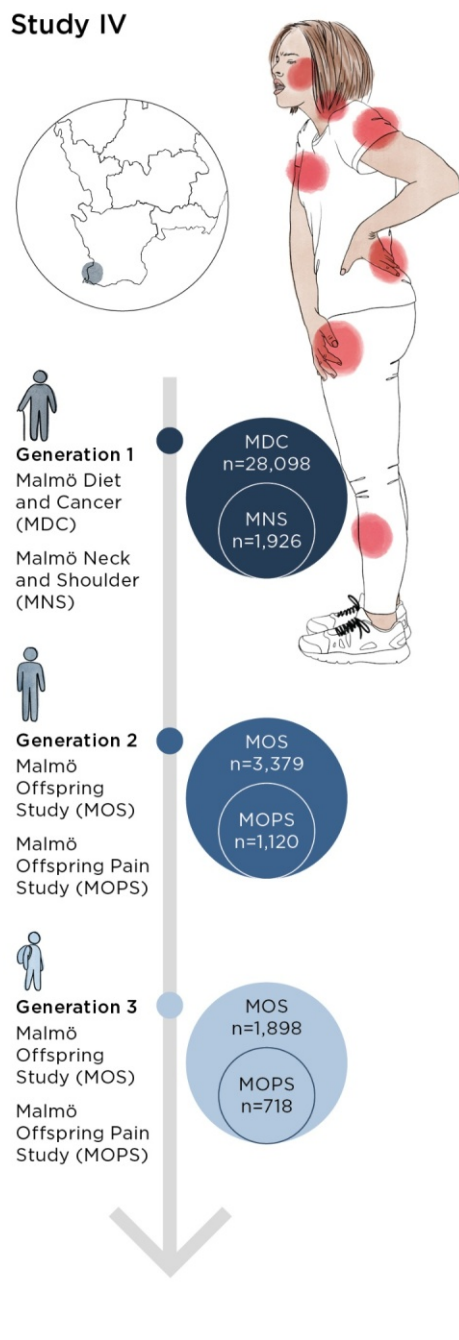


Figure 2. Data flowchart illustrates the data used in the included studies

Methods

This project uses data from multiple sources. All included studies are observational and employ cross-sectional or cohort designs. Studies I–III use longitudinal data from Västerbotten County, Sweden, while Study IV uses cross-sectional, multigenerational data from Malmö, in southern Sweden (Figure 2). An overview of the studies, including their aims, study samples, designs, and methods, is provided in Table 1.

All studies were granted ethical approval: studies I–III (approval nos. 2018-393-31 and 2018-1818-32M) and Study IV (approval no. 2019-02887). Individuals participating in the Västerbotten Intervention Programme gave their consent for their information to be used for research. For Public Dental Health Service data, approval was granted by the Swedish Ethical Review Authority to analyse the data without obtaining individual consent, as this was considered infeasible considering the large number of individuals involved. All individuals participating in Study IV agreed to participate.

Study population

Studies of TMD (studies I–III)

Studies I–III all utilized data on TMD obtained from the Public Dental Health Service (PDHS) in Västerbotten for the 2010–2017 period. As part of routine dental check-ups, typically performed bi-annually, patients were asked the three previously described mandatory screening questions (3Q/TMD). Throughout this thesis research, TMD status was defined based on responses to these questions. In total, 192,253 individuals with Swedish social security numbers provided answers to the 3Q/TMD questions during 567,989 visits to the PDHS. The inclusion criteria for each individual study and use of the data sources are shown in Figure 2.

For studies II and III, PDHS data were linked to health survey data from the Västerbotten Intervention Programme (VIP). The VIP is a community intervention programme with the aim of reducing morbidity and mortality from cardiovascular disease and diabetes (76). The programme was launched in 1985 in the small municipality of Norsjö in inland Västerbotten and has since been implemented across all municipalities in the county. By 2018 (the year of data extraction for the present studies), approximately 110,000 individuals had participated. The programme is currently integrated into the primary care routine, and participants are invited for a health screening at the ages of 40, 50, and 60 years. Historically, individuals aged 20–30 years have occasionally been invited, resulting in a limited number of individuals younger than 40 years being included in the VIP. In addition to a health screening, participants were asked to report on medical conditions, social situation, lifestyle, and self-perceived health by completing a questionnaire.

Study I

Individuals were included if they were 18–72 years of age and had undergone at least two routine dental checkups at the PDHS with complete answers to the 3Q/TMD questions. Information on sex and age was extracted from PDHS records. In total, 94,769 individuals were included, contributing 400,260 person-years.

Study II

All individuals with recorded answers to the 3Q/TMD questions and making at least one visit to the VIP between 1985 and 2017 were included, provided they were 15–74 years of age. The age range was chosen to match that of the Swedish working-age population (77). However, no individuals younger than 23 years old were included in the final study sample. In total, 52,961 individuals were included.

Study III

All individuals included in Study II were also included in Study III, provided they had undergone at least two routine dental checkups with complete answers to the 3Q/TMD questions and had made at least one VIP visit within nine years prior to their PDHS visits. If an individual made multiple visits to the VIP during follow-up, information from the most recent such visit prior to the PDHS visit was included.

Study of widespread pain (Study IV)

Study IV utilized cross-sectional data from three databases: the Malmö Neck and Shoulder Study (MNS), Malmö Offspring Study (MOS), and Malmö Offspring Pain Study (MOPS) databases. Together, these databases cover three generations, consisting of parents, children, and grandchildren.

Data for generation 1 (parents) were extracted from the database of MNS, which includes participants from Malmö born between 1926 and

1945. These were all originally participants in a larger study, the Malmö Diet and Cancer Study (78), randomly sampled from the general population in Malmö. The cohort consists of all participants who completed the baseline examination in the Malmö Diet and Cancer Study between February 1992 and December 1994, completed a follow-up examination one year later, and answered both the baseline and follow-up questions on pain. Of the total of 14,556 invited individuals, 12,607 (87%) participated in MNS.

For generations 2 (children) and 3 (grandchildren), data were collected in 2013 through the Malmö Offspring Study, exploring family patterns linked to conditions such as cardiovascular disease and diabetes (79). Generations 2 and 3 were the descendants of generation-1 participants, forming a multigenerational dataset. In total 5,148 individuals from generations 2 and 3 participated.

In the Malmö Offspring Study (MOPS), participants were re-invited to complete additional questionnaires between 2019 and 2020. Of the 5,148 individuals who participated in the original Malmö Offspring Study, 2,506 (49%) participated in MOPS. Generation 2 comprised 1,572 individuals born between 1955 and 1971, and generation 3 comprised 936 individuals born between 1980 and 1996. This cohort is described in more details in a previous study (80).

In Study, IV the MNS cohort was linked to MOPS to create a multigenerational study sample. The study sample yielded information on 1,926 individuals that can be linked from generations 1 and 2 and/or generation 3 (Figure 2). Among these, 1,120 individuals belonged to generation 2 and 718 to generation 3. Two individuals were included in both generations, as they were both children and grandchildren of individuals in generation 1.

