From the Department of Dental Medicine
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CAUSES AND CONSEQUENCES OF TEMPOROMANDIBULAR JOINT DISEASES

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Karolinska Institutet

Stockholm 2023

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2023

ISBN 978-91-8016-984-4
Cover illustration by Lucy Bai

Causes and consequences of temporomandibular joint diseases

Thesis for Doctoral Degree (Ph.D.)

By

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The thesis will be defended in public at the Department of Dental Medicine, lecture hall 9Q, Alfred Nobels Allé 8, Huddinge, Friday June 16, 2023, 13:00

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Si nada nos salva de la muerte, al menos que el amor nos salve de la vida.
Pablo Neruda

Popular science summary of the thesis

Temporomandibular disorders (TMD) include several conditions that may affect the muscles of mastication and the temporomandibular joint (TMJ). TMD affect up to 20% of the general population and impair daily life activities such as eating and speaking. Common symptoms are tenderness in the muscles of mastication, pain associated with jaw opening, and limitation of the jaw opening movement. More women than men are affected. Although the causes for TMD are still largely unknown, it is believed that TMD has several biological, psychosocial, and behavioral components, creating a complex relationship of contributing factors. TMD located in the TMJ is referred to as temporomandibular joint disorders (TMJD), a subgroup of TMD. In Sweden, most individuals with TMD are treated within the dental care system with non-invasive treatments such as relaxation training and occlusal splints, but some patients with TMJD may require surgical treatment. These patients are treated in the hospital care system and will automatically be recorded in national patient registries, which can be used for research purposes.

The most common causes of work disability (sick leave and disability pension) are mental and behavioral disorders (MBD) and diseases of the musculoskeletal system and connective tissue (MSD). Both MBD and MSD have a strong association to TMD, but no studies have investigated how these coexisting diseases influence work disability among individuals with TMD and/or TMJD.

This thesis, which uses registry-based data collected from the National Board of Health and Welfare (Socialstyrelsen) and Statistics Sweden (SCB), investigates whether MBD and MSD increase the probability of developing TMJD. In addition, this thesis investigates whether TMJD patients suffer from more work disability than the average population and if co-existing diseases such as MBD and MSD influence the number of annual days on sick leave and disability pension.

The four studies in this thesis show that many MBD and MSD increase the risk of TMJD, indicating that some of these conditions contributes to the development of TMJD. The studies also show that TMJD patients have 2–3 times more mean annual days of work disability than the general population and that co-existing MSD and MBD have a large impact on the number of days on sick leave and disability pension.

The results are important as they highlight possible risk factors for TMJD from a novel perspective, using national patient registry data to demonstrate how other diseases interact with the development of TMJD. They are also important as we now clearly see that patients with TMJD suffer from immense disease burden. These findings raise important issues regarding the funding of the treatment of these disorders as the patients' costs depend on whether the examination and treatment are conducted within dental or hospital care in Sweden.

Abstract

Temporomandibular joint disorders (TMJD), a subgroup of Temporomandibular disorders (TMD), has a multifactorial etiology with still largely unknown pathophysiology. Although many risk factors have been proposed, few population-based studies have been conducted. There are known associations between TMJD and mental and behavioral disorders (MBD) and musculoskeletal diseases (MSD). MBD and MSD cause high work disability and are the leading causes for sick leave (SL) and disability pension (DP) both globally and in Sweden. However, no studies have investigated work disability among patients with TMJD (pwTMJD) or the effect of MBD and MSD comorbidity on work disability among pwTMJD.

This thesis includes all Swedish citizens aged ≥18 registered between 1998 and 2016 in the National Patient Registry with a TMJD diagnosis or TMJD surgical procedure code. These pwTMJD (n=33 316) were matched to a comparison cohort (n=333 160) from the Total Population Registry. pwTMJD were categorized depending on whether they had received surgical treatment or not, and on the number of surgical procedures.

Study I shows that pwTMJD have 2–3 times more mean annual days of SL and DP than the general population and that patients who had undergone several surgical treatments were most dependent on these benefits. The increased work disability among pwTMJD was noticeable as early as five years before first time diagnosis or treatment.

Study II and **Study III** investigate the probability of developing TMJD among individuals with and without MBD/MSD. **Study II** shows that many MBD increase the probability of TMJD and that individuals with MBD had a higher risk of needing repeated surgical procedures compared to individuals with no MBD. **Study III** shows that virtually all MSD increase the probability of TMJD, especially TMJD that require repeated surgical procedures.

Study IV further examines the impact of MBD and MSD comorbidity on mean annual days of SL and DP among pwTMJD compared to the general population, by using strata of comorbidity. The results show that both MBD and MSD comorbidity by themselves have a large impact on the use of social insurance benefits but that combined MBD/MSD comorbidity had the largest impact on SL and DP. Regardless of comorbidity, pwTMJD displayed the highest mean annual days of SL and DP in almost all strata of comorbidity.

In conclusion, the results in this thesis show that MBD and MSD are strong predictors for the development of TMJD. The results also show that pwTMJD have more work disability than the general population, and that this increased dependence on social insurance benefits is strongly influenced by comorbidities. These findings emphasize how pwTMJD are suffering from their condition and that a multimodal approach is warranted, preferably steered by national guidelines designed by specialists in orofacial pain and function, oral and maxillofacial surgeons, and colleagues from the medical field.

List of scientific papers

I. **Salinas Fredricson A**, Krüger Weiner C, Adami J, Rosén A, Lund B, Hedenberg-Magnusson B, Fredriksson L, Svedberg P, Naimi-Akbar A. Sick leave and disability pension in a cohort of TMD-patients – The Swedish National Registry Studies for Surgically Treated TMD (SWEREG-TMD).
BMC Public Health. 2022;22(1):916

II. **Salinas Fredricson A**, Krüger Weiner C, Adami J, Rosén A, Lund B, Hedenberg-Magnusson B, Fredriksson L, Naimi-Akbar A. The Role of Mental Health and Behavioral Disorders in the Development of Temporomandibular Disorder: A SWEREG-TMD Nationwide Case-Control Study.
J Pain Res. 2022;15:2641-55

III. **Salinas Fredricson A**, Naimi-Akbar A, Adami J, Lund B, Rosén A, Hedenberg-Magnusson B, Fredriksson L, Krüger Weiner C. Diseases of the musculoskeletal system and connective tissue in relation to temporomandibular disorders-A SWEREG-TMD nationwide case-control study.
PLoS One. 2022;17(10):e0275930

IV. **Salinas Fredricson A**, Krüger Weiner C, Adami J, Rosén A, Lund B, Hedenberg-Magnusson B, Fredriksson L, Svedberg P, Naimi-Akbar A. Sick leave and disability pension among TMD patients with musculoskeletal diseases, mental and behavioural disorders - a SWEREG-TMD population-based cohort study.
BMC Public Health. 2023;23(1):852.

Scientific paper not included in the thesis

I. **Salinas Fredricson A**, Khodabandehlou F, Weiner CK, Naimi-Akbar A, Adami J, Rosén A. Are there early signs that predict development of temporomandibular joint disease?
J Oral Sci. 2018;60(2):194-200

Contents

List of abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
AS	Ankylosing Spondylitis
BMI	Body Mass Index
DC/TMD	Diagnostic Criteria for Temporomandibular Disorders
DD	Disc Derangement
DDwR	Disc Displacement with Reduction
DDwoR	Disc Displacement without Reduction
DEGURBA	Degree of Urbanization
DJD	Degenerative Joint Disease
DP	Disability Pension
ED	Eating Disorders
GDPR	General Data Protection Regulation
GEE	Generalized Estimating Equations
ICD-10	International Classification of Diseases (10^{th} revision)
ID	Internal Derangement
ILCD	International List of Causes of Death
LD	Lyme Disease
LISA	Longitudinal Integrated Database for Labor Market and Health Insurance Studies
MAR	Missing at Random
MBD	Mental and Behavioral Disorders
MCAR	Missing Completely at Random
MI	Mulitple Imputation
MICE	Multiple Imputation by Chained Equations
MNAR	Missing Not at Random
MSD	Musculoskeletal and connective tissue disorders
NBHW	National Board of Health and Welfare
NCSP	NOMESCO Classification of Surgical Procedures
NE	Non-exposed cohort
NHIS	National Health Interview Survey
NOMESCO	Nordic Medico-Statistical Committee
NPR	National Patient Registry
NS	Non-surgical cohort
OA	Osteoarthritis
OPPERA	Orofacial Pain Prospective Evaluation and Risk Assessment
OR	Odds Ratio
pwTMJD	Patients with Temporomandibular Joint Disorders
RA	Rheumatoid Arthritis
RTW	Return To Work
PIN	Personal Identification Number
PPV	Positive Predictive Value

S	Surgical cohort
SB	Sleep Bruxism
SCB	Statistics Sweden
SIA	Swedish Social Insurance Agency
SL	Sick Leave
SLE	Systemic Lupus Erythematosus
ST1	TMJD with one subsequent surgical treatment procedure
ST2	TMJD with two or more subsequent surgical treatment procedures
TMD	Temporomandibular Disorders
TMJ	Temporomandibular Joint
TMJD	Temporomandibular Joint Disorders
TPR	Total Population Registry
TTH	Tension Type Headache
YLD	Years Lived with Disability
WAD	Whiplash Associated Disorders
WHO	World Health Organization

NOMESCO classification of surgical procedures

EDC00	Condylotomy of mandible
EGA00	Arthroscopy of mandibular joint
EGA20	Biopsy of mandibular joint
EGB00	Condylectomy of mandible
EGB10	Meniscectomy of mandibular joint
EGB20	Synovectomy of mandibular joint
EGC00	Open reduction of dislocation of jaw
EGC10	Arthroplasty of mandibular joint without graft
EGC20	Arthroplasty of mandibular joint with bone or other graft
EGC30	Prosthetic replacement of mandibular joint
EGC99	Other reconstructive operation on mandibular joint
TEG10	Injection of diagnostic or therapeutic substance into mandibular joint

ICD-10 abbreviations

K07.6	Temporomandibular joint disorders
F00–F99	5th chapter of ICD-10: Mental and behavioral disorders
F00–F09	Organic, including symptomatic, mental disorders
F10–F19	Mental and behavioral disorders due to psychoactive substance use
F20–F29	Schizophrenia, schizotypal and delusional disorders
F30–F39	Mood affective disorders
F40–F48	Neurotic, stress-related and somatoform disorders
F50–F59	Behavioral syndromes associated with physiological disturbances and physical factors
F60–F69	Disorders of adult personality and behavior
F70–F79	Mental retardation
F80–F89	Disorders of psychological development
F90–F98	Behavioral and emotional disorders with onset usually occurring in childhood and adolescence
F99	Unspecified mental disorder
M00-M99	13th chapter of ICD-10: Diseases of the musculoskeletal system and connective tissue
M00–M25	Arthropathies
M30–M36	Systemic connective tissue disorders
M40–M54	Dorsopathies
M60–M79	Soft tissue disorders
M80–M94	Osteopathies and chondropathies
M95–M99	Other disorders of the musculoskeletal system and connective tissue
S02.4	Fracture of malar, maxillary and zygoma bones
S02.6	Fracture of the mandible
S13	Dislocation and sprain of joints and ligaments at neck level

Introduction

The temporomandibular joint (TMJ), an arthrodial hinge joint that connects the mandible and the skull, consists of a lower and an upper compartment, which is created by the TMJ disc. The squamous bone of the base of the skull articulates to the condyle of the mandible, which is lined by fibrocartilage. Anteriorly, the disc is fused with the anterior disc capsule and attached to the lateral pterygoid muscle. Posteriorly, the disc continues as a retro-discal tissue (i.e., the posterior disc attachment) which is fully vascularized and innervated. The disc itself, however, lacks nerve endings and blood supply. During jaw opening, the joint both rotates and translates. During translation the condyle moves toward the articular eminence, while the disc maintain its position between the fossa and condyle. Both the anatomy and biomechanics of the TMJ are highly complex.[1]

As any other joint, the TMJ is susceptible to several diseases and derangements, including disc derangements (DD) such as disc displacement with reduction (DDwR) and disc displacement without reduction (DDwoR). The TMJ can also be affected by adherences, ankylosis, hypermobility disorders, dislocations, fractures, inflammatory diseases, degenerative joint disease (DJD), gout, hyperplasia, hypoplasia, osteonecrosis, neoplasms, and infections. Generally, the conditions are characterized by pain, functional impairment, and joint sounds. Collectively, they can be referred to as temporomandibular joint disorders (TMJD).[2-10]

Often, TMJD is preceded by or coincides with other painful symptoms in the orofacial area and masticatory system. The term temporomandibular disorders (TMD) has been used to denote conditions that affect the TMJ, the muscles of mastication, and the surrounding associated structures.[9] The clinical management of these patients is performed from an odontological and biopsychological perspective, often bordering between dental and medical care. Although the majority of both the muscular and intra-articular disorders are treated within dental care, some patients with TMJD (pwTMJD) require surgical treatment performed within medical care.

The etiology of TMJD is multifaceted and complex and still largely unknown. The gaps of knowledge emphasize the need for larger epidemiological studies where risk factors and societal impacts are investigated in population-based approaches. This thesis investigates the association between TMJD, mental and behavioral disorders (MBD), and diseases of musculoskeletal system and connective tissue (MSD). In addition, this thesis investigates the impact of TMJD on work disability—e.g., sick leave (SL) and disability pension (DP)—and the impact of MBD and MSD on work disability among pwTMJD. As with most research methods, this thesis has some limitations. However, the exclusive possibilities for registry-based research available in Sweden offer unique opportunities to conduct research on a vast amount of data. This thesis presents new findings based on novel methods for this specific patient group that may contribute to the future research and well-being of individuals suffering from TMJD.

1 Literature review

1.1 Prevalence and incidence

Several studies have investigated the prevalence of TMD and TMJD in the general population over a long period, although these studies often have diverging results. This section covers a sample of some of the studies that have investigated the prevalence and incidence of TMD with special emphasis on the articular disorders.

In 1987, Kircos et al., using magnetic resonance imaging (MRI), found that 32% of the joints of asymptomatic individuals had an anteriorly displaced disc. These findings were important as they suggested that a large part of the population have asymptomatically displaced discs, and that this may be an anatomical variant that does not always cause symptoms or dysfunction.[11] Lundh et al. , who also investigated the prevalence of internal derangement (ID) among an asymptomatic population (n=403), found signs of ID in 19% of the population, 7% with clicking sounds and 12% with a history of clicking sounds and later limited jaw movement.[12] Similarly, Ribeiro et al. found a 25% prevalence of DD among asymptomatic volunteers.[13] In a 15-year prospective study of both asymptomatic and symptomatic non-patient volunteers, Salé et al. found that as many as 31% of the asymptomatic volunteers displayed TMJ DD when examined with MRI, whereas 89% of the symptomatic volunteers had DD.[14] However, any study based on volunteers is susceptible to selection bias.