Variable definitions

Variables from PDHS (studies I–III)

TMD – an affirmative answer to any of the 3Q/TMD questions

TMD pain – an affirmative answer to at least one of the two questions on pain (Q1 or Q2)

Functional limitations – an affirmative answer to the third question (Q3)

Functional limitations with pain – an affirmative answer to at least one of Q1 or Q2 in combination with an affirmative answer to Q3

Age – age at the time of each dental check-up (age at PDHS visit)

Gender – derived from the Swedish social security number

Calendar year – defined as year of dental check-up (year of PDHS visit)

Onset – any transition from no pain to TMD pain

Remission – any transition from TMD pain to no pain

Variables from VIP (studies II and III)

Education – defined as university education or no university education/no information

Physical activity – self-reported physical activity was determined using the Cambridge Index (81). The four original categories (inactive, moderately inactive, moderately active, and active) were dichotomized to inactive (sedentary job and no physical recreational activity) and active.

Sick leave – self-reported prolonged sick leave, defined as sick leave lasting six months or more

Place of residence – defined as the location of the healthcare provider, i.e., where the VIP examination was conducted

Marital status – categorized as living alone, living alone with child, living with partner, or other

Smoking status – categorized as smoker, former smoker, non-smoker, or no information

BMI – defined as weight in kilograms divided by the square of height in metres

Health-related quality of life – measured by the Standard Swedish Version (1.0) of the Short Form 36 Health Survey Questionnaire (SF-36) (82)

The SF-36 is an instrument that assesses health-related quality of life (HRQoL), addressing the perceived impact of disability or illnesses on physical and mental capacity (83-85). SF-36 is widely used in medical research to assess patient-reported HRQoL and can be used to identify

differences in health status among groups and over time (85). The instrument, in its shortened version, the 12-Item Short Form (SF-12), has also been used to estimate disability weights for the Global Burden of Disease study (86). SF-36 consists of 36 questions related to physical and psychological health. The questions cover the following eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. The score for each domain is summed and transformed into a 0–100 scale, where 100 represents the best possible health and 0 the worst (82). SF-36 also features two summary scores, i.e., the Physical Component Summary (PCS) and Mental Component Summary (MCS), which aggregate information from the eight domains to provide an overall representation of physical and mental well-being (Figure 3).

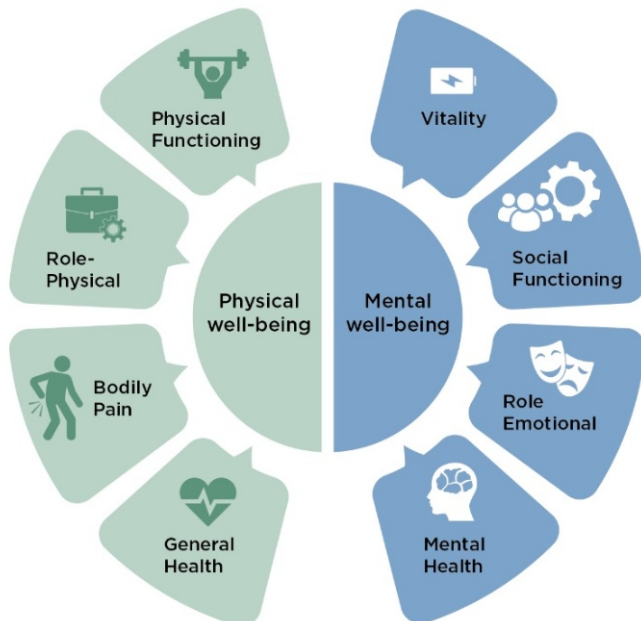


Figure 3. Conceptual illustration of the relationships between the eight domains of SF-36 and the summary scores physical well-being and mental well-being.

The summary scores are derived by weighting and summing the domain scores (87). The weights are calculated with factor analysis designed to separate physical and mental components. The weights are based on normative data. PCS is mainly made up of physical functioning, role physical, bodily pain, and general health, and MCS is mainly made up of vitality, social functioning, role emotional, and mental health (87). However, there is overlap and, in particular, general health, vitality, and social functioning correlate with both summary scores (88). The summary scores are standardized to have a mean of 50 and a standard deviation of 10 (87). In Study III, PCS and MCS are used to measure physical well-being and mental well-being, respectively. The SF-36 questionnaire was introduced in the VIP in 2003 (76), and thus is not available for the whole study sample.

Variables from MNS and MOPS (Study IV)

Widespread pain (WSP) is determined by calculating the cumulative number of painful body areas marked on standardized pain manikins. In generation 1, the manikin comprised 16 areas, whereas in generations 2 and 3, it comprised 13 areas. To ensure comparability across the three generations, the scoring was harmonized to align with validated criteria (80, 89), making the maximum score 14 (Figure 4). A score of six or more was defined as WSP.

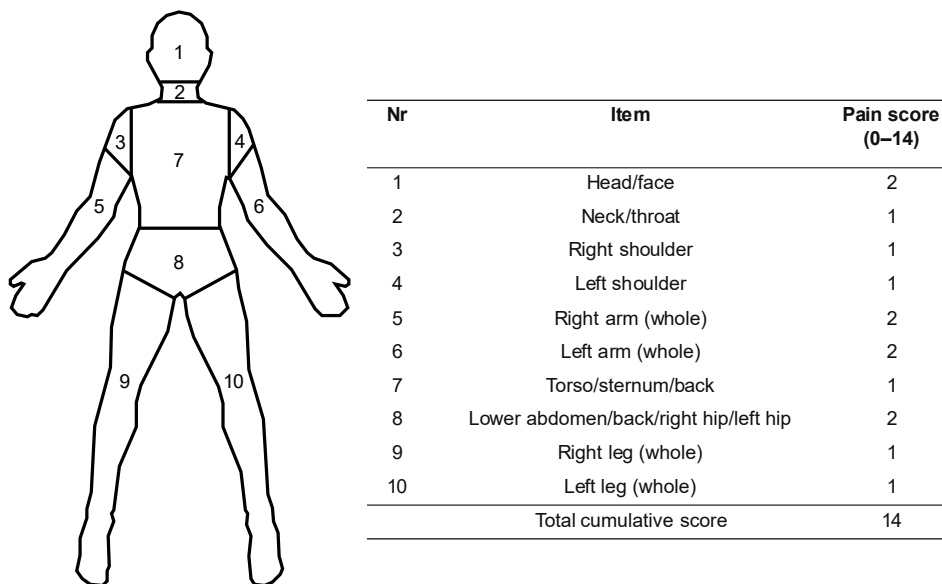


Figure 4. The standardized pain manikin used for reporting widespread pain is shown on the left and the scoring matrix is shown on the right.

Substantial sick leave (only generation 1) – Sick leave data were available only in the MNS database and were therefore available only for generation 1. Participants reported pain-related sick leave during the previous year for neck, shoulder, or back problems. The following answers were possible: “Have not experienced problems in the region”, “No, not been on sick leave”, “Yes, 1–7 days”, “Yes, 8–30 days”, “Yes, 31–90 days”, and “Yes, more than 90 days”. “Substantial sick leave” was defined as sick leave longer than seven days, as follows: “Yes, 8–30 days”, “Yes, 31–90 days”, and “Yes, more than 90 days”. All other answers were classified as no substantial sick leave.

Age – age at data collection for each generation, defined as the age at which the questionnaire was completed

Statistical methods

Markov multi-state model (studies I and III)

A Markov multi-state model is used to analyse stochastic processes in which an individual can move between different states over time. A key assumption is the Markov property, i.e., that the transition to a new state depends only on the current state and not on previous states.

In Study I, multi-state models with calendar year as the continuous time scale were used to analyse the association between gender and transitions between the four states: “no TMD”, “TMD pain”, “functional limitations”, and “functional limitations with pain” (Figure 5).

Individuals were considered to be at risk of transitioning between states from the first observed visit to the PDHS until the last observed visit. It was assumed that individuals remained in the same state until a new state was observed (i.e., individuals could only change state at PDHS visits, so the transition times were treated as exactly observed).

For Study III, three separate multi-state models were fitted to assess associations among the explanatory variables, i.e., sick leave, mental well-being, and physical well-being, and transitions between TMD pain and no pain (Figure 5). As TMD pain status was observed only at PDHS visits, the exact times of transitions were unknown. To handle this, transition times were interval censored between visits. Therefore, a multi-state model with calendar year as the continuous time scale for panel data was used (i.e., intermittently observed). Individuals were considered to be at risk of transitioning between states from the first observed visit to the PDHS until the last observed visit. Each model was adjusted for age at PDHS visit, time between VIP visit and PDHS visits, and gender. To account for a non-linear relationship, age was modelled using restricted cubic splines. Additionally, models that were not

stratified by gender were adjusted for gender. For sick leave, the hazard ratios (HRs) compare transition rates between the individuals reporting sick leave and those not reporting sick leave. An HR >1 indicates a higher transitioning rate among individuals reporting sick leave. For physical and mental well-being, the HR represents the multiplicative change in rate per 10-unit increase.

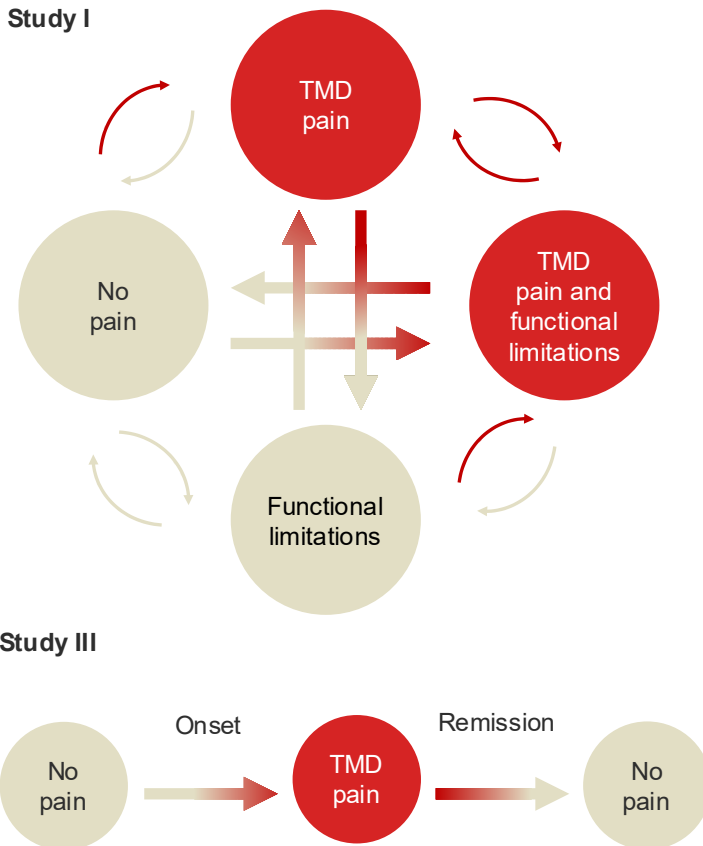


Figure 5. States and possible transitions used in the Markov multi-state models in studies I and III. Study I included four states, whereas Study III included the onset and remission of pain, i.e., the transition between no pain and TMD pain. Painful states are indicated in red.

Inverse probability weighting (Study II)

Inverse probability weighting is a method commonly used to adjust for imbalances in observational data, especially when there is a risk of selection bias. The basic idea of inverse probability weighting is to assign more weight to observations from underrepresented groups, based on their propensity to belong to a particular group. This is done, for each observation, by estimating the propensity to belong to a particular group. The weights are then calculated as the inverse of the estimated propensity score from each observation.

In Study II, inverse probability weighting was used to weight the observed annual prevalences of TMD, TMD pain, and functional jaw limitations by accounting for differences in the propensity to visit the PDHS across different community subgroups. Propensity scores were estimated using a logistic regression model with “PDHS visit/no visit” as the dependent variable, and gender, place of residence, marital status, age, BMI, smoking status, education, and TMD at any time as the independent variables. To account for a non-linear relationship, age and BMI were modelled using restricted cubic splines. Since there is no straightforward way to derive confidence intervals for the weighted annual prevalences, confidence intervals were estimated using non-parametric bootstrapping with 2000 replicates.

Poisson regression (studies II and IV)

Poisson regression is a type of generalized linear model used for modelling count data, with the assumption that the dependent variable follows a Poisson distribution. Specifically, Poisson regression assumes that the logarithm of the expected value can be expressed as linear combinations of the independent variables. When applying robust

covariance matrix estimation to binary outcomes, Poisson regression estimates the relative risk or the prevalence ratio (90).

In Study II, adjusted period prevalence ratios for TMD, TMD pain, and functional jaw limitations were estimated using Poisson regression with robust covariance matrix estimation, with sick leave, place of residence, marital status, smoking, snuff use, and physical activity included as explanatory variables. The regression models were adjusted for age using restricted cubical splines. Poisson regression was also used to assess the association between TMD, TMD pain, and functional jaw limitations, respectively, and HRQoL.

In Study IV, Poisson regression with robust covariance matrix estimation was used to estimate the adjusted risk ratio of WSP in generations 2 and 3, respectively, across substantial sick leave due to pain and WSP in generation 1.

Adjustment for misclassification bias (Study IV)

Because most participants in generations 2 and 3 had data from only one participating ancestor, the independent variables were derived using information from one ancestor. Consequently, some individuals classified as having no ancestors with WSP or pain-related sick leave may in fact have had an affected non-participating ancestor. This may lead to false negative misclassification, introducing bias.

A correction was applied to account for such misclassification. The correction assumed non-differential misclassification, i.e., that misclassification was equal among individuals with and without WSP or pain-related sick leave, and that pain-related sick leave occurred independently between spouses in the ancestral generation. Moreover, assuming no false positives, the specificity was set to 1, meaning that no

pain-free individuals were misclassified as having pain. The sensitivity of the classification was estimated as the ratio between the observed prevalence of exposure and the expected true prevalence, based on the probability that at least one ancestor was affected. These parameters were then used to construct a 2×2 table adjusted for misclassification from which corrected relative risks were calculated. The 95% confidence intervals (95% CIs) were then calculated with 3000 non-parametric bootstrap replicates.

Results

Study I

The analysis included 94,769 individuals, with a mean age at first visit of 37 years, contributing 400,150 person-years of follow-up. Men and women made a similar number of PDHS visits on average, and most individuals made two to four visits during the study period. The TMD pain prevalence was 9% during the study period.

Compared with men, women had worse outcomes, i.e., higher transition rates from no TMD to all other states and lower transition rates from TMD pain to no TMD.