In a 1997 review article, LeResche made an important observation: Although TMD includes multiple disorders, most epidemiological research that covers TMD approach it as a single disease. This generic approach can complicate and obscure any possible conclusions. LeResche's literature review exclusively included population-based studies and was able to distinguish findings on TMD pain, TMJ pain, and TMJ sounds. TMJ pain in adults was reported to be 3.5–7.9%, varying over age and sex. TMJ sounds such as clicks and crepitus also fluctuated with age and sex, with a prevalence of 2.9–40%.[15]

In 2008, Isong et al., using the National Health Interview Survey (NHIS) from 2002, investigated the prevalence of self-reported TMD pain by age and gender. The study, which included 30 978 individuals, found the overall prevalence of TMD pain to be 4.6%, although higher in women than in men.[16] Plesh et al., also using the NHIS but including data spanning over several years and with 189 977 subjects, found that the prevalence was the same, but also that many comorbidities accompanied TMD pain, such as severe headaches, joint pain, and neck and lower back pain.[17] TMD prevalence was also shown to differ over age groups, sex, and ethnicity in women more than in men.[18] Although important findings, the NHIS studies did not distinguish between subcategories of TMD, opting to pool the entire patient group, a consequence of the use of self-reported questionnaires.

In 2011, Manfredini et al. acknowledged the issue raised by LeResche in 1997 and approached the question with a review paper that exclusively included articles that had

used the Research Diagnostic Criteria for TMD (RDC/TMD). The review included papers based on both patient populations and general populations, which totaled to 3463 subjects. For the general population, the meta-analysis revealed an overall prevalence of 11.4% for disc displacements and 2.6% for joint disorders, with substantially higher figures in the patient population-based samples, suggesting possible selection bias.[19]

In 2016, Lövgren et al. published a paper with a cross-sectional design based on 137 718 individuals with self-reported TMD pain and dysfunction. The questionnaire was based on three questions asked and recorded in conjuncture with visits at public dental care units in Northern Sweden. The authors found a TMD pain prevalence of 5.2% among women and 1.8% among men. Pain on jaw movement had a prevalence of 2.5% for women and 0.9% for men and frequent jaw locking had a prevalence of 2.7% for women and 1.2% for men. The prevalence was highest during adulthood, gradually fading over time, much like the findings of Plesh et al.[18,20]

In 2021, Valesan et al. conducted another systematic review that more specifically focused on the prevalence of TMJD, including only studies based on RDC/TMD or Diagnostic Criteria for TMD (DC/TMD). The 21 studies that comprised the review included a total of 11 535 subjects, with most of the subjects categorized according to RDC/TMD. As expected, a large heterogeneity was found between the studies, which was attributed to bias, methodological differences, and variability in the samples. Nevertheless, the overall prevalence of TMJD among adults was 31.1%, 19.1% for DD, and 9.8% for DJD. The most common condition for both adults and children/adolescents was DDwR.[21]

The annual incidence of TMD has been proposed to be around 4%, with substantially higher incidence in individuals with comorbid conditions such as headaches, low back pain, genital pain, and IBS.[22] The incidence rate is also strongly influenced by sociodemographic characteristics, psychosocial functioning, and pain sensitivity.[23] Häggman-Henrikson et al. reported an incidence rate of onset TMD of 2.5% for women and 1.2% for men and showed that women are at higher risk of developing persistent TMD pain.[24] Remarkably, few studies have studied the incidence of isolated TMJD, but in MRI-based prospective follow-up data the incidence of DD was reported to be 4%.[14]

The differences in prevalence can be attributed not only to customary limitations in research but also to a historical lack of consensus in the diagnostics and categorization of TMD as well as the heterogeneity of the patient group. Obviously, subgroups of TMD, such as TMJD, may have very different prevalences when looked at separately, stressing the importance of thoroughly stipulating the population the research refers to and perhaps more importantly the conclusions that are inferred. Multiple standardized research and diagnostic tools have been introduced over the years to enable more uniform perspectives on the TMD conundrum; these will be described in the following chapter.

1.2 Diagnostic instruments and taxonomy

The amalgamation of the large variety of diagnoses within TMD, including TMJD, creates complexity and some controversy when assessing epidemiological considerations such as risk factors, prevalence, and societal effects, as the concept of TMD varies. To better understand the epidemiology of TMD, researchers must be familiar with the subclassifications of the term. The complexity of the disorders is reflected in their taxonomy, which will be described in the following chapter from both historical and contemporary perspectives to contextualize the still ongoing discussion regarding the different approaches to classification, with a focused view on the taxonomy of TMJD.

Perhaps the most used and acknowledged definition criteria are the RDC/TMD and the DC/TMD. The RDC/TMD was introduced in 1992 and provided standardized examination methods that offered researchers a shared tool for defining and diagnosing TMD.[25] The RDC/TMD offers criteria for both physical diagnoses (Axis I) and psychosocial assessments (Axis II). Both Axes have been translated into 20 languages and were used extensively in TMD research after the publication of RDC/TMD, although criticized for not being adapted to clinical practice.[8,10] Subsequently, several studies and consortiums continuously worked to improve the diagnosing and management of TMD patients.

In 2014, Schiffman et al. published the DC/TMD, a development of the RDC/TMD that fulfilled the goals set for both validity and reliability for the most common painful TMD conditions but only for one of the intra-articular temporomandibular disorders.[9] The DC/TMD includes a taxonomy over common and more unordinary TMD diagnoses which is more comprehensive than the one first presented in RDC/TMD. The diagnoses are established mainly by palpations and/or provocation testing of the attributed pain area as well as replication of the pain to exclude incidental signs.

The abundance of categorization systems may confuse any non-initiated individual but gives a very specific picture of how multifaceted TMD and the subcategories are, and further accentuates the gaps of knowledge that still exist. Although there are many other different approaches to the categorization of TMD, the RDC and DC/TMD remain the principal instruments for research and clinical assessment. DC/TMD, however, holds quite low sensitivity and specificity for the intra-articular disorders, so the diagnoses are usually confirmed by imaging, preferably MRI as suggested by both Schiffman et al. and Larheim et al.[10,26] Therefore, DC/TMD is used more as a screening tool for intra-articular conditions, which generates a need for complementary instruments when assessing patients for surgical treatment. Several classification systems have been suggested by Wilkes, Holmlund, Scrivani, Dimitroulis, de Bont, and many more.[2,4,5,8,27] Some systems focus on intra-articular findings to anticipate surgical outcomes, some on tissue-based classifications, and some have approached TMD as an entity classifying both muscular and intra-articular disorders. The taxonomy of TMJD in accordance with RDC/TMD, DC/TMD and some of the other classification systems is depicted in Figure 1.

While there are many validated instruments, the discussion must inevitably deal with what is used in the clinical setting. As this thesis revolves around pwTMJD diagnosed in a hospital setting and/or surgically treated pwTMJD, defined by an International Classification of Diseases (ICD) code, rather than instruments such as DC/TMD, the following chapter will briefly describe the history and implementation of ICD.

1.2.1 The International Classification of Diseases

The World Health Organization's (WHO) ICD is an international classification system used in both clinical and research settings. The need to classify diseases has a long history and early efforts of categorization were made by scientists such as François Boissier de Sauvages, Carl von Linné, and William Cullens in *Nosologia Methodica*, *Genera Morborum*, and *Synopsis Nosologiae Methodicae*, respectively.[28] Responding to a request from the First International Statistical Congress in 1853, William Farr presented a classification called the International List of Causes of Death (ILCD) in an attempt to create an international and formal classification.[29] The ILCD was developed and adopted over the course of the 19th century until the WHO in 1948 funded the ICD, which also included morbidity coding. Sweden introduced a primary care version of ICD in the 1970s but started using ICD-6 as early as in 1951.[28,30]

ICD was further developed during the 20th century, and the most significant transition was made between ICD-9 and ICD-10.[31] ICD-10 has been adopted in many specific national versions, including a Swedish version. The diversity of the different national versions of ICD-10 has led to a discussion where the main concern is international comparability of the codes. To account for such variety in country-specific codes, the WHO decided in 2002 to develop ICD-11. ICD-11 is the first attempt at a web-based codebook, which is revised biannually and is coherent and broad enough to eliminate the need of country-specific codes and therefore reduce the risk of omissions and errors in international research and comparisons. ICD-11 was globally launched January 1, 2022.

Although ICD-10 is the most widely and globally used statistical classification system, it has been criticized. For example, musculoskeletal or connective tissue disorder can be specified to an exact site, not only which hand but also which finger that may be affected. The clinical relevance of this specificity has been questioned.[32] On the contrary, TMJD and all its subcategories is reduced to a single ICD-10 code: Temporomandibular joint disorders (K07.6).

1.2.2 Classification of surgical procedures

The classification of surgical procedures did not really emerge until after World War II. In the Nordic countries the Nordic Medico-Statistical Committee (NOMESCO), has been responsible for developing surgical procedure codes for statistical purposes and international comparisons. The NOMESCO Classification of Surgical Procedures (NCSP) was published in 1996, it is frequently maintained and updated, and it is the classification system used in Sweden and the other Nordic countries.[28]

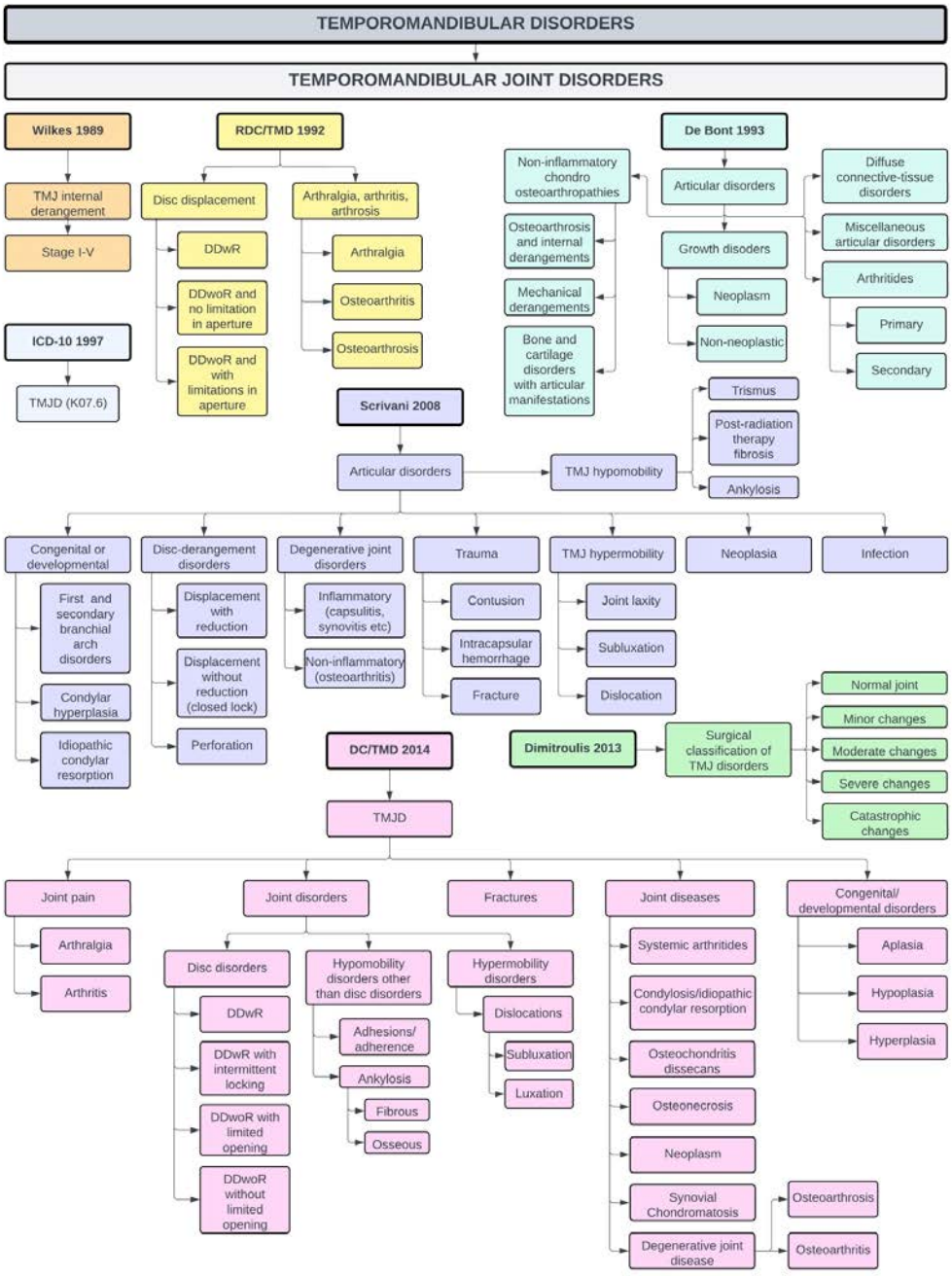

***Figure 1**. Examples of TMJD taxonomies found in the literature.*

1.3 Treatment

The treatment of TMD and TMJD is based on methodological diagnostics and tailored to the specific condition presented. The initial treatment is almost always non-invasive. The most described treatment methods are occlusal splints therapy, physiotherapy, pharmacological treatment, biobehavioral therapy and cognitive behavioral therapy, and an interdisciplinary approach that combines different treatment strategies is usually preferable.[33-43]

A limited number of TMD patients, less than 1%, that suffer from strictly TMJ-related conditions may be considered for surgical intervention.[44] As with the conservative treatments, the preferable surgical treatment is based on preoperative clinical and diagnostic findings. One such example is Wilkes's criteria where stages III and IV typically would be eligible for surgical treatment.[2,45] Surgical treatments vary from minimally invasive methods to open joint surgery. It is highly important to differentiate TMD patients with failed conservative treatment in need of chronic pain management from those who can benefit from surgical interventions. Such indications include severely limited jaw movement and mechanical interferences such as painful DDwR or DDwoR.[46]

Arthrocentesis, a minimally invasive procedure where the joint is irrigated with saline solution, has been shown to have good effects on pain relief but inferior to arthroscopy regarding the improvement of mouth opening.[47,48] Arthroscopy is conducted via a preauricular incision that gives access to the superior joint compartment; it is conducted with thorough lavage of saline solution and is much less invasive than open joint surgery, such as discectomy, with high success rates in reduced pain and increased range of motion.[44,49,50] The effectiveness of arthroscopy has, however, been debated and a Cochrane report published in 2011 suggested that arthroscopy had little or no evidence of relieving pain more effectively than non-surgical treatment and was less effective than open surgery. Nevertheless, the report's analysis did not separate the patients with DDwR from the ones with DDwoR.[51] In 2014, Al Baghdadi et al. published a review on the management of DDwoR, including both non-invasive and surgical treatment methods. The results showed inconclusive results with no significant differences between the treatment modalities, suggesting that the treatment should be initiated with the least invasive treatment method available.[52] The authors criticized the quality of much of the available literature, and agreed with earlier publications that had concluded that the literature on comparisons between non-surgical and surgical treatment of TMJD lacks methodical quality.[53]

Open joint surgery includes various treatment methods such as discectomy, where the TMJ disc is removed completely, or condylotomy.[54-58] In condylotomy, the condyle is sagged in an inferior position, creating an enlarged joint space.[44] TMJ pain and dysfunction in patients with arthritic diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA) may also be relieved through surgical treatments such as arthrocentesis, lysis, discectomy, and synovectomy.[59,60]

In 2020, Lund et al. proposed a classification scheme with a disease-focused approach to offer standardized clinical evaluation methods.[61] A modified version of the authors' presented flowchart is seen in Figure 2. The surgical treatment of virtually all TMJD is usually delayed in favor of non-surgical or conservative treatment, except for specific conditions such as TMJ ankyloses, tumors and infectious arthritis, where the latter requires acute and speedy surgical intervention.[46,61] The order of the treatment modalities seen in Figure 2 should not be seen as a ranking of the most suitable methods, although many times a less invasive treatment method is chosen initially.