More specifically, compared with men, women had higher transitions rates from no TMD to all other states: *TMD pain only* (hazard ratio [HR]: 2.40, 95% CI: 2.22–2.59), *functional limitations only* (HR: 1.81, 95% CI: 1.59–2.07), and *TMD pain and functional limitations* (HR: 2.80, 95% CI: 2.28–3.43). Women also had a higher rate of transition from *functional limitations only* to *TMD pain and functional limitations* (HR: 1.62, 95% CI: 1.15–2.30). Finally, women had a lower rate of transition from *TMD pain only* to *no TMD* (HR: 0.83, 95% CI: 0.75–0.91).

Study II

The study sample consisted of 52,961 individuals (50.6% women) aged 23–74 years. Most individuals made their first VIP visit at age 40 years (53.3%), followed by 50 (26.2%), 30 (10.8%), and 60 years (9.7%). The TMD pain prevalence was 7.5% during the study period, with a higher prevalence in women (12.9%) than men (5.4%). With an average

difference of 0.4% points, the weighted prevalence estimates were only slightly lower than the unweighted prevalence estimates.

Sick leave was statistically significantly associated with a higher prevalence of TMD pain, with an adjusted prevalence ratio of 2.02 (95% CI: 1.89–2.17). Additionally, in both men and women, TMD pain was negatively associated with all eight domains of HRQoL (all $p < 0.001$), meaning that it was associated with lower quality of life across all eight domains of HRQoL (all $p < 0.001$). This is illustrated in Figure 6, where the mean scores of the SF-36 domains were lower for individuals with TMD pain than those with no TMD pain.

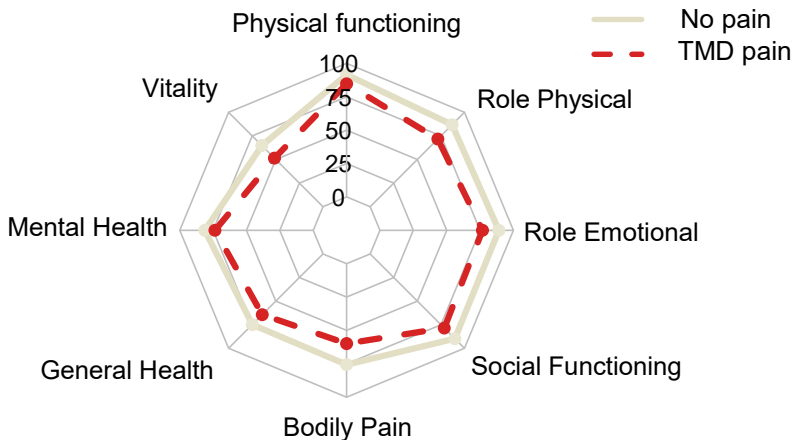


Figure 6. The mean scores of the eight SF-36 domains stratified by no TMD pain and TMD pain. The mean score for no TMD pain is displayed in beige and for TMD pain is displayed in red.

In addition, TMD pain was negatively associated with both the Physical Component Summary and Mental Component Summary (Figure 7).

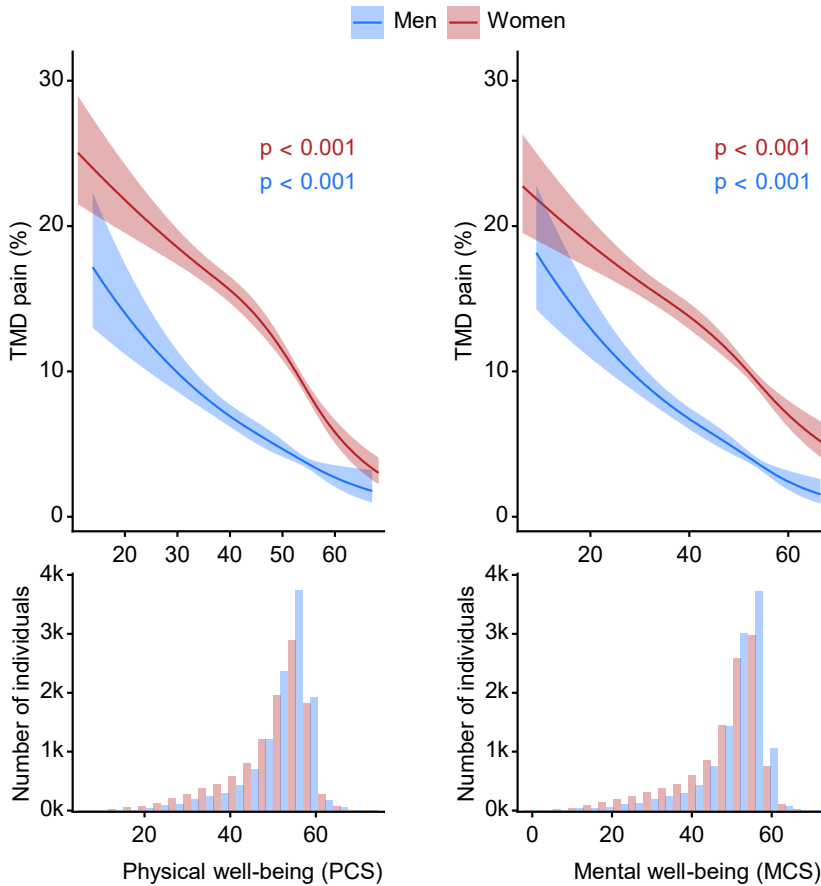


Figure 7. Association between quality of life, represented by physical well-being (PCS) and mental well-being (MCS), respectively, and prevalences of temporomandibular pain (TMD pain), as estimated with robust Poisson regression using restricted cubic splines. The upper panels show decreasing TMD pain prevalences as physical well-being and mental well-being increases. The trends are consistent for both women (red) and men (blue), with shaded areas representing 95% confidence intervals. The lower panels show the distributions of physical well-being and mental well-being scores, respectively, stratified by gender. P -values indicate the significance of the association between TMD-pain prevalence and physical well-being and mental well-being, respectively.

Study III

The study included 33,571 individuals, with a mean age of 52 years at first visit, who made a total of 109,650 PDHS visits. As in Study I, most individuals made two to four visits during the study period. At first PDHS visit (i.e., inclusion), 6.9% of women and 2.5% of men reported TMD pain.

Sick leave was associated with higher rates of TMD-pain onset (HR: 1.18, 95% CI: 1.03–1.36) and lower remission rates (HR: 0.49, 95% CI: 0.46–0.53). Better physical well-being was associated with lower rates of onset and higher rates of remission (HR per 10-unit increase: 0.90, 95% CI: 0.84–0.96; and 1.68, 95% CI: 1.62–1.75). Finally, better mental well-being was associated with lower rates of onset and higher rates of remission (HR per 10-unit increase: 0.84, 95% CI: 0.79–0.89; and 1.33, CI: 1.28–1.37).

Study IV

In total, the study sample comprised 3,852 individuals: 1,926 from generation 1, 1210 from generation 2 (children), and 718 from generation 3 (grandchildren). The proportion of women was 58% in generation 1, 54% in generation 2, and 58% in generation 3. The mean ages at questionnaire administration were 59, 56, and 31 years in generations 1, 2, and 3, respectively. Most, i.e., 1,821, included individuals had one ancestor, 102 individuals had two ancestors, and three individuals had three ancestors each. Pain was reported in a median of three sites across all generations, and women reported more sites than did men. WSP was reported by 23%, 20%, and 19% in generations 1, 2, and 3, respectively.

In generation 1, 41 individuals reported sick leave due to neck pain, 45 due to shoulder pain, and 47 due to back pain. Overlap between different

types of sick leave was common, with the greatest overlap between neck and shoulder pain, which was reported by 36 individuals (Figure 6).

Sick leave in generation 1 due to neck or shoulder pain was associated with WSP in later generations. More specifically, in generation 2, the risk ratios were 2.36 (95% CI: 1.52–3.65) for sick leave due to neck pain and 2.00 (95% CI: 1.24–3.24) for sick leave due to shoulder pain (Figure 8). The corresponding associations were also found in generation 3 (neck: 2.82, 95% CI: 1.63–4.87, and shoulder: 2.98, 95% CI: 1.81–4.92). In contrast, neither sick leave due to back pain nor WSP in generation 1 was associated with WSP in generation 2 or 3. Finally, after adjusting for misclassification bias, the results remained largely unchanged.

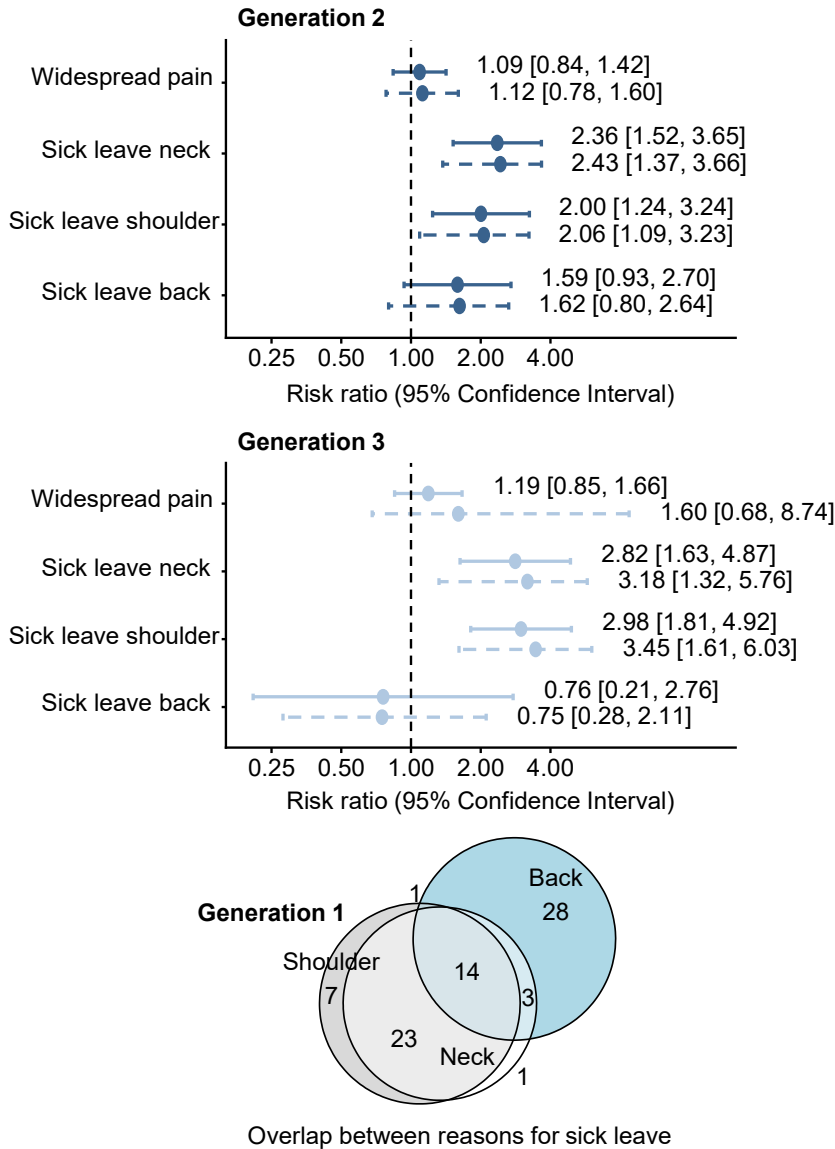


Figure 8. Risk ratios for widespread pain (WSP) in generations 2 and 3 with 95% confidence intervals (95% CIs) from the Poisson regression analysis across the following variables from generation 1: WSP, sick leave due to neck pain, sick leave due to shoulder pain, and sick leave due to back pain. Solid lines indicate uncorrected 95% CIs and dotted lines indicate 95% CIs corrected for misclassification bias. The upper panel shows generation 2 (dark blue) and the lower panel shows generation 3 (light blue). The Venn diagram at the bottom illustrates overlap among different types of sick leave, i.e., sick leave due to shoulder pain, neck pain, and back pain, in generation 1.

Discussion

In this thesis, the chronic pain conditions TMD pain and WSP were explored to provide a better understanding of pain variations over time and generations. The main finding was that women had higher onset rates of TMD pain and lower remission rates of TMD pain, indicating an overall poorer prognosis compared with men. In addition, onset and remission were associated with physical well-being and mental well-being. More specifically, individuals with better physical and mental well-being had higher rates of TMD-pain remission and lower rates of onset. In contrast, individuals with a history of prolonged sick leave had higher rates of TMD-pain onset and lower rates of remission. In the general population, TMD pain was associated with sick leave and with lower quality of life. Finally, substantial sick leave due to pain in a parental generation was associated with WSP in later generations. All in all, these findings underline the burden of pain beyond the individuals themselves.

Current knowledge of chronic pain variations and associated factors is largely based on cross-sectional studies or studies with short follow-up periods. Such studies have been important for describing the prevalence of chronic pain and its associations with physical health, mental health, and socioeconomic status. However, such designs provide limited insight into how pain varies over time and across generations.

Shared theme

Sick leave

In this thesis, self-reported sick leave was used as an independent variable in three of the studies. The term independent variable was chosen to avoid conflating sick leave with active exposure, although it may still be conceptualized as an exposure in a broad sense rather than in a strict causal sense. For the VIP cohort in studies II and III, self-reported sick leave of six months or more for any (unspecified) reason was used, whereas for the MNS cohort in Study IV, sick leave of more than seven days due to pain was used. For the VIP cohort, the question was phrased as a yes/no (dichotomous) question, so it was not an active choice to set the limit to six months or more. In MNS there were multiple choices for the length of sick leave. The cut-off at seven days was chosen because sick leave of more than seven days required an assessment by a physician and documentation via a medical certificate (91). Thus, this reflects a more severe pain, as it was perceived as severe enough to warrant seeking health care.

Because the definition of sick leave differed across studies, the findings of all studies should not be assumed to have the same meaning or interpretation, so the measures are not directly comparable between studies. The following section provides a discussion of the definition of sick leave and its implications.

In the Nordic welfare states, sick leave is income compensation for individuals whose work capacity is reduced or lost due to illness or injury (92). It is intended to provide financial security and support return to work once the underlying condition has improved and work capacity has been restored. As such, sick leave can be understood as an indicator of reduced work capacity due to poor physical or psychological health.