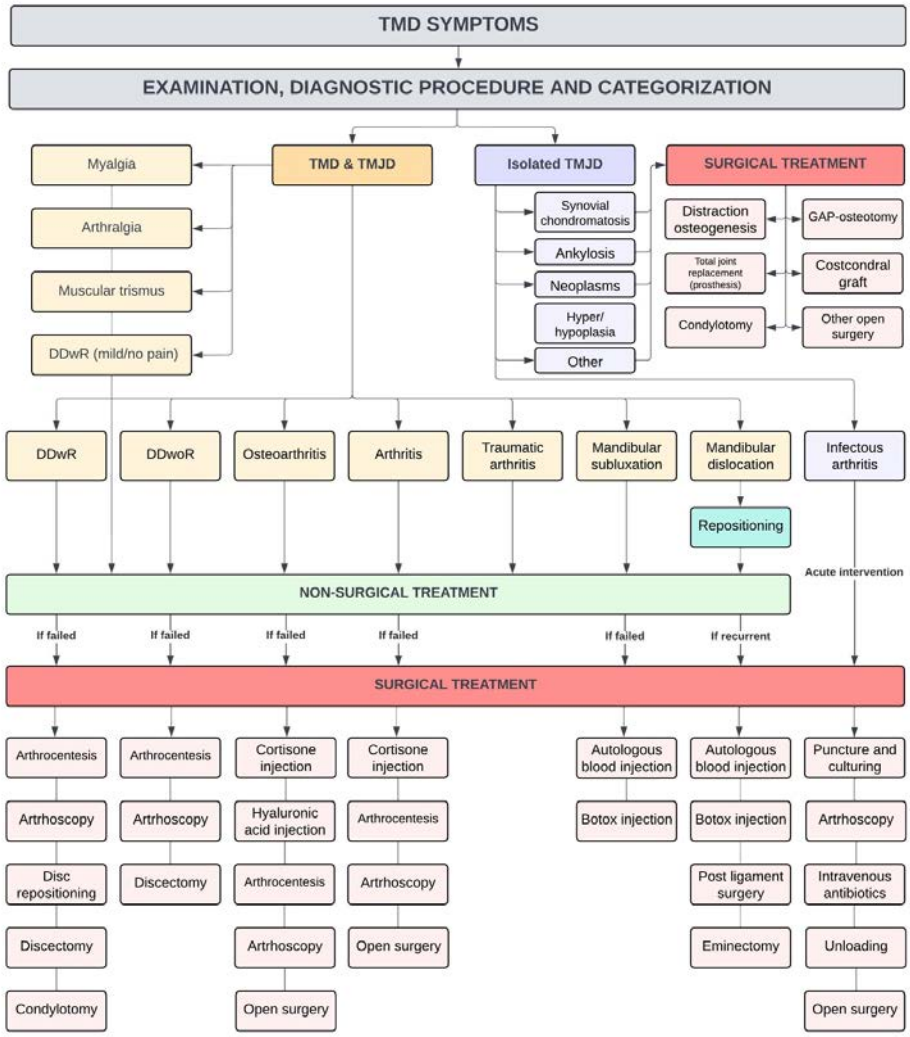

***Figure 2**. Flowchart of possible TMJD treatment procedures, adapted from Lund et al.*[61]

1.4 Etiology

The etiology of TMD and TMJD is considered a multifactorial nexus of causes, many times described in terms of a biopsychosocial model which is depicted in Figure 3, an adaptation from the works of Engel et al. and Suvinen et al.[62,63]

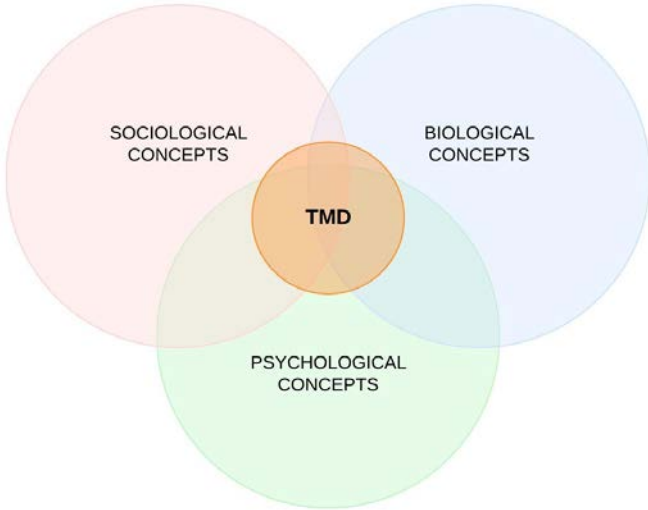

***Figure 3**. Biopsychosocial model described by Engel et al. and Suvinen et al.* [62,63]

1.4.1 Sex, age and educational level

There is a predominance of female pwTMJD, specifically in the group of patients who seek medical help for their condition, and the male to female ratio is reported to be between 1:2 and 1:5.[3,64–67] A systematic review and meta-analysis of five included cross-sectional studies published in 2018 showed an odds ratio of 2.24 of being a woman and having TMD in comparison to a man.[68] A potential explanation to the skewed proportion is that women tend to have higher health awareness and are more prone to seek professional aid when needed.[69] Another explanatory model is the involvement of estrogen and estrogen receptors in the TMJ, and 17β-estradiol has been found to be higher in TMD patients than in healthy controls.[70,71] The possible reasons for the female dominance, however, are still speculative and further research is needed.

Although studies show that TMD symptoms debut during adolescence and peak during midlife, age is a debated risk factor for TMD.[18,20] Some studies have found positive associations between age and TMD, while others have found no or dubious associations to age.[3,64–67] Prevalence of TMD among 50- to 60-year-olds seems to be fairly consistent over time, and generational differences have been proposed as a result of different experiences in societal changes, economic burden, etc.[72] Unell et al., investigating the prevalence of TMD symptoms in subjects aged 65 and 75, found that less than 4% of the participants considered their TMD symptoms to be great or severe, and the majority of the subjects who reported more grave issues were female.[73] Examples of younger cohorts

can be found in a Norwegian study investigating the prevalence of TMD in adolescents aged 13-19 , which reported a prevalence of 7%, and a higher risk of suffering from TMD in subjects with divorced parents and less physical activity.[74] In a cohort of adolescents aged 12–19, it was shown not only that the girls had higher incidence of TMD than the boys but also that the incidence increased with age and more so in girls than in boys.[75]

The inconsistencies also apply when it comes to the association to income, educational level, and other sociodemographic properties as some studies have found a higher risk for TMD among subjects with lower education and some studies paradoxically report an increased risk among subjects with higher education.[65,67] Lifestyle factors such as smoking and increased intake of alcohol consumption have also been found to increase the risk of concurrent TMD.[76] The study in question, however, was conducted on a relatively young sample and had a cross-sectional design, limiting it to mere speculation regarding causality. In a more suitable methodological approach to assess smoking as a risk factor for TMD, a 6-year cohort study found no significant differences in smokers and non-smokers regarding signs of TMD.[77]

1.4.2 Comorbid conditions and potential risk factors

Comorbidity refers to one or several additional diseases that coexist with an index disease in one individual.[78] For TMD, many comorbid conditions have been established including chronic overlapping pain conditions such as headache, low back pain, fibromyalgia, and irritable bowel syndrome, as well as chronic fatigue syndrome, stomach pain, sleep disorders, allergies, and tinnitus.[79-89] The associations are in many cases unclear; as in fibromyalgia, where there are still speculations whether it should be considered as a precursor for TMD, vice versa, or simply a concurrent condition.[86]

Various sorts of headaches such as migraine and tension type headache (TTH) are also found concurrently with TMD.[82] Specifically, myofascial TMD and TTH share many common attributes, such as tenderness and pain on palpation, but despite the obvious overlap between the two conditions, they should still be considered as two individual entities.[83] High prevalence of tinnitus has also been found in TMD populations, and Mottaghi et al. even suggested in a review article that there might be a causal relationship, which is perplexing considering that all the articles included in the review were of cross-sectional design.[87]

These coexistent, many times painful, comorbidities emphasize the complexity of the patient group, and Lim et al. insightfully suggest that these patients should be approached in a more multidimensional manner, stressing the importance of taking comorbid conditions into consideration.[89,90]

Many of the reported comorbid conditions have also been reported as risk factors for incident TMD, such as preexisting pain conditions and sleep disorders.[22,91] Other suggested risk factors include headache, malocclusion, hormonal factors, genetical variations, and psychosocial factors.[91-93]

Parafunctional behaviors such as bruxism have traditionally been closely linked to TMD. In a literature review published in 2010, the authors found a positive association between bruxism and TMD pain; however, this association was much stronger in studies where the bruxism was self-reported. The association was much weaker in studies with more specific diagnosing methods of both bruxism and TMD. The authors further criticized not only the level of evidence in many of the studies but also the inconsistency in defining the conditions.[94] Another literature review of 51 publications concluded that the literature does not support a causal relation between bruxism and painful musculoskeletal symptoms, but that there is an association highly influenced by other factors such as age.[95] A standardized tool to assess bruxism was recently published, which will hopefully streamline the methods to approach and evaluate the role of bruxism in the development of TMD.[96]

Trauma to the head and neck area is another reported cause of TMD. Sharma et al. presented a four-fold increase in probability to develop TMD among individuals with any jaw injury but with no increase in rate after multiple traumas.[97] Although interesting findings, the study excluded almost half of the initially enrolled subjects, leaving room for speculations on selection bias. More specifically, the association between whiplash trauma and TMD is reported in several studies. Whiplash trauma is defined as a translatory trauma to the neck pursued by a hyperextension-flexion trauma and is often caused by car accidents.[98] Most patients recover from the injury, although there is a group of patients that develop whiplash associated disorders (WAD).[99] A review of the literature on TMD and WAD showed a high prevalence and incidence of TMD pain after whiplash trauma but also highlighted the fact that the TMD patients who had not suffered a prior whiplash trauma were more susceptible to customary TMD treatment, suggesting different pathophysiology of the conditions.[98] A more recent study also shows a high incidence of jaw pain in patients that have experienced whiplash trauma, as early as one month after the accident, with indications that psychosocial factors play a part in the severity of the subsequent pain.[100] In a 2-year follow up study after whiplash trauma, subjects with prior trauma showed higher pain intensity, neck disability, jaw disability, jaw pain related disability, jaw pain and dysfunction than controls. The high degree of initial symptoms of depression seemed to level out at follow-up, a finding explained by the immediate psychological response after trauma being reduced along with the recuperation.[101]

Psychosocial factors such as stress, anxiety, depression, somatic syndromes, and pain catastrophizing are also believed to play important roles in the development and severity of TMD.[93,102-107] The following chapters will look closer at the available literature on the association between TMD, MBD, and MSD.

1.4.3 TMD and MBD

The 5th chapter of ICD-10 covers MBD and encompasses an extensive assortment of diagnoses with diverging etiology, prevalence and pathophysiology that are pooled together. The literature on the relation between various MBD and chronic pain is vast, but papers on the relation to TMD are rarer. Table 1 displays an assortment of publications on MBD as a predictor for TMD or where the association between MBD and TMD is investigated. Most studies use a cross-sectional design with convenience sampling and obvious risk for selection bias. The most well-designed studies are mainly focused on depressive and anxiety disorders.[76,102,103,108-123]

This is also where the most interesting findings have been made, with regards to the associations between TMD and depression, somatic symptoms, psychological stress, and affective distress. While affective disturbances often are a consequence of orofacial pain, diminished central inhibition or generalized hypervigilance might precede TMD and be part of the causal pathway.[124] Indications of causal relationships have also been found in a cohort study from the Orofacial Pain Prospective Evaluation and Risk Assessment (OPPERA), where Fillingim et al. reported that many psychological variables such as somatic symptoms, psychological stress, and affective distress increased the risk of first onset TMD.[103] Additionally, the association between depression and TMD has been investigated in registry-based designs in Taiwan with large study populations of almost 1 million subjects and in German cohort studies, where indications of a causal relationship have been found.[102,115,117]

Several cross-sectional and case-control design studies as well as case reports have found associations between TMD and Alzheimer's disease, substance abuse, schizophrenia, eating disorders, sexual dysfunction, sleep dysfunction, paranoid ideations, mental retardation, and attention-deficit/hyperactivity disorder (ADHD).[76,108,111-113,123,125-132] Collectively, they all indicate that there is an association between TMD and many MBD, but the sampling and the general design of many of the studies limit the possibilities of drawing conclusions about causality.

Table 1. Overview of selected observational studies on the association between MBD and TMD.