However, many studies suggest that sick leave may have consequences beyond the direct effects of the underlying condition. A Norwegian study found that, early in their sick leave, individuals experienced problems related to personal identity and social life (93), whereas a Danish study reported that self-efficacy was significantly lower among individuals on sick leave (94). In addition, psychosocial factors have been linked to sick leave longer than six months (95), and better psychosocial well-being is associated with lower rates of sick leave (96).

Sick leave may also be viewed as a marker of social disadvantage, as it is associated with socioeconomic background and work-related strain (97-99). In addition, self-reported sick leave is associated with future disability pension (100), which itself may be associated with lower income and social isolation. All in all, sick leave may be interpreted as a marker of a non-specific vulnerability, which may reflect the combined influence of physical, mental, social, and economic factors.

Studies I–III

TMD pain is often described as a chronic pain condition. However, the instrument used in this thesis, 3Q/TMD, does not necessarily capture the chronicity per se. However, as the 3Q/TMD is a validated instrument to measure TMD pain (72). TMD is commonly chronic in nature, as reflected in a previous study in which fewer than 15% of participants reported remission of persistent TMD pain (67). Therefore, TMD pain is considered as a chronic pain condition in this thesis.

Because TMD pain status before the first PDHS visit is unknown, onset and remission refer to any observed transition during the study period rather than to the first onset or first remission.

TMD fluctuations

For individuals with chronic pain, pain intensity can fluctuate considerably over time (101, 102). In practice, this means that individuals can experience chronic pain for years, but its intensity and frequency vary over time. For the individual, flare-ups or increased pain intensity can make the pain feel more unpredictable. This may affect functioning, activity levels, and mental well-being and may also lead to activity avoidance (103). The reasons for these fluctuations are poorly understood, but they likely reflect the complex nature of chronic pain and the influence of biological, psychological, social, and contextual factors, in line with the biopsychosocial model. A recent clinical review found associations between pain intensity and sleep in individuals with chronic musculoskeletal pain (104). For clinicians it seems important to acknowledge that pain intensity may vary over time and that flare-ups are common in individuals with chronic pain. The NICE guidelines explicitly recommend discussing this variability with patients (43). Therefore, assessments based on a single time point may not correctly reflect the total burden of pain. Both for individuals and society it is important to understand not only these shorter bursts of painful episodes, but the pattern of onset and remission over extended periods of time.

TMD is often described as fluctuating over time, though there is sparse evidence for this in the current literature (63, 64). As discussed above, understanding the course of a condition is important for all stakeholders. Two studies in this thesis examined the onset and remission of TMD pain. Once TMD pain had developed, the condition appeared relatively stable, reflected by the low 1-year probability of remission in Study I and the few observed remissions in Study III. However, 3Q/TMD was not designed to capture changes in pain intensity. It is therefore possible

that the condition may remain present while the pain intensity varies over time, with periods of lower and higher intensity.

Gender differences and perspectives

One of the main findings of this thesis is that women as a group were worse off than were men, i.e., women reported higher transition rates to pain and lower transition rates from pain. This is in line with a recent study of individuals 50 years or older from the English population, which found that women and individuals with lower socioeconomic status were worse off in terms of pain onset and remission (105).

Generally, women have a higher prevalence of chronic pain conditions (15, 106), and this has previously been shown to be true for TMD pain as well (67). The causation of this is likely multifaceted, but several reasons have been suggested. Biological explanations have been proposed, such as hormonal factors (106). In support of this, it has been shown in previous studies that that TMD pain often begins after puberty and declines in prevalence after menopause (67). Before puberty, boys and girls report TMD at approximately the same rate (67). However, the evidence found when studying the more direct influence of oestrogen on TMD pain was inconclusive (107). Research has shown that women and men may experience pain differently, and women as a group may have a lower pain threshold than do men (108). However, the previously mentioned explanations are probably not sufficient to fully explain the gender difference in prevalence. Anxiety and depression are also more common in women, and both may negatively affect the pain experience (18), contributing to the observed gender differences. Finally, one theory is that gender roles shape how pain is experienced and expressed. Women may be socialized to be more attentive to pain and to report it more openly, whereas men may be encouraged to suppress it. This

suggests that some, or perhaps most, of the observed gender differences in pain may reflect differences in reporting and expression rather than differences in the pain itself (109, 110).

Sick leave in relation to studies II and III

The results of studies II and II are aligned with a Swedish register-based study that found that individuals with TMD diagnoses were more dependent on sick leave than was the general population (71). As shown in previous studies, TMD pain is related to several other comorbidities (55, 68). At least in Study III, sick leave was found to have occurred before the PDHS visit, although temporality cannot be established because TMD pain may have been present before the visit. As noted above, sick leave can be seen as an adverse life event with several negative consequences for the affected individual. Such circumstances may make the individual more vulnerable to pain and less able to manage painful symptoms. In this sense, sick leave may be viewed as a non-specific marker of vulnerability. As reflected by the biopsychosocial model, many factors probably interact. This underlines the need for a holistic perspective when assessing these patients and for consideration of their other burdens as well.

Health-related quality of life (SF-36)

One advantage of SF-36 is that it includes two summary scores, i.e., the Physical Component Summary (PCS) and the Mental Component Summary (MCS), making it possible to distinguish between physical and mental well-being. In this thesis, PCS is used as a measure of physical well-being and MCS as a measure of mental well-being.

Physical well-being

Previous studies have shown that chronic pain is associated with lower with lower quality of life (14, 24, 25). However, few studies have explored

this in relation to pain onset and remission. A cohort study from the USA found that better baseline physical well-being was associated to lower TMD pain intensity eight years later (111), which is in line with the present finding that better physical well-being was associated with higher remission rates. Better physical well-being was also associated with lower onset rates, suggesting that physical well-being may be relevant both for the development and recovery of TMD pain. The reasons for the observed associations are likely multifaceted. One reason could be that individuals with better physical well-being may have fewer of the somatic symptoms and comorbidities commonly observed in individuals with TMD pain (55, 68, 112). This may provide more favourable conditions for recovery and help build better resilience. Another reason might be that individuals with better physical well-being may have better sleep and may be more physically active, both of which are associated with lower pain prevalence (27, 113, 114).

However, temporality cannot be established for any of the VIP measures, so TMD pain may have been present before the visit to the PDHS. Thus, it is not possible to say whether it is the TMD pain or another comorbidity that reduces the physical well-being. Therefore, it is not possible to rule out the possibility that individuals with TMD pain even before their first visit to the PDHS had worse physical well-being for that reason or due to the numerous comorbidities associated with TMD pain (58, 68, 112).

All in all, this suggests that physical well-being could potentially be used to improve assessment, in choosing rehabilitation or management plans for individuals with TMD pain. However, this should be confirmed in studies designed for this purpose.

Mental well-being

The association between chronic pain conditions and mental health factors such as depression and anxiety are well established (26). This has also been found to be true for individuals with TMD pain (60). However, previous studies have not answered the question about the onset and remission of TMD pain. More specifically, better mental well-being was associated with lower rates of TMD-pain onset and higher rates of TMD-pain remission.