Authors	Region	Study design	Study population	Exposure	Outcome/ TMD measure	Main findings
F00-F09 Organic, including symptomatic, mental disorders						
De Souza Rolim et al., 2014.[125]	Brazil	Case-control	n=59	Alzheimer's disease	RDC/TMD	Higher prevalence of OA, DD, and orofacial pain in patients with AD than in healthy comparison subjects.
F10-F19 Mental and behavioral disorders due to psychoactive substance use						
Rommel et al., 2016.[118]	Germany	Cross-sectional	n=200	Methamphetamine abuse	Questionnaire and clinical examination	Reported that 47% of substance abusers presented with TMJ pain; however, no corresponding number for the comparison subjects is given. Substance abusers had significantly more signs of bruxism than healthy comparison subjects.
Miettinen et al., 2017.[76]	Finland	Cross-sectional	n=8678	Smoking, snuff, and alcohol consumption	Self-reported	Smoking was associated with increased TMD symptoms but not TMJ clicking. Drinking alcohol was associated with facial pain, TMJ pain on movement and rest, and TMJ clicking.
F20-F29 Schizophrenia, schizotypal and delusional disorders						
Velasco-Ortega et al., 2005.[108]	Spain	Case-control	n=100	Schizophrenia	Clinical examination)	Patients with schizophrenia showed significantly more signs of TMD than healthy comparison subjects.
Gurbuz et al., 2009.[111]	Turkey	Cross-sectional	n=446	Schizophrenia	RDC/TMD	Significant differences in joint pain and joint sounds between patients with schizophrenia and healthy comparison subjects.
F30-F39 Mood affective disorders						
Fillingim et al., 2011.[114]	U.S.A	Case-control	n=1818	Psychosocial function, affective distress, psychosocial stress, somatic awareness, catastrophizing.	DC/TMD	Patients with TMD had significantly higher levels of psychological and affective distress, perceived stress, catastrophizing, and increased somatic awareness.
Liao et al., 2011.[115]	Taiwan	Cohort	n=37 682	Depression	ICD-9-CM	2.65 times higher incidence of TMD among patients with depression. HR for TMD among patients with depression was 2.21, with higher risk for women.
Kindler et al., 2012.[102]	Germany	Cohort	n=3006	Depression	Clinical examination	Subjects with depression had increased risk of TMD, RR 2.1. Anxiety symptoms were related to joint pain.
Fillingim et al., 2013.[103]	U.S.A	Cohort	n=2737	Psychological function, affective distress, psychosocial stress, somatic symptoms, catastrophizing etc.	RDC/TMD	Somatic symptoms, general psychological symptoms, stress, and negative mood were predictive of TMD. Catastrophizing was not significantly predictive of TMD.
Lin et al., 2016.[117]	Taiwan	Cohort	n=926 560	Depression (divided into two propensity groups)	ICD-9-CM	Chronic depression increases the risk of TMD, HR 1.64 for propensity group 2.
Wu et al., 2021.[121]	China	Cross-sectional	n=754	Depression, Anxiety	DC/TMD	Higher prevalence of depression and anxiety among TMD subjects compared to healthy comparison subjects.
Hu et al., 2022.[122]	China	Case-control	n=200	Depression, Anxiety, Severity of symptoms	DC/TMD and MRI	Anxiety, depression, and somatic symptoms were risk factors for joint sounds. Depression was a risk factor for TMD pain.
F50-F59 Behavioral syndromes associated with physiological disturbances and physical factors						
Emodi Perlman et al., 2008.[110]	Israel	Cross-sectional	n=127	Eating disorders (bulimia, anorexia, and other)	RDC/TMD	Patients with ED had significantly higher prevalence of muscle pain, depression, somatization, and anxiety.
Johansson et al., 2010.[113]	Sweden	Case-control	n=108	Eating disorders (bulimia, anorexia, and other)	Questionnaire	Orofacial pain and TMD signs were more common in patients with ED than in healthy comparison subjects.
Sanders et al., 2016.[119]	U.S.A	Cohort	n=3263	Sleep disorder	DC/TMD	Higher incidence of TMD among subjects with poor sleep quality at baseline, HR 2.04.
F70-F79 Mental retardation						
Gurbuz et al., 2010.[112]	Turkey	Cross-sectional	n=222	Mental retardation	RDC/TMD	TMD signs were more common in patients with mental retardation.
Vitor et al., 2021.[120]	Brazil	Cross-sectional	n=50	Intellectual disability	DC/TMD	No significant differences in pain threshold of musculus masseter/temporalis between patients and healthy comparison subjects.
F90-F98 Behavioral and emotional disorders with onset usually occurring in childhood or adolescence						
Suligowska et al., 2021.[123]	Poland	Cross-sectional	n=284	ADHD	Questionnaire and clinical examination	Symptoms of TMD and parafunctional behavior were significantly more frequent in patients with ADHD than in healthy comparison subjects.

1.4.4 TMD and MSD

After chronic low back pain, TMD is the most common MSD that results in pain and disability.[9] Consequently, it is not improbable to consider that other MSD might impact the development of TMD. There is a vast number of publications on the matter and this chapter will cover some of the available literature. Table 2 lists an overview of many of the observational studies on the association between MSD and TMD.[81,133-151]

Many observational studies on the association between MSD and TMD are of cross-sectional design, showing that several MSD coincide with TMD, but with limited, not to say nonexistent, possibilities of causal conclusions. There are, however, Asian, and North American population-based cohort studies that show interesting results. The largest cohort study on MSD exposure and the development of TMD is from the American Veterans Musculoskeletal Disorders Cohort with an impressive study population of over 3 million subjects.[139] Although this cohort study includes a very large number of subjects, it uses a cohort exclusively recruited from military veterans. This cohort's limitations include a skewed male to female ratio, one that does not mirror the general population. Moreover, veterans are known to have high presence of persistent pain strongly influenced by mental health status.[152] Nonetheless, the influence of psychological factors in the association between MSD and TMD should not be ignored, and reviews on even rare conditions such as systemic lupus erythematosus (SLE) and ankylosing spondylitis (AS) show strong associations to TMD with the possible influence of stress, anxiety, and depression.[153,154]

Often, the literature fails to establish a causal relationship between the proposed exposure and outcome due to a range of methodological shortcomings or limitations. This failure results in an abundance of studies that may report the prevalence of coexistent pathologies, but with restricted or no potential to infer causal relationships. The quantity of cross-sectional studies and case reports on the association between MSD and TMD is astounding; however, despite interesting cohort-designed approaches that investigate possible causal relationships, there are no European counterparts to the existing large studies reported in the Asian and North American literature. Obviously, there is a need for more epidemiological research on potential risk factors for the development of TMD and TMJD, preferably in population-based samples and with prospectively collected data.

Table 2. Overview of selected observational studies on the association between MSD and TMD.

Authors, year	Region	Study design	Study population	Exposure	Outcome/ TMD measure	Main findings
Fenton et al., 2018.[139]	United States of America	Cohort	n=3 874 625	ICD-9 MSD	ICD-9	TMD patients were younger and more likely female in a cohort of MSD patients. TMD was associated with several non-MSD comorbidities.
M00-M25 Arthropathies						
Abrahamsson et al., 2017.[136]	Norway	Cross-sectional	n=54	Hand OA	TMJ OA (CBCT)	TMJ OA was common in patients with OA in the hand. No significant differences in age, sex, and BMI for TMJ OA.
Lin et al., 2017.[137]	Taiwan	Cohort	n=34 634	ICD-9-CM RA	ICD-9-CM	Higher risk of developing TMD among RA patients, HR 2.5. Lower risk among men and individuals over 40 years old. Higher risk among individuals with insomnia, stroke, and MBD.
Byun et al., 2020.[142]	South Korea	Cohort	n=15 610	ICD-10 RA	ICD-10	Increased risk of TMD in RA patients, HR 2.52. Lower risk for men over 60 years.
Fischer et al., 2020.[144]	Norway	Cross-sectional	n=441	JIA	DC/TMD	TMD was more common in JIA patients than in healthy comparison subjects.
Ma et al., 2022.[150]	Taiwan	Cohort	n=13 944	JIA	RDC/TMD	Higher risk of TMD among JIA patients, relative risk 2.047, compared to unexposed comparison subjects.
M30-M36 Systemic connective tissue disorders						
Aliko et al., 2011.[134]	Albania	Cross-sectional	n=248	SLE, RA, systemic sclerosis	clinical examination	Significantly higher prevalence of TMD among patients with SLE, RA, and systemic sclerosis.
Aceves-Avila et al., 2013.[135]	Mexico	Cross-sectional	n=171	SLE, osteoarthrosis, ankylosing spondylitis	Clinical examination	TMD signs were found in 26/39/38% of RA/AS/OA patients. RA, AS, and SLE more common among middle-aged individuals and OA more common in older patients.
Crincoli et al., 2018.[138]	Italy	Cross-sectional	n=144	Sjögren's syndrome	RDC/TMD	Higher prevalence of TMD signs among patients with SS than in healthy comparison subjects although not for TMJ sounds.
Crincoli et al., 2020.[143]	Italy	Cross-sectional	n=110	SLE	DC/TMD	SLE patients had more frequent complaints of TMJ symptoms, but only TMJ movement had significant difference between SLE patients and healthy comparison subjects.
Crincoli et al., 2021.[146]	Italy	Cross-sectional	n=104	Inflammatory myopathies	Clinical examination and questionnaire	No significant difference in arthralgia between patients and healthy comparison subjects. Significant difference was found in muscle pain. TMJ sounds were more frequent in patients.
M40-M54 Dorsopathies						
Wiesinger et al., 2007.[133]	Sweden	Case-control	n=288	Back pain	Clinical examination	Frequent TMD symptoms more common among patients with back pain than in healthy controls, OR 7.3.
Kim et al., 2019.[140]	South Korea	Cross-sectional	n=24 750	ICD-10 M40, M41, M43, M50, M51, M53, M54, M99	DC/TMD	A strong association between TMD and spinal pain with stronger association in more severe TMD.
Bilgin et al., 2020.[141]	Turkey	Cross-sectional	n=98	Ankylosing spondylitis	DC/TMD	Smoking, high disease activity, neck disability, and bruxism were associated with TMD among patients with AS.
Lee et al., 2020.[145]	Taiwan	Cohort	n=260 484	ICD-9-CM Low back pain	ICD-9-CM	Increased risk of developing TMD among patients with low back pain, HR 1.561. Higher risk of TMD in younger patients.
Huang et al., 2021.[147]	Taiwan	Cohort	n=16 020	ICD-9-CM AS	ICD-9-CM	Increased risk of TMD among AS patients, HR 2.66. Increased risk of AS in TMD patients, HR 1.49, indication bidirectional association.
Uçar et al., 2022.[151]	Turkey	Cross-sectional	n=58	Idiopathic scoliosis	Clinical examination and MRI	More TMD symptoms in patients with scoliosis but no differences in masseter muscle volume.
M60-M79 Soft tissue disorders						
Aaron et al., 2000.[81]	USA	Cross-sectional	n=94	Fibromyalgia	Clinical examination	Patients with fibromyalgia had significantly higher prevalence of TMD than healthy comparison subjects.
M80-M94 Osteopathies and chondropathies						
Lee et al., 2021.[148]	Taiwan	Cohort	n=52 652	ICD-9-CM Osteoporosis	ICD-9-CM	Higher risk of TMD in patients with osteoporosis than without, HR 2.564.
Kim et al., 2022.[149]	South Korea	Cohort	n=122 640	ICD-10 Osteoporosis	ICD-10	Higher risk of TMD in patients with osteoporosis, HR 1.96. Higher risk in older subjects.

1.5 Swedish social insurance benefits

Unemployed, employed, and self-employed Swedish citizens are covered by social insurances from the Swedish Social Insurance Agency (SIA). Two main types of compensation systems are available in Sweden: sick leave (SL) and disability pension (DP). Collectively, these can be referred to as work disability. Long-term SL (>60 days) in Sweden have fluctuated over the years due to changes in generosity of reimbursement and public health indicators, including alcohol sales, smoking habits, and sleeping habits. The fluctuations may be hard to interpret as decreases in DP may increase long-term SL and increases in DP may decrease long-term SL. Increased wages and psychosocial environment could also explain the fluctuations. Women have considerably more work disability than men, and factors such as living conditions and educational level play crucial roles.[155-157] In addition, women are on more long-term SL (>60 days) than men, a phenomenon greatly influenced by occupational situation and psychosocial work environment.[158]

1.5.1 Sick leave

SL can be awarded from the age of 16 in case of disease or injury. SL requires a doctor's certificate from the 8th day of absence. The first 14 days of absence are reimbursed by the employer. After day 14, SIA covers the reimbursement costs. SL is awarded in levels of 25, 50, 75, or 100% of the employment and covers nearly 80% of the individual's salary, up to a certain limit. After a year on SL, the coverage is lowered to 75% unless certain requirements are met.[157]

1.5.2 Disability pension

Individuals aged 19-64 with long-term incapacity to work can be granted DP, which amounts to almost 65% of lost income. The nomenclature has changed over the years and currently individuals under the age of 30 apply for "activity compensation" and individuals over 30 apply for "sickness compensation"; these reimbursements are collectively referred to as DP. Like SL, DP is awarded in coverage of 25, 50, 75, or 100%. Individuals with congenital disorders or diseases acquired during adolescence are available for DP compensation with no requirements of being employed or seeking employment.[156,157]

1.5.3 Morbidities' impact on sick leave and disability pension

The most common causes for SL are MBD (ICD-10 F00-F99), MSD (ICD-10 M00-M99), and injury and poisoning (S00-T98). MBD account for the longest SL spells, and the lowest rates of return to work (RTW) together with malignant neoplasms and cardiovascular disease.[159] The need for SL among individuals with MBD is highly influenced by age, sex, and occupation.[160] MBD include hyperkinetic disorders such as ADHD (ICD-10 F90), which also has been linked to an increased need of DP.[161,162] For MSD, the longest SL spells are found among individuals with disc disorders (ICD-10 M51), with overall higher mean annual days among women. Chronic inflammatory diseases such as RA also represent high numbers and require repeated spells.[163] MSD, MBD, diabetes, and endocrine diseases are the leading causes of years lived with disability (YLD).[164] Furthermore, for countries with

high sociodemographic index, the leading causes for YLD during the last 30 years have been low back pain, headache disorders, depressive disorders, anxiety disorders, and diabetes.[165] Sweden is no exception. A report from SIA shows that the most common cause for both SL and DP in Sweden is MBD, which is followed by MSD. Together, these conditions accounted for more than 50% of SL costs and 90% of all DP costs in 2020.[166]

Few studies have investigated the impact of TMD and TMJD on work disability. Two Finnish studies, one in 1983 and one in 1997, show that patients with TMD and TMJD had more frequent and longer SL spells than healthy comparison subjects.[167,168] On the other hand, the individual and societal financial burdens of TMD and other types of chronic pain have been described in other terms, such as increased number of health care visits, increased work absenteeism, and increased risk of leaving the labor market.[169,170] In the United States of America, TMD has been estimated to cause 17.8 million lost workdays for every 100 million working adults.[93]

Clearly, there is a knowledge gap regarding the need for social insurance benefits among pwTMJD. The strong association between MBD, MSD, and TMD/TMJD and the notion that these comorbidities have a strong impact on the need for SL and DP calls for further studies that investigate not only the reliance on social insurance benefits among pwTMJD, but also the impact of comorbidities on the reliance.

2 Research aims

2.1 General aim

Using a population-based and epidemiological approach, this thesis aims to increase the knowledge of potential predictors of TMJD, the work disability among these patients, and how comorbidities impact the trajectory of SL and DP among pwTMJD. In addition, this thesis compares differences in these inquiries between pwTMJD diagnosed in a hospital setting and pwTMJD that have undergone surgical treatment.

2.2 Specific aims

Study I aims to increase knowledge on the need for social insurance benefits, more specifically SL and DP, among patients with TMJD compared to a unexposed cohort representing the general population.

Study II aims to clarify the association between mental and behavioral disorders and the development of TMJD.

Study III aims to explore the association between musculoskeletal and connective tissue disorders and TMJD and to increase the understanding of how age interacts with such associations.

Study IV aims to further examine how MBD and MSD comorbidity impact the trajectory of SL and DP among pwTMJD compared to the general population.

3 Materials and methods

3.1 Study designs

This thesis is compiled of four studies: two case-control studies and two cohort studies. A summary of the study designs is presented in Table 3.

Table 3. Study designs and methods of Study I-IV.

Study	Study design	Sources	Subjects	Exposure	Outcome	Covariates	Statistics
I	Retrospective cohort study on prospectively collected data	NPR, TPR, LISA	219 255	TMJD, divided into three subcategories: NS, ST1, and ST2	Annual days of sick leave and disability pension	Gender, age, DEGURBA, educational level, year of inclusion, and country of birth	Generalized estimating equations
II	Case-control study	NPR, TPR, LISA	366 437	MBD	TMJD, divided into three subcategories: NS, ST1, and ST2	DEGURBA, educational level, country of birth, maxillofacial/neck trauma, and MSD comorbidity	Conditional logistic regression
III	Case-control study	NPR, TPR, LISA	366 437	MSD	TMJD, divided into three subcategories: NS, ST1, and ST2	DEGURBA, educational level, country of birth, and MBD comorbidity	Conditional logistic regression, conditional logistic regression with interaction terms
IV	Retrospective cohort study on prospectively collected data	NPR, TPR, LISA	219 255	TMJD, divided into two subcategories: NS and S	Annual days of sick leave and disability pension	Gender, age, DEGURBA, educational level, year of inclusion, and country of birth	Generalized estimating equations, stratified on comorbidity groups

3.2 Data sources

There are several national Swedish registries that store information on citizens regarding educational level, marital status, source of income, taxation, work disability, medical information, and much more. This thesis uses some of these registries to form the study population and collect data on exposures, outcomes, and covariates. These will be described in the following chapter.

3.2.1 The Personal Identity Number

A crucial part of registry-based research is to link individuals between different sets of registries; in Swedish registry-based research, this is enabled by a 12-digit Personal Identity Number (PIN). The PIN, introduced in 1947, includes information on birth date and the sex of the individual. It serves as a unique identifier in many areas of Swedish society, including statistics of income, immigration, migration, tax information, and health care, where it is frequently used for journal purposes and referrals. The PIN is assigned to every individual born in Sweden and to everyone registered in the Swedish Population Registry, regardless of citizenship status. The PIN also serves for general vital status of the Swedish population, and 93% of all deaths and 90% of all births are estimated to be reported within 10 days. A PIN is changed only under very rare circumstances such as after gender-

affirming surgery or when a resident is in a life-threatening situation that requires a new identity. The PIN is undoubtedly highly personal, and the use of it normally requires informed consent. However, according to Swedish regulations, the PIN is allowed to be used in registry-based research, where consent is unobtainable due to the large sample sizes often included in such studies. Therefore, the PIN serves as a highly trustworthy identifier and the biggest pitfall for researchers is the very few PINs that have been changed or are reused. However, these occurrences are so uncommon that they are unlikely to influence the outcome of the research when using large population-based samples.[171]

3.2.2 Population registries in Sweden

There are two population registries in Sweden, the Population Register (PR-Tax) and the Total Population Register (TPR). PR-Tax is managed by the Swedish Tax Agency and is mainly used, often by authorities, to obtain data that give an overview of the Swedish population. The TPR is managed by Statistics Sweden (SCB) and includes the same variables as the PR-Tax but is intended for statistical calculations and is more commonly used in research. The TPR was introduced in 1968 and includes information on all births, deaths, emigrations, immigrations, migrations within Sweden, living addresses, marital status, country of birth and gender. It has a coverage of 100% of all births and deaths, and over 90% of immigrations and emigrations are reported within 30 days.[172] The TPR may be used to identify matched study groups to serve as controls or unexposed comparison subjects in registry-based research.

3.2.3 Patient registries

The Swedish National Inpatient Registry (NPR) was instituted in 1964 and holds complete national coverage since 1987. Roughly 99% of all somatic and psychiatric hospital discharges are registered to the NPR in accordance with the national ICD system. The methodical gathering of this data is essential as it is used to plan, assess, and ultimately fund health care in Sweden. The positive predictive value (PPV) of NPR depends on the type of diagnosis. The overall PPV is 85–95% but with a lower sensitivity. Severe diseases are more commonly correctly registered than milder afflictions, and inpatient care has higher coverage than outpatient care.[173]

3.2.4 LISA

The Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA) is a registry that stores information on occupation, education, income, and work disability, among many other sociodemographic variables. All citizens from 16 years of age are included in the registry. It was initially launched in 1990 as a response to an increasing level of SL in Sweden. Data from LISA can be used in medical research for exposure and outcome measures, gathering of covariates, or longitudinal changes in repeated measurements, for example, measuring the disposable income after a severe diagnosis.[174]

3.3 Study population

3.3.1 pwTMJD

pwTMJD were identified during the initial stage of the data collection. The definition of TMJD was the ICD-10 code K07.6 (temporomandibular joint disorders) and NCSP codes used in the surgical treatment of TMJD. The following NCSP codes were used as proxies for TMJD:

1. EDC00 Condylotomy of mandible
2. EGA00 Arthroscopy of mandibular joint
3. EGA20 Biopsy of mandibular joint
4. EGB00 Condylectomy of mandible
5. EGB10 Meniscectomy of mandibular joint
6. EGB20 Synovectomy of mandibular joint
7. EGC00 Open reduction of dislocation of jaw
8. EGC10 Arthroplasty of mandibular joint without graft
9. EGC20 Arthroplasty of mandibular joint with bone or other graft
10. EGC30 Prosthetic replacement of mandibular joint
11. EGC99 Other reconstructive operation on mandibular joint
12. TEG10 Injection of diagnostic or therapeutic substance into mandibular joint

All Swedish individuals aged 18 or above, with any of the NCSP codes or K07.6 recorded in the NPR between 1998 and 2016 were included. They were included the first time a main diagnosis was recorded or the first time a surgical treatment was provided. Collection of data regarding procedure codes was not discontinued after inclusion to enable categorization into subgroups, which is described later. In Study II and III, this data was used to define the outcome; in Study I and IV, it was used to define the exposure.

3.3.2 Comparison subjects

The PIN was used to match the pwTMJD 1:10 on age, gender, and region to individuals from the TPR. The subjects collected from the TPR were used as controls in the case-control studies (Study II and III) and as an unexposed comparison cohort in the cohort studies (Study I and IV).

3.4 ICD codes

ICD codes were used as exposures in Study II and III and for stratification of comorbidity status in Study IV. The codes were collected via the NPR from 1964 to inclusion into the study or 2016, which ever came first. As ICD versions have changed over time, codes from ICD-7, ICD-8, ICD-9, and ICD-10 were included. The translation from earlier versions of ICD to ICD-10 was conducted using a codebook provided by the NBHW.

3.4.1 MBD

MBD was defined by the 5th chapter of ICD-10 but has historically been defined by other codes contained in earlier versions of ICD (Table 4). Figure 6 displays a presentation of all the diagnoses included in the chapter.

Table 4. Current and historical classifications of MBD according to ICD.

ICD-7 (1958–1968)
Psychoses (300–309)
Psychoneurotic disorders (310–318)
Disorders of character, behavior, and intelligence (320–326)
ICD-8 (1969–1986)
Psychoses (290–299)
Neuroses, personality disorders and other nonpsychotic mental disorders (300–309)
Mental retardation (310–315)
ICD-9 (1987–1996)
Organic psychotic conditions (290–294)
Neurotic disorders, personality disorders and other nonpsychotic mental disorders (300–316)
Mental retardation (317–319)
ICD-10 (1997–)
Mental and behavioral disorders (F00–F99)

3.4.2 MSD

MSD was defined by the 13th chapter of ICD-10; the historical definitions of MSD are seen in Table 5. Figure 7 displays a presentation of all the diagnoses included in the chapter.

Table 5. Current and historical classifications of MSD according to ICD.

ICD-7 (1958–1968)
Arthritis and rheumatism, except rheumatic fever (720–727)
Osteomyelitis and other diseases of bone and joint (730–738)
Other diseases of musculoskeletal system (740–749)
ICD-8 (1969–1986)
Arthritis and rheumatism, except rheumatic fever (710–718)
Osteomyelitis and other diseases of bone and joint (720–729)
Other diseases of musculoskeletal system (730–738)
ICD-9 (1987–1996)
Arthropathies and related disorders (710–719)
Dorsopathies (720–724)
Rheumatism, excluding the back (725–729)
Osteopathies, chondropathies and acquired musculoskeletal deformities (730–739)
ICD-10 (1997–)
Diseases of the musculoskeletal system and connective tissue (M00–M99)

3.5 Registry inquiry and amalgamation of data

This thesis used Swedish PINs to collect registry data from NPR, LISA, and TPR via the NBHW and SCB. The inquiry of registry data in Sweden requires an ethical permit from the Regional Ethical Committee. When a permit is obtained, an application is sent to the NBHW registry service as well as to SCB for microdata inquiry. Both the NBHW and SCB conduct their own ethical vetting before commencing data collection from the registries. Case managers are appointed from the NBHW and SCB to collaborate in the registry data inquiry, which is initiated on behalf of the NBHW. A schematic figure of the registry inquiry is seen in Figure 4.

The data sets are delivered as separate data files for inpatient and outpatient care, and LISA data are delivered in files based on calendar year. Therefore, data must be merged to compile an amalgamation of information, unique for the specific research project at hand.

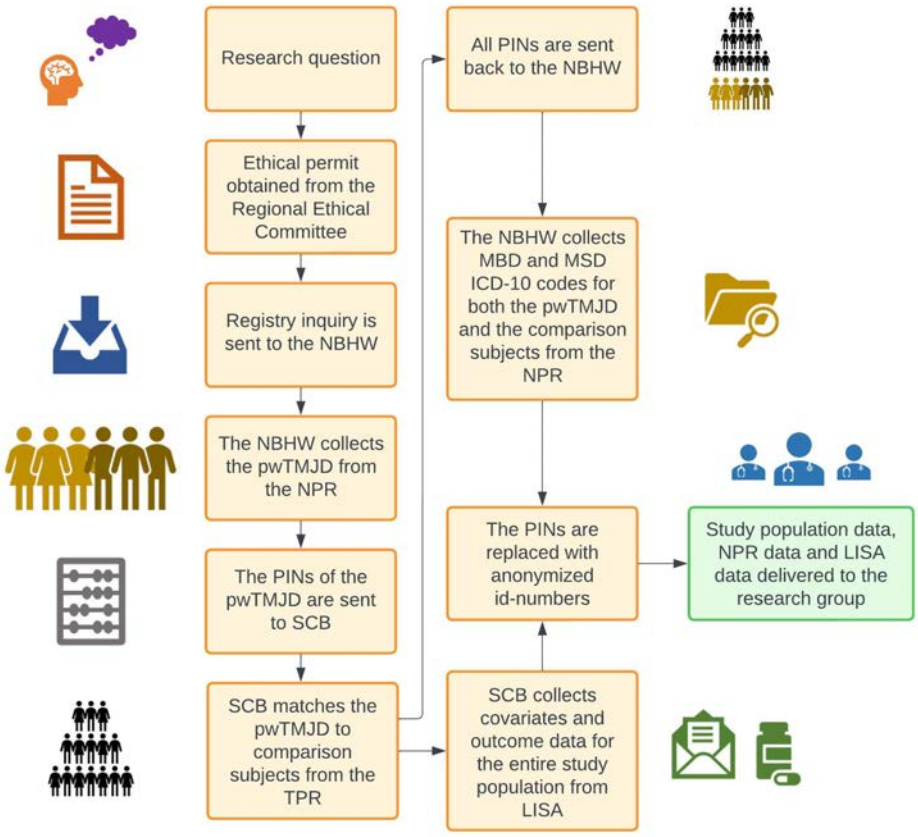

***Figure 4**. Flowchart of registry inquiry and recruitment of study population.*

3.6 Study II and III

Study II and III investigated MBD and MSD as predictors for TMJD.

3.6.1 Exposure

For both Study II and III, exposure data were collected via the NPR from 1964 until inclusion in the study, when the cases received their first TMJD diagnosis or surgical treatment. The exposure data was collected for the control group at the same time as for the cases they were matched to (Figure 5).

Exposure in Study II was MBD recorded in the NPR before the outcome. The exposures were divided into eleven diagnostic categories in accordance with ICD-10; each category contains several diagnoses. The eleven diagnostic categories and the contained diagnoses are depicted in Figure 6.

Exposure in Study III was MSD recorded in the NPR before the outcome. The exposures were divided into six diagnostic categories in accordance with ICD-10; each category contains subcategories and several diagnoses, which are depicted in Figure 7.

3.6.2 Outcome

Outcome in Study II and III was TMJD, which was defined according to the description in 3.3.1. The outcome was further subcategorized based on the number of surgical procedures as follows:

1. TMJD with no subsequent surgical treatment (NS);
2. TMJD with one subsequent surgical treatment procedure (ST1); and
3. TMJD with two or more subsequent surgical treatment procedures (ST2).