One possible explanation is that that self-efficacy is important for pain rehabilitation in general (115) and for TMD treatment in particular (116). Self-management is therefore a central part of TMD treatment and is recommended in national guidelines in both Sweden (117) and the UK (118). Self-efficacy itself is closely related to mental well-being. In addition, individuals with better mental well-being may be more psychologically resilient and have better coping abilities, which may be related to lower levels of worry and pain catastrophizing (119). As mentioned previously, temporality cannot be established, so TMD pain may have been present before the visit to the PDHS and this might have caused poorer mental well-being in affected individuals. Thus, a certain caution is required, particularly when interpreting the results regarding TMD-pain onset.

Taken together, this finding suggests that mental well-being could potentially be used to improve assessment in choosing rehabilitation or management plans for individuals with TMD pain. However, this possibility would need to be confirmed in studies designed for this purpose.

Study IV

WSP is often considered a chronic pain condition (20, 120). However, as the questionnaire used in this thesis did not capture pain duration, chronicity could not be established. As chronic WSP is usually defined by combining WSP distribution with a duration criterion of at least three months, the present classification should be interpreted as WSP rather than chronic WSP at the individual level. However, at the group level, in about half of individuals reporting chronic WSP, the condition remains years later (121).

Inherited pain

When discussing the intergenerational transmission of pain, several mechanisms may be involved. Pain may be transmitted through both genetic and psychosocial mechanisms. In this thesis, no attempt is made to distinguish between the individual mechanisms.

As discussed previously, sick leave may be interpreted as a non-specific marker of vulnerability, reflecting a combined influence of health, work capacity, social conditions and economic strain. This interpretation is still relevant when discussing pain-related sick leave. The finding that substantial sick leave due to neck and shoulder pain in the first generation was associated with WSP in later generations indicates that pain may be transmitted across generations within families. Although the estimate for back pain in generation 2 was not statistically significant, it was in the same direction and similar in magnitude as for neck and shoulder pain. In generation 3, the estimate for back pain was in the opposite direction, but the 95% CI was wide, indicating considerable uncertainty. Overall, the results do not suggest a clear difference between pain locations, albeit with clear trends suggesting an overall link between generations. This finding is in line with previous

studies showing that pain in a previous generation is associated with pain in a later generation (29-31).

A possible explanation could be shared living conditions, environmental factors, and norms of reporting pain. This would be in line with previous research that found an association between parental and offspring sick leave (122). Closely related to this is socioeconomic status, as previous studies have shown associations between lower socioeconomic status and chronic pain (123). However, in one study, this association was explained by psychological factors (124). This highlights the complexity of studying pain. Several related factors may covary, and socioeconomic, psychological and lifestyle factors are often closely related, making it difficult to determine their separate contributions to pain development. Another possible explanation is that pain-related sick leave may reflect musculoskeletal problems (125). In this context, pain-related sick leave may reflect not only presence of pain, but also limitations in everyday life, as well as social and economic consequences. This may indicate more severe or persistent problems than WSP, particularly since WSP was classified without assessing chronicity.

Since WSP as such in an earlier generation was not associated with WSP in later generations, what is transmitted across generations is likely not simply pain, but rather the broader social and environmental circumstances surrounding more severe pain, including pain-related sick leave. The findings may therefore indicate that the inheritance of pain is more related to the consequences of pain, such as financial strain, altered family routines, and psychosocial stress, rather than to the pain itself. Expanding on this, WSP is a broad and heterogeneous pain condition. Although WSP is defined by pain in multiple body regions, the underlying mechanisms may differ among individuals and may include

stress-related factors, sleep disturbance, depression, or other forms of multisite pain (126).

In summary, these findings suggest that pain may be transmitted within families and across multiple generations. The underlying mechanism is however unclear. The mechanism is likely to be multifactorial, with biological, psychosocial, behavioural and environmental factors. These patterns may also reflect the intergenerational transmission of health inequities. Thus, a family history of pain may therefore provide valuable information in pain assessment as an indicator of a broader vulnerability. This finding should preferably be confirmed in a study designed for this purpose and with a higher statistical power. Although, this should be confirmed in a study specifically designed for this purpose.

Methodological considerations

Studies I–III

A major strength of all three studies is their large sample sizes, providing statistical power and enabling subgroup and interaction analyses.

The 3Q/TMD instrument is validated for assessing TMD pain, with a positive answer to at least one of the two questions on pain (Q1 or Q2) having demonstrated high sensitivity and specificity (72). However, the instrument may not fully discriminate between TMD pain and other orofacial pain conditions such as toothache. In addition, the instrument captures symptoms occurring once a week or more without assessing pain duration. Thus, chronicity cannot be established with criterion validity.

Study I

One limitation of Study I is that individuals were assumed to remain in the same state until a transition was observed. Since individuals were only observed at PDHS visits, typically every two to three years, transitions occurring between visits may have been missed. This may have led to imprecise estimates of the transition rates. In addition, both studies I and III relied on the assumption that observation times were non-informative, meaning that the timing of PDHS visits was assumed to be independent of the underlying TMD pain status. This assumption may not have been fully met as visits to the PDHS can be influenced by individual health-seeking behaviour. However, since TMD status was collected during routine dental check-ups, and TMD pain is treated at specialist clinics, this bias is not likely to have substantially influenced the transition rates.

Studies II and III

A major strength of the VIP data is its good population coverage and low socioeconomic selection bias (127). Given that nearly 80% of the adult population in Västerbotten regularly visits a dentist, and that about half of these visits take place within the PDHS, the study sample can be considered representative of the general population in Västerbotten aged 40 years and older. (76). When measuring variables such as sick leave and HRQoL, there is an inherent overlap with TMD pain. Individuals may already have had TMD pain before being classified as having TMD pain at the PDHS. As discussed previously, this makes it difficult to establish the temporal relationship between exposure and outcome, and therefore impossible to determine what influences what. This is complicated by the multifactorial nature of pain. Several factors may co-occur or have a bidirectional relationship with TMD pain, while others may be caused by the consequences of the pain itself. The findings

should therefore be interpreted only as associations and not as causal relationships. Another limitation is the fixed age of inclusion in the VIP. This means that almost no data are available for individuals younger than 30 years of age. It is also only possible to study individuals who attended both the VIP and the PDHS, which may introduce selection bias related to non-attendance of either VIP or the PDHS. An additional limitation is that data collection was not synchronized, so the time lag between the VIP visit and the PDHS visit can be substantial. Because sick leave, mental well-being, and physical well-being were measured at the VIP visit, the association with later TMD pain may be weakened as the time between the VIP visit and the PDHS visit increases. Therefore, the presented models were adjusted for the time between the VIP visit and PHDS visit.

A strength is the use of inverse probability weighting, which reduced the risk of prevalence estimates being affected by potential differences in attendance of the PDHS across subgroups. Since the weighted and unweighted estimates were very similar, differences in attendance of the PDHS across subgroups likely had little impact on the prevalence.

Study IV

Few, if any, previous studies have explored pain across three generations, making the intergenerational perspective a particular strength and a contribution to the field. Using pain manikins to measure WSP is a validated way to capture pain (52, 53). Different versions of the manikin were used between generation 1 and generations 2 and 3. This limits the possibility of comparing the prevalence between the generations, although this was not the aim of this research.

MNS was not dimensioned to look at outcomes in later generations, which limits the possibility of subgroup analysis. It is likely that this

contributed to the imprecise estimate of associations in the third generation.