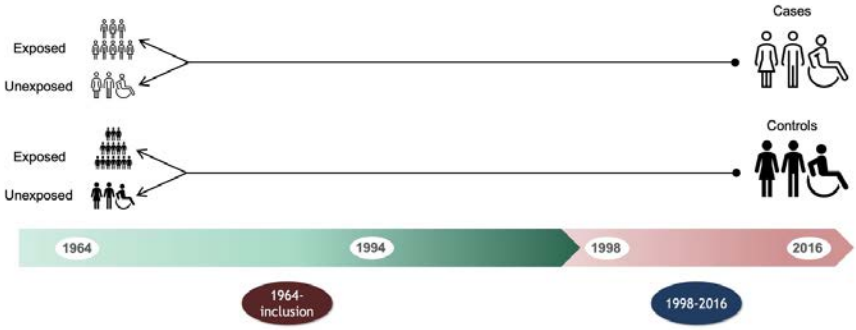

***Figure 5**. Timeline of data collection for Study II and III. Outcome data was collected between 1998 and 2016. Information on exposure of MBD and MSD was collected from 1964 to the outcome. Both exposure and outcome data were collected from the NPR.*

***Figure 6**. MBD taxonomy according to ICD-10.*

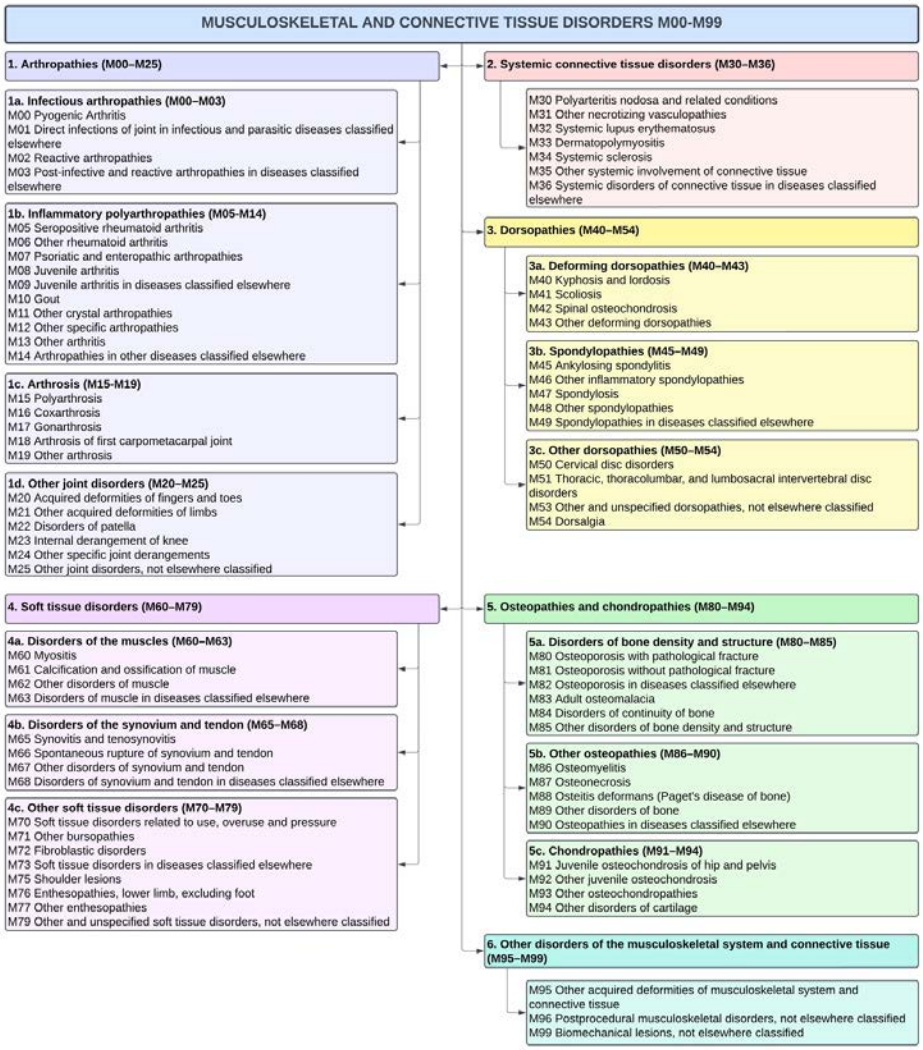

***Figure 7**. MSD taxonomy according to ICD-10.*

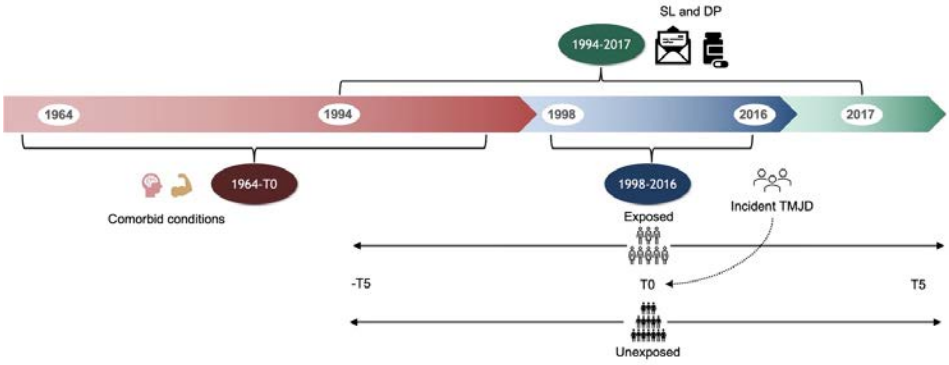

***Figure 8**. Timeline of data collection for Study I and IV. The collection of MBD and MSD ICD codes from the NPR was from 1964 to inclusion (T0). Time of inclusion demarks T0 for both exposed and unexposed subjects. The collection of exposure (TMJD) from the NPR was between 1998 and 2016. The collection of main the outcomes SL and DP from LISA was from -T5 to T5. Modified figure from Study IV.*

3.7 Study I and IV

Study I compared the mean annual days of work disability among pwTMJD with an unexposed cohort representing the general population. Study IV compared the trajectory of SL and DP among these cohorts stratified on MSD and MBD comorbidity.

3.7.1 Exposure

The exposure in Study I was TMJD divided into three subcategories of exposure based on the number of surgical procedure codes recorded between 1998 and 2016:

1. TMJD with no subsequent surgical treatment (NS);
2. TMJD with one subsequent surgical treatment procedures (ST1); and
3. TMJD with two or more subsequent surgical treatment procedures (ST2).

In Study IV, the subdivision of TMJD was limited to two categories of exposure to maintain an adequate number of observations and subjects in each subgroup and strata:

1. TMJD with no subsequent surgical treatment (NS) and
2. TMJD with subsequent surgical treatment procedure(s) (S).

Data on comorbidity was collected from 1964 until inclusion in the study (T0) – e.g., when the exposed subjects were first defined as exposed. The comorbidities were collected simultaneously for the unexposed cohort. The cohorts were also stratified into categories of comorbidity:

1. Group I: No prior comorbidity recorded;
2. Group II: MSD comorbidity recorded, but no MBD comorbidity;
3. Group III: MBD comorbidity recorded, but no MSD comorbidity; and
4. Group IV: Both MSD and MBD comorbidity recorded.

3.7.2 Outcome

Outcomes in Study I and IV were mean annual net days of SL and DP, which are recorded as repeated measures on an annual basis in LISA. The collection of outcome data from LISA was conducted between 1994 and 2017. The follow-up time for the outcomes was five years before inclusion (-T5) to five years after inclusion (T5) (Figure 8). Only individuals aged 23–59 were included in Study I and IV; subjects who did not meet the age criteria were excluded to ensure completeness of the follow-up time as SL and DP are available for individuals aged 18–64 and 19–64, respectively.

3.8 Covariates

The studies included in this thesis used several covariates. Most covariates were collected through LISA and were included in the models in all the studies in a similar way. The covariates used were sex, age, level of education, country of birth, degree of urbanization, MSD comorbidity, MBD comorbidity, and maxillofacial and neck trauma (Table 6). Calendar year was included as a dummy variable in Study I and IV to account for changes in generosity of reimbursement over time.

Degree of urbanization was used as a categorical variable categorized into three groups according to Eurostat's Degree of Urbanization (DEGURBA).[175] Sweden's 290 municipalities were divided according to Statistics Sweden's January 1, 2019 publication on regional divisions.[176]

In Study II, MSD was used as a binary variable to adjust for the possible impact of MSD on both the exposure and outcome. MSD was defined as having acquired an MSD diagnosis before inclusion (ICD-10 M00-M99).

In Study II, maxillofacial and neck trauma was used as a binary variable to account for its possible impact on both the exposure and the outcome. Maxillofacial trauma was defined by the ICD-10 codes for fracture of malar, maxillary and zygoma bones (S02.4), fracture of the mandible (S02.6), and dislocation and sprain of joints and ligaments of the neck (S13).

In Study III, MBD was used as a binary variable to adjust for the possible impact of MBD on both the exposure and outcome. MBD was defined as having acquired an MBD diagnosis before inclusion (ICD-10 F00-F99).

Table 6. Covariates used in Study I–IV.

Variable	Source	Study	Variable type	Values
Sex	LISA	I–IV	Binary	1. Male 2. Female
Country of birth	LISA	I–IV	Categorical	1. Sweden 2. Other Nordic countries 3. Other European countries 4. Non-European countries
Educational level	LISA	I–IV	Ordinal	1. Primary/lower secondary school (0-9 years) 2. Upper secondary school (9-12 years) 3. Post-secondary school (>12 years)
Degree of urbanization	LISA	I–IV	Categorical	1. Cities 2. Towns and suburbs 3. Rural areas
Calendar year	LISA	I and IV	Categorical	Year 1994-2017
Age	LISA	I and IV	Ordinal	1. 23-25 years 2. 26-30 years 3. 31-35 years 4. 36-40 years 5. 41-45 years 6. 46-50 years 7.51-55 years 8. ≥56 years
MSD comorbidity	NPR	II	Binary	0. No MSD comorbidity 1. MSD comorbidity
Maxillofacial/neck trauma	NPR	II	Binary	0. No Trauma 1. Trauma
MBD comorbidity	NPR	III	Binary	0. No MBD comorbidity 1. MBD comorbidity

3.9 Statistical methods

STATA SE 16.1 software (Stata Corporation LLC, College Station, U.S.A) was used for all statistical analyses. P-values higher than 0.05 were considered statistically insignificant.

3.9.1 Imputing of missing data

Missing data in a study sample is quite common in epidemiological research and the handling of it is important to minimize potential bias and misinterpretation of the results. In 1976, Rubin classified missing data into three categories: missing completely at random (MCAR); missing at random (MAR); and missing not at random (MNAR). MCAR means that the probability of data being missing is unrelated to any other observed or unobserved variable–i.e., the cause for the missing data is unrelated to the data itself. MAR, a much broader term, implies that the missingness of data is related to one or more observable variables. This is more realistic than MCAR causing it to be more frequently used in research. For MNAR, neither MCAR nor MAR is applicable, and data are missing due to unknown reasons.[177] Complete case analysis means that subjects with missing data are excluded from any statistical model; this method is also called listwise deletion. For MAR and MNAR, listwise deletion may be associated with bias but can be effective when it means discarding only a small part of the sample.[178] When using listwise deletion, it is essential to estimate the cause for missing data and closely consider possible causal effects and effect modifications.[179]

How much missing data is tolerable? That is a question that has been debated rigorously, and 5–10% missing is considered acceptable.[180] There are several approaches to handling missing data other than listwise deletion, including multiple imputation (MI). In short, MI creates multiple copies of the dataset with replaced values for missing values. The replacement of the missing data is sampled from a prediction based on other observed data or variables in the dataset. The values of the multiple new datasets are then pooled into imputed measures for the missing data, filling the gaps of where the data once contained missing values.[181] The number of imputations or simulated datasets have historically been recommended to vary between three to five, but there are suggestions that the number of imputations should be 20.[182]

In this thesis, a method of MI called Multiple Imputation by Chained Equations (MICE) was used. In MICE, multiple predictive variables are included in the regression model, including the outcome.[183,184] The missing values for level of education, DEGURBA, and country of birth were imputed with 20 imputations per missing data, assuming MAR. To impute DEGURBA and country of birth, multinomial logistic regression was used, and ordinal logistic regression was used for educational level.

3.9.2 Generalized estimating equations

Generalized Estimating Equations (GEE), a regression model for data constructed around repeated measures correlating within a subject or a cluster of subjects, can be used to model population averages. When fitting a GEE model, one must specify the link to be used, the distribution of the dependent variable, and the correlation structure of the dependent variable.[185] In Study I and IV, annual number of days on SL and DP were modelled as repeated measures and regressed using GEE. The log link function was used assuming Poisson distribution and an autoregressive correlation structure, as repeated measures close to each other in time were expected to correlate more than measures further away from each other. The model also included the cohorts, year as a dichotomized dummy variable, and the interaction between time and the cohorts. Adjustment variables were educational level, sex, country of birth, DEGURBA, and year of inclusion. The analyses were performed in relation to inclusion year (T0)–i.e., the first time of diagnosis or first surgical intervention, depending on the nature of inclusion, between five years before inclusion (-T5) and five years after inclusion (T5), where T0 was set as reference for time.

3.9.3 Conditional logistic regression

Logistic regression can be used when the dependent variable is binary, such as alive and diseased, or TMJD and no TMJD. The predictor variable or variables can be binary, continuous, or categorical. The logistic regression models predictors or independent variables to estimate the likelihood (i.e., odds) of the outcome.[186] For example, the likelihood of the cases to have the exposure versus the likelihood of the controls to have the exposure. Logistic regression can be both unconditional and conditional. In the unconditional regression, all observations are pooled, while in the conditional logistic regression the observations are stratified. This is an efficient way to control for bias since the subjects from different groups are only compared to their matched set of subjects.[187] In Study II, conditional logistic regression was used to estimate the likelihood of TMJD (outcome/dependent variable) among subjects with and without MBD (exposure/independent variable). The model was adjusted for DEGURBA, educational level, country of birth, MSD, and maxillofacial and neck trauma. A similar approach was conducted in Study III on the association between MSD and TMJD, but adjustments were made for DEGURBA, educational level, country of birth, and MBD comorbidity. Gender and age were not included in the models as the cases and controls were matched on those variables and subsequently handled by the conditional logistic regression.

3.9.4 Interaction terms

When an independent variable has different effects on the dependent variable depending on another independent variable, an interaction occurs.[188] For example, the likelihood of TMJD among subjects with MSD may differ depending on age or gender. In Study III, interaction terms were used to visualize the interaction of age on the association between the independent variable MSD and the dependent variable TMJD.

3.10 Ethical considerations

The research was conducted in accordance with the Declaration of Helsinki and was approved by the Regional Ethical Committee in Stockholm (Dnr: 2018/401-31). In conjunction with the registry inquiry, the NBHW and SCB conducted a separate ethical vetting before initiating data collection.

All research is associated with ethical concerns that must be reflected, and registry-based research is no exception. One of the main ethical considerations is to ensure that the handling of personal data is done in accordance with the General Data Protection Regulation (GDPR). Another chief concern is the use of informed consent, which was not feasible due to the large number of individuals. Therefore, it is essential to consider the violation of personal integrity with the use of registry data and ensure that the gained knowledge from the studies is worth the violation. In Sweden, informed consent is not required when conducting research on large scale registry data. There are several reasons for this exception, including costs, reduced research quality, inevitable risk for selection bias, and unrealistic acquirement of informed consent from such large study populations.[171]

Therefore, it is important to conduct research of high quality that may benefit the greater good. In situations where informed consent cannot be acquired, the benefits of the research must be rationalized. The studies included in this thesis did not pose any risk of physical or psychological harm to the included subjects, results were only reported on group level, and no identifying information was published. The data was de-identified by the NBHW and SCB before delivery and data handling was only conducted by the researchers involved in this project. The results from the studies may in a long-term perspective improve the well-being of patients afflicted by TMJD. Therefore, the potential intrusion of patient integrity with the use of registry data is balanced by the possible benefits of the research.

4 Results

4.1 Recruitment

The NBHW identified 33 397 subjects who matched the inclusion criteria for TMJD as defined by the registry inquiry. Of these, 33 316 were matched to individuals from the TPR. During the merging phase, a few individuals were excluded. Figure 9 shows a flow chart describing the recruitment of the study population for Studies I–IV. For the cohort studies, 147 182 subjects were excluded due to age restrictions.

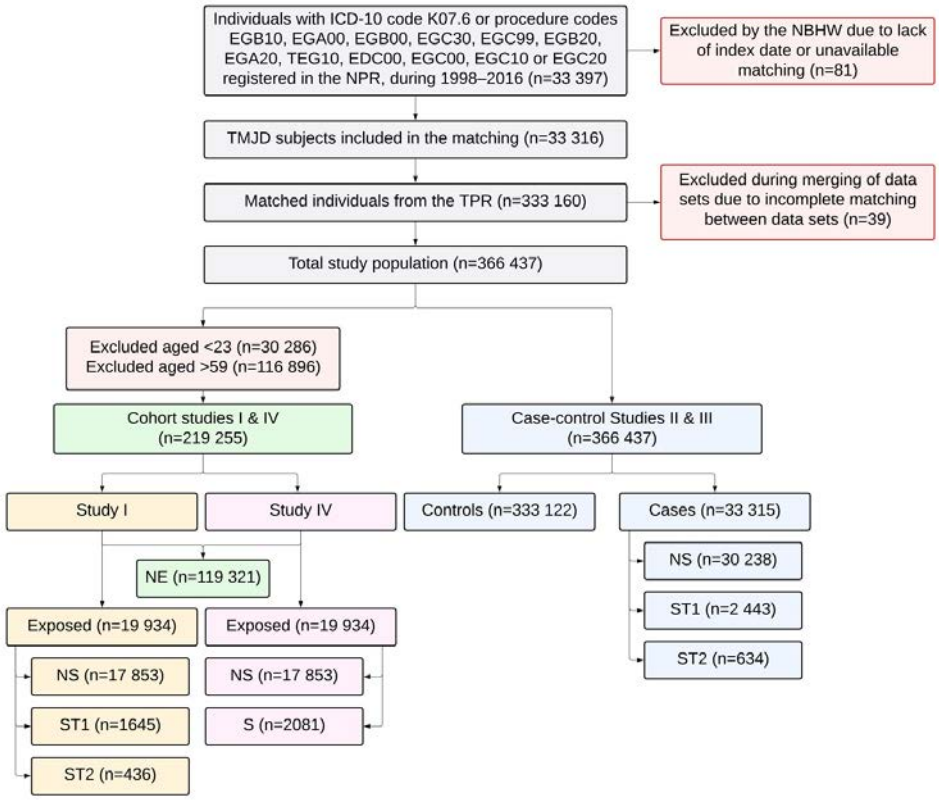

***Figure 9**. Flowchart describing the study population and recruitment.*

4.2 Study population

The distribution of the study population's characteristics is found in Table 7. The Table shows the values for the entire study population as well as the distribution among the subgroups. It should be noted that the table includes all ages, unlike the study population in Study I and IV.

Table 7. Baseline characteristics of the study population.

	Comparison subjects	pwTMJD			
	n=333 122 (%)	All pwTMJD n=33 315	NS n=30 238 (%)	ST1 n=2443 (%)	ST2 n=634 (%)
Sex					
Female	242 868 (72.91)	24 289 (72.91)	21 887 (72.38)	1869 (76.50)	533 (84.07)
Male	90 254 (27.09)	9026 (27.09)	8351 (27.62)	574 (23.50)	101 (15.93)
Educational level					
Primary/lower secondary school	64 265 (19.29)	6467 (19.41)	6005 (19.86)	368 (15.06)	94 (14.83)
Upper secondary school	138 488 (41.57)	14 552 (43.68)	13 102 (43.33)	1149 (47.03)	301 (47.48)
Post-secondary school	125 833 (37.77)	11 989 (35.99)	10 837 (35.84)	914 (37.41)	238 (37.54)
Data unavailable	4536 (1.36)	307 (0.92)	294 (0.97)	12 (0.49)	1 (0.16)
Country of birth					
Sweden	269 829 (81.00)	25 885 (77.70)	23 222 (76.80)	2099 (85.92)	564 (88.96)
Other Nordic countries	11 772 (3.53)	1219 (3.66)	1099 (3.63)	97 (3.97)	23 (3.63)
Other European countries	22 960 (6.89)	2297 (6.89)	2192 (7.25)	87 (3.56)	18 (2.84)
Non-European countries	28 530 (8.56)	3913 (11.75)	3724 (12.32)	160 (6.55)	29 (4.57)
Data unavailable	31 (0.01)	1 (<0.01)	1 (<0.01)	0 (0)	0 (0)
DEGURBA					
Cities	150 065 (45.05)	14 631 (43.92)	13 092 (43.30)	1237 (50.63)	302 (47.63)
Towns and suburbs	89 917 (26.99)	9876 (29.64)	9106 (30.11)	597 (24.44)	173 (27.29)
Rural areas	90 570 (27.19)	8609 (25.84)	7861 (26.00)	591 (24.19)	157 (24.76)
Data unavailable	2570 (0.77)	199 (0.60)	179 (0.59)	18 (0.74)	2 (0.32)
Age					
Mean	49.15	49.15	49.96	41.62	39.31
IQR 25	34	34	35	26	25
Median	49	49	50	40	37
IQR 75	64	64	64	54	51
Range	18-104	18-104	18-104	18-97	18-89
Marital status					
Married	142 671 (42.83)	14 674 (44.05)	13 544 (44.79)	890 (36.43)	240 (37.85)
Not married	119 186 (35.78)	11 350 (34.07)	9899 (32.74)	1140 (46.66)	311 (49.05)
Divorced	46 442 (13.94)	5108 (15.33)	4720 (15.61)	320 (13.10)	68 (10.73)
Widow/widower	22 017 (6.61)	1952 (5.86)	1870 (6.18)	70 (2.87)	12 (1.89)
Other*	236 (0.07)	32 (0.10)	26 (0.09)	5 (0.20)	1 (0.16)
Data unavailable	2570 (0.77)	199 (0.60)	179 (0.59)	18 (0.74)	2 (0.32)

Other: Registered partner, divorced partner, surviving partner.*

4.3 ICD codes

The distribution of the MBD, MSD, maxillofacial and neck trauma ICD-10 codes is found in Table 8.

Table 8. Distribution of ICD codes in the different cohorts.

	Comparison subjects	pwTMJD			
	n=333 122 (%)	All pwTMJD n=33 315 (%)	NS n=30 238 (%)	ST1 n=2443 (%)	ST2 n=634 (%)
MBD					
F00–F99	**40 486 (12.15)**	**6201 (18.61)**	**5608 (18.55)**	**456 (18.67)**	**137 (21.61)**
F00–F09	6214 (1.87)	708 (2.13)	635 (2.10)	60 (2.46)	13 (2.05)
F10–F19	9919 (2.98)	1181 (3.54)	1034 (3.42)	117 (4.79)	30 (4.73)
F20–F29	4044 (1.21)	436 (1.31)	385 (1.27)	41 (1.68)	10 (1.58)
F30–F39	17 075 (5.13)	2635 (7.91)	2382 (7.88)	192 (7.86)	61 (9.62)
F40–F48	22 271 (6.69)	4015 (12.05)	3656 (12.09)	273 (11.17)	86 (13.56)
F50–F59	10 044 (3.02)	1523 (4.57)	1352 (4.47)	124 (5.08)	47 (7.41)
F60–F69	7684 (2.31)	1209 (3.63)	1076 (3.56)	99 (4.05)	34 (5.36)
F70–F79	712 (0.21)	87 (0.26)	80 (0.26)	5 (0.20)	2 (0.32)
F80–F89	3603 (1.08)	496 (1.49)	426 (1.41)	48 (1.96)	22 (3.47)
F90–F98	8469 (2.54)	1343 (4.03)	1195 (3.95)	109 (4.46)	39 (6.15)
F99	6884 (2.07)	981 (2.94)	871 (2.88)	80 (3.27)	30 (4.73)
MSD					
M00–M99	**93 875 (28.18)**	**15 231 (45.72)**	**13 781 (45.58)**	**1122 (45.93)**	**328 (51.74)**
M00–M25	48 165 (14.46)	8009 (24.04)	7090 (23.45)	702 (28.74)	217 (34.23)
M30–M36	4852 (1.46)	1091 (3.27)	963 (3.18)	96 (3.93)	32 (5.05)
M40–M54	28 592 (8.58)	5716 (17.16)	5173 (17.11)	414 (16.95)	129 (20.35)
M60–M79	43 775 (13.14)	8280 (24.85)	7605 (25.15)	511 (20.92)	164 (25.87)
M80–M94	9104 (2.73)	1553 (4.66)	1406 (4.65)	107 (4.38)	40 (6.31)
M95–M99	2736 (0.82)	543 (1.63)	482 (1.59)	49 (2.01)	12 (1.89)
Maxillofacial and neck trauma					
All trauma	**3845 (1.15)**	**971 (2.91)**	**841 (2.78)**	**100 (4.09)**	**30 (4.73)**
S02.4	415 (0.12)	110 (0.33)	94 (0.31)	12 (0.49)	4 (0.63)
S02.6	393 (0.12)	183 (0.55)	145 (0.48)	32 (1.31)	6 (0.95)
S13	3051 (0.92)	697 (2.09)	618 (2.04)	57 (2.33)	22 (3.47)

4.4 NCSP codes

The distribution of the NCSP codes in relation to region is found in Table 9. The most common treatments were arthroscopy (EGA00) and discectomy (EGB10). The distribution of the treatment codes in relation to time can be seen in Figure 10.

Table 9. Distribution of procedure codes in Sweden's 21 regions during the years of inclusion, 1998–2016.

Region	EDC00	EGA00	EGA20	EGB00	EGB10	EGB20	EGC00	EGC10	EGC20	EGC30	EGC99	TEG10	Total
Stockholm	3	488	11	14	640	8	25	104	77	30	13	124	**1537**
Uppsala	1	4	0	0	24	0	1	0	1	5	3	109	**148**
Södermanland	1	6	1	3	45	3	1	4	8	4	5	3	**84**
Östergötland	0	126	1	0	68	0	6	9	3	11	1	37	**262**
Örebro	1	28	1	2	42	0	3	13	10	0	2	62	**164**
Västermanland	1	3	1	1	22	0	3	2	4	1	1	6	**45**
Jönköping	1	1	0	2	44	0	1	1	4	0	0	2	**56**
Kronoberg	0	2	0	0	14	0	0	3	2	0	1	2	**24**
Kalmar	0	26	9	1	20	2	0	1	1	2	0	6	**68**
Gotland	0	21	0	1	9	0	0	2	0	1	0	0	**34**
Blekinge	3	8	0	14	27	0	5	7	5	0	0	19	**88**
Skåne	23	474	9	16	251	3	11	15	31	6	17	58	**914**
Halland	2	2	1	1	5	0	4	4	0	1	0	1	**21**
Västra Götaland	9	12	9	23	197	6	17	34	19	8	13	14	**361**
Värmland	2	1	0	4	7	0	2	2	7	5	2	2	**34**
Dalarna	0	0	0	1	11	1	0	2	2	1	1	0	**19**
Gävleborg	0	1	2	2	29	0	1	6	5	1	2	2	**51**
Västernorrland	1	1	0	1	22	0	2	0	1	0	3	2	**33**
Jämtland	0	1	0	1	7	0	0	1	2	0	0	0	**12**
Västerbotten	2	9	0	9	112	0	3	2	4	0	5	0	**146**
Norrbotten	1	63	0	1	47	0	12	0	1	1	7	4	**137**
Missing	1	0	3	2	2	0	7	6	0	1	1	0	**23**
Total	**52**	**1277**	**48**	**99**	**1645**	**23**	**104**	**218**	**187**	**78**	**77**	**453**	

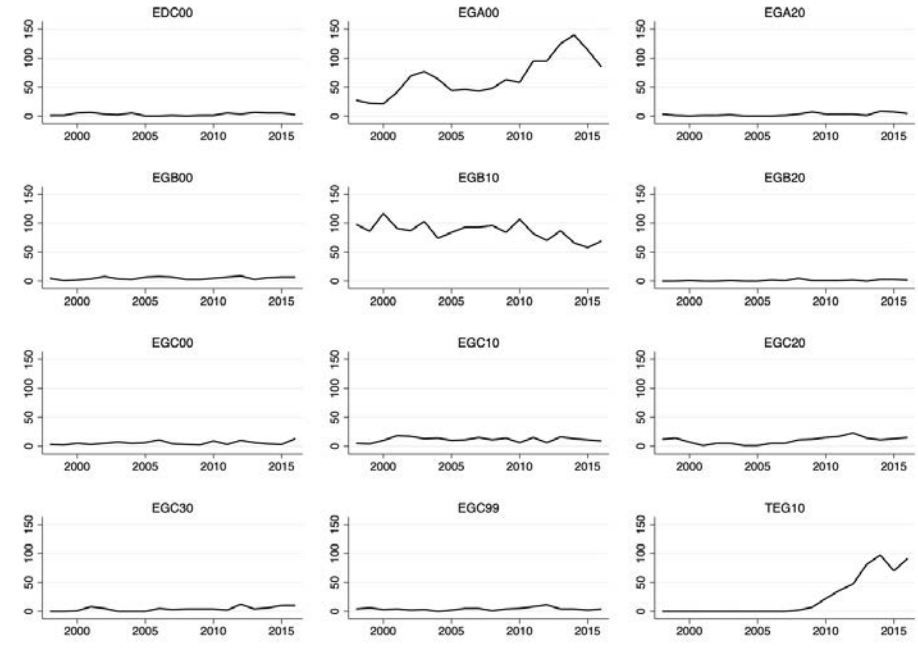

***Figure 10**. Number of surgical interventions during the inclusion period, 1998–2016.*

4.5 Study II and III: predicting TMJD

Study II and III included 366 437 subjects, 33 315 cases, and 333 122 controls. The study population was comprised of 73% women and most subjects had at least nine years of education, were born in Sweden, and lived in cities, towns, or suburbs. The mean age for the controls was 49.15, and the mean age for the surgically treated groups was 41.62 (ST1) and 39.31 (ST2).