Overall

All studies relied solely on self-reported data. For sick leave, register-based information from the Social Insurance Agency would ideally have been preferred, as it would have provided more detailed information on the duration, primary diagnosis, and time of sick leave. These data would likely not have been available for the MNS cohort, given that the sick leave occurred in the early 1990s, but they may have been possible to obtain for the VIP data.

Clinical implications

The findings of this thesis are associations from observational data, so the possibility of drawing extensive clinical implications is limited. However, some general conclusions can be drawn, namely, that women had a worse TMD prognosis than men, with higher rates of onset and lower rates of recovery, particularly for TMD pain. This suggests that it is important to consider gender differences as early as the treatment planning stage for individuals with TMD pain.

Furthermore, the observed associations of physical and mental well-being with TMD-pain remission suggest that a perspective broader than a purely physical one is needed. Sick leave, physical well-being, and mental well-being were all associated with remission from TMD pain, indicating that these factors may be relevant to clinical decision-making and management. Together, these findings support the importance of a holistic approach to pain assessment. Better mental and physical well-being were also associated with lower rates of TMD-pain onset, whereas sick leave was associated with higher rates of onset, suggesting that these

factors may be important not only for management but also for prevention. In an intergenerational context, pain-related sick leave may represent a pathway linking parental pain consequences to pain vulnerability in descendants, and thus to the transmission of health inequities. This information could be useful in pain assessment.

Personal reflection

As a statistician working in medical research, I have often found it challenging to adapt my language and choice of terms. There is a constant balancing act between being statistically precise and making the text understandable for readers without a statistical background. This challenge has helped me understand statistics from another perspective. I would like to think that this experience has made me a better statistician, especially by improving my ability to communicate statistical concepts in a clearer and more accessible way.

Future directions

Given the overall poorer prognosis of women, future studies should explore how this knowledge can be translated into treatment planning and management to improve outcomes for individuals, especially women, with TMD pain. Future research should also investigate whether information on physical and mental well-being can be used to improve TMD pain management. This research should also aim to build an understanding of the mechanisms underlying these associations. Finally, to further explore the intergenerational link between parental pain consequences and pain vulnerability in descendants, a cohort study specifically powered to detect such effects would be valuable.

Main findings

- Women had higher onset rates and lower remission rates of TMD pain, indicating an overall poorer prognosis compared with men.
- Individuals with better physical and mental well-being had higher rates of TMD-pain remission and lower rates of onset.
- Individuals with a history of sick leave had higher rates of TMD-pain onset and lower rates of remission.
- Pain-related sick leave in the parental generation was associated with WSP in later generations, whereas parental WSP was not.

Conclusions

- The higher onset rates and lower remission rates of TMD pain in women indicate a poorer overall prognosis compared with men. These gender differences should be considered when planning treatment for patients with TMD pain.
- Better physical well-being and mental well-being are associated with more favourable outcomes for both TMD-pain onset and remission. This may be useful in clinical assessment when planning rehabilitation or management strategies for individuals with TMD pain.
- Substantial pain-related sick leave in the parental generation was associated with WSP in later generations, whereas parental WSP was not. This may suggest that pain is transmitted across generations within families through social and environmental mechanisms, rather than through biological heredity alone.

Thesis at a glance

Temporomandibular disorder (TMD) is the most common cause of chronic orofacial pain.



Data from the public dental health services in Västerbotten.

No pain

Onset

TMD pain

Remission

No pain

Women report TMD pain onset more frequently and remission less frequently.

TMD pain was more common among individuals reporting sick leave, and individuals with TMD pain reported poorer quality of life.

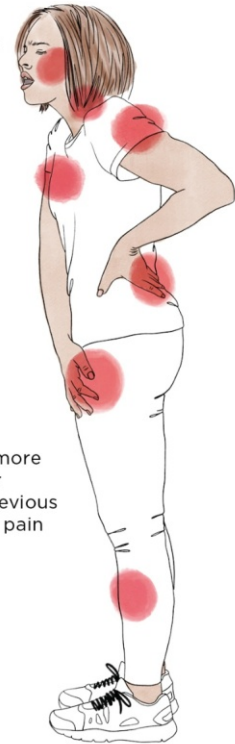
Better mental and physical well-being was associated with lower rates of TMD pain onset and higher rates of remission, whereas sick leave was associated with higher rates of onset and lower rates of remission.

Widespread pain refers to pain that is present in multiple body regions.



Three generations from Malmö.

Widespread pain is more prevalent in the later generations if the previous generation reported pain related sick leave.



Acknowledgement

I would like to thank everyone who has supported, encouraged, and helped me throughout my PhD studies. I would especially like to express my gratitude to the following people:

Anna Lövgren, my main supervisor, thank you for giving me this opportunity and for believing in me. Thank you also for your support, for helping me find my way and for allowing me to grow throughout this process. Thank you for always taking the time to answer my questions, read my drafts, and guide me. Last but not least, thank you for all the laughs along the way.

Per Liv, my co-supervisor, thank you for all your support and help, and for always taking the time to answer my questions and guide me forward. I can honestly say that, if it were not for you, I would never have finished this thesis.

Fredrik Hellström, my co-supervisor, thank you for all your advice, wise words, and valuable insights along the way. I am also deeply grateful for all the feedback you have given on my thesis. It would not have been nearly as good without your input.

Birgitta Häggman Henrikson, thank you for all your thoughtful feedback on my writing, for all the articles you shared with me, and for inviting me to work with you and Nikola on the MOPS project. Finally, thank you for facilitating my research visit in Malmö.

Corinne Visscher and Frank Lobbezoo, thank you for sharing your knowledge and for your valuable feedback, which has truly elevated this project.

Nikola Stanisic, thank you for all your hard work on the MOPS project, for your enthusiasm, and for being such a great fellow PhD student to work alongside.

My examiner, Pernilla Lif, thank you for your support and your positive attitude throughout my doctoral studies.

Carina Öhman, thank you for kindly helping me with all the administrative work needed to complete my PhD studies.

Christel Häggström, thank you for being my sounding board and for providing valuable feedback on my thesis.

Gabriel Granåsen, thank you for supporting me by approving my leave of absence so that I could begin and complete my doctoral studies, and for showing such enthusiasm for my PhD journey.

Alicia Böthun, thank you for your valuable feedback on my thesis, for being such a great fellow PhD student, and for all the laughs along the way.

Wendy Wu and Anders Wänman, thank you for taking the time to read my thesis and for your valuable feedback.

My base group at Umeå University, Anastasiya, Alicia, Fredrik, and Lina, thank you for making our meetings both valuable and enjoyable, and for all the thoughtful feedback along the way.

Fellow PhD students at Umeå and Malmö, Axel, Evelina, Hessam, Mohamed, and Tessa, thank you for making the seminars interesting and for all the good conversations along the way.

Marlene Lahti, thank you for the beautiful illustrations and cover page.

My colleagues at Registercentrum, thank you for showing interest in my research and for your encouragement along the way. A special thanks to Clara, Fredrik, Ludvig, Rebecka, and Oscar for all your hard work and support.

To all my friends who have cheered me on, encouraged me, and reminded me that I could do this, thank you all.

My dear parents, Eva and Thomas, thank you for always believing in me and for supporting me in everything I do. Without your support, I would never have begun this journey, let alone finished this thesis.

My girlfriend, Stina, thank you for believing in me, encouraging me, and always being there for me with your love and support. I could not have done this without you. You are my river!

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