In Study II, various MBD and diagnostic groups could predict subsequent TMJD diagnosis, and the associations were stronger with TMJD that required surgical treatment, particularly repeated treatment. The associations between the eleven categories of MBD and TMJD are found in Table 10.

Table 10. Associations between MBD and TMJD found in Study II. Derived from conditional logistic regression adjusted for educational level, country of birth, DEGURBA, MSD, and history of maxillofacial and neck trauma.

	All cases		NS		ST1		ST2	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
F00–F99	**1.7**	**(1.6–1.7)**	**1.6**	**(1.6–1.7)**	**1.9**	**(1.7–2.2)**	**2.3**	**(1.9–2.8)**
F00–F09	1.1	(1.0–1.2)	1.1*	(1.0–1.2)	1.4	(1.1–1.9)	1.3*	(0.7–2.5)
F10–F19	1.1	(1.0–1.1)	1.0*	(1.0–1.1)	1.6	(1.3–1.9)	1.4*	(0.9–2.2)
F20–F29	1.1*	(1.0–1.2)	1.0*	(0.9–1.2)	1.3*	(1.0–1.9)	1.5*	(0.7–3.1)
F30–F39	1.4	(1.4–1.5)	1.4	(1.4–1.5)	1.5	(1.3–1.8)	1.9	(1.4–2.6)
F40–F48	1.7	(1.7–1.8)	1.7	(1.7–1.8)	1.6	(1.4–1.9)	2.2	(1.7–2.9)
F50–F59	1.4	(1.3–1.5)	1.4	(1.3–1.5)	1.5	(1.2–1.8)	2.2	(1.6-3.2)
F60-F69	1.4	(1.3–1.5)	1.4	(1.3–1.5)	1.5	(1.2–1.9)	2.3	(1.5–3.6)
F70–F79	1.2*	(0.9–1.5)	1.2*	(0.9–1.5)	0.8*	(0.3–2.1)	2.1*	(0.4–10.4)
F80–F89	1.3	(1.2–1.4)	1.2	(1.1–1.4)	1.4	(1.0–2.0)	2.9	(1.7–5.0)
F90–F98	1.4	(1.4–1.5)	1.4	(1.3–1.5)	1.4	(1.2–1.8)	2.3	(1.5–3.5)
F99	1.3	(1.2–1.4)	1.3	(1.2–1.4)	1.4	(1.1–1.8)	2.2	(1.4–3.4)

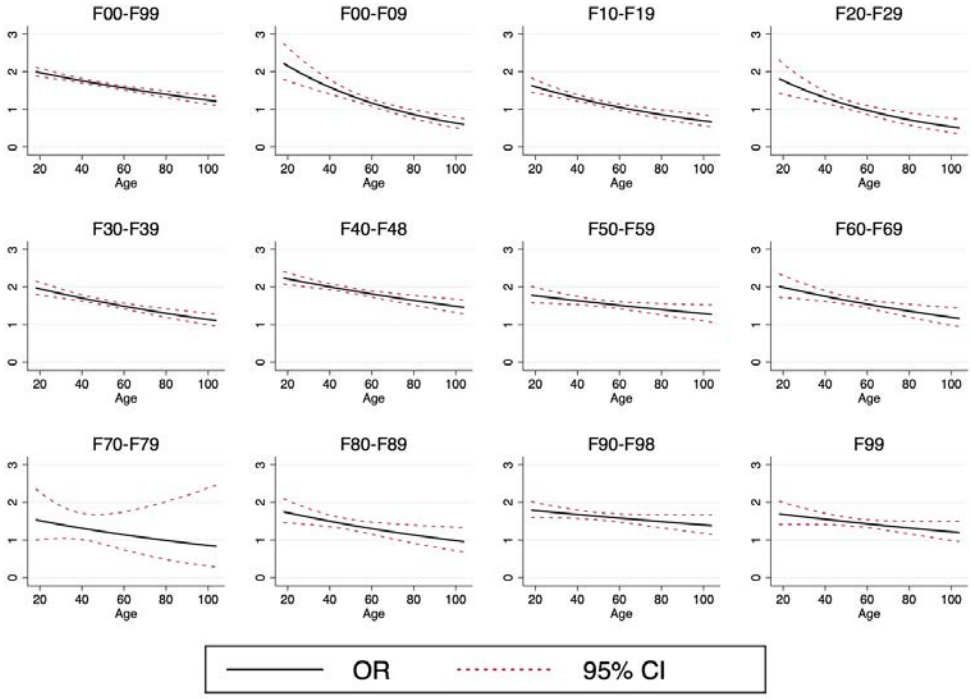

***Figure 11**. Interaction of age on for all MBD (F00–F99) and for the eleven different MBD categories. Derived from conditional logistic regression adjusted for DEGURBA, level of education, and country of birth.*

Figure 11 depicts the interaction of age on the probability of TMJD in the eleven different categories of MBD. For all individuals with MBD (F00–F99), the association to TMJD decreased with age. This pattern was repeated in all categories of MBD with the highest ORs among individuals aged 20–40 and with a gradual decrease in probability with increasing age.

In Study III, virtually all diagnoses within the MSD chapter of ICD-10 were predictive of TMJD, with stronger associations for surgically treated TMJD. The strongest associations were found in subgroup with multiple surgical interventions (ST2). A summary of the results for all six diagnostic categories, including subgroups, is seen in Table 11.

For all diagnostic categories, except for dorsopathies (M40-M54) and osteopathies and chondropathies (M80-M94), the association to TMJD decreased with age. For dorsopathies, the association did not interact with age and were constant over all age groups; however, for osteopathies, the likelihood of TMJD slightly increased with age. Figure 12 depicts the interaction with age.

Table 11. Associations between MSD and TMJD found in Study III. Adjusted for DEGURBA, level of education, country of birth, and MBD.

	All cases		NS		ST1		ST2	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
M00–M99	**2.3**	**(2.2–2.3)**	**2.2**	**(2.1–2.2)**	**3.7**	**(3.4–4.0)**	**5.0**	**(4.1–6.0)**
M00–M25	2.0	(1.9–2.0)	1.8	(1.8–1.9)	4.0	(3.6–4.4)	5.6	(4.6–6.9)
M00–M03	1.9	(1.7–2.0)	1.7	(1.5–1.8)	4.1	(3.1–5.4)	3.8	(2.2–6.5)
M05–M14	2.4	(2.2–2.5)	2.0	(1.9–2.1)	6.9	(5.8–8.1)	11.7	(8.6–15.9)
M15–M19	1.7	(1.6-1.8)	1.6	(1.6–1.7)	3.3	(2.8–3.9)	4.2	(3.0–5.9)
M20–M25	1.9	(1.8–2.0)	1.8	(1.8–1.9)	3.1	(2.7–3.5)	3.9	(3.1–4.8)
M30–M36	2.3	(2.1–2.4)	2.2	(2.0–2.3)	3.4	(2.7–4.3)	4.8	(3.1–7.5)
M40–M54	2.2	(2.1–2.2)	2.1	(2.0–2.2)	2.9	(2.6–3.3)	4.0	(3.1–5.0)
M40–M43	1.8	(1.7–1.9)	1.7	(1.6–1.8)	2.4	(1.9–3.1)	2.8	(1.8–4.4)
M45–M49	2.0	(1.9-2.1)	1.9	(1.8–2.0)	3.2	(2.6–4.0)	5.1	(3.4–7.7)
M50-M54	2.2	(2.1–2.3)	2.1	(2.1–2.2)	2.9	(2.5–3.3)	3.7	(2.9–4.8)
M60–M79	2.2	(2.2–2.3)	2.2	(2.1–2.3)	2.7	(2.4–3.0)	3.7	(3.0–4.6)
M60–M63	1.9	(1.7–2.1)	1.9	(1.7–2.0)	1.9	(1.3–2.7)	3.6	(2.1–6.2)
M65–M68	1.8	(1.7–1.9)	1.8	(1.7–1.8)	2.2	(1.8–2.7)	3.5	(2.5–4.9)
M70–M79	2.3	(2.2–2.3)	2.2	(2.2–2.3)	2.8	(2.4–3.1)	3.9	(3.1–4.9)
M80–M94	1.7	(1.6-1.8)	1.7	(1.6–1.8)	2.2	(1.7–2.7)	3.6	(2.5–5.4)
M80–M85	1.7	(1.6–1.8)	1.7	(1.5–1.8)	2.2	(1.7–3.0)	3.7	(2.1–6.3)
M86–M90	1.7	(1.5–1.8)	1.6	(1.4–1.7)	2.6	(1.9–3.5)	4.0	(2.3–6.7)
M91–M94	1.7	(1.5–1.9)	1.6	(1.5–1.8)	1.9	(1.4–2.7)	3.3	(1.8–5.9)
M95–M99	1.9	(1.8–2.1)	1.9	(1.7–2.1)	2.7	(1.9–3.7)	2.9	(1.5–5.7)

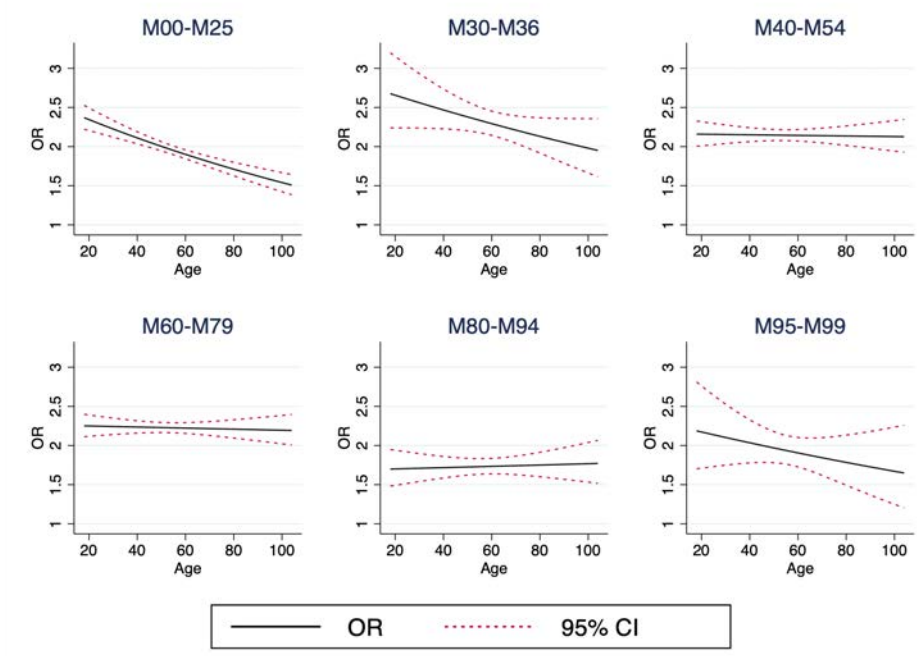

***Figure 12**. Interaction of age. OR in the six different diagnostic categories of MSD. Adjusted for DEGURBA, level of education, and country of birth. Reproduced from Study III.*

To conclude, many MBD and most MSD could predict TMJD, with the absolute strongest associations in pwTMJD with multiple surgical interventions. Age interacted with the association of both MBD and MSD on TMJD.

4.6 Study I and IV: sick leave and disability pension

Study I and IV included 219 255 subjects: 19 934 exposed subjects and 199 321 unexposed subjects. Women comprised 73% of the entire cohort. Most subjects were born in Sweden (78–88%), and approximately half of the population lived in larger cities. The mean age for the entire cohort was 41.63, and it was slightly lower in the surgically treated subgroups. For both studies, the follow-up period was 10 years, and the entire cohort (n=219 255) was followed from -T5 to T1. Table 12 shows the gradual drop in subjects until T5 (n=131 592), as subjects introduced late in the study were unable to contribute with all five follow-up years.

Table 12. Number of subjects in the cohorts at different times during the 10-year follow-up.

	Unexposed	Exposed		
		NS	ST1	ST2
-T5	199 321	17 853	1645	436
-T4	199 321	17 853	1645	436
-T3	199 321	17 853	1645	436
-T2	199 321	17 853	1645	436
-T1	199 321	17 853	1645	436
T0	199 321	17 853	1645	436
T1	199 321	17 853	1645	436
T2	180 575	16 058	1576	425
T3	161 469	14 238	1503	407
T4	139 755	12 203	1393	380
T5	119 629	10 346	1279	338

For Study I, the mean annual days of SL and DP are described in Table 13. The mean annual days of both outcomes increased in the subgroups that had received surgical treatment, and the number of days on SL and DP were higher for women in all groups. The relation to time (-T5 to T5) for mean annual days of SL and DP among men and women is seen in Figure 13.

Table 13. Number of mean annual days of SL and DP among men and women in the different cohorts.

	Unexposed		Exposed					
			NS		ST1		ST2	
	n=199 321		n=17 853		n=1645		n=436	
SL	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Men	6.6	[6.6–7.3]	14.0	[13.6–14.5]	20.5	[18.3–22.6]	26.2	[20.6–31.7]
Women	12.7	[12.6–12.8]	23.8	[23.4–24.2]	30.7	[29.4–32.1]	38.5	[35.7–41.3]
Both	11.0	[11.0–11.1]	21.0	[20.7–21.4]	28.4	[27.3–29.6]	36.4	[33.9–38.9]
DP	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Men	15.3	[15.1–15.5]	27.9	[27.1–28.7]	39.5	[36.1–43.0]	53.8	[44.9–62.7]
Women	22.8	[22.7–23.0]	44.6	[44.0–45.2]	49.5	[47.5–51.5]	70.6	[66.4–74.8]
Both	20.8	[20.6–20.9]	39.9	[39.4–40.4]	47.3	[45.6–49.0]	67.8	[64.0–71.6]

Using GEE, a significant association between the exposed group and both outcome measures (SL and DP) was shown, with a P-value of less than 0.0001. For SL, there was an increase of benefits until the point of inclusion (T0), with a gradual decrease in all TMJD subgroups thereafter. For DP, the pattern was different: the reliance gradually increased from -T5 to T0 but continued to rise until T5. For both SL and DP, the strongest dependence was found among patients who had undergone multiple surgical interventions.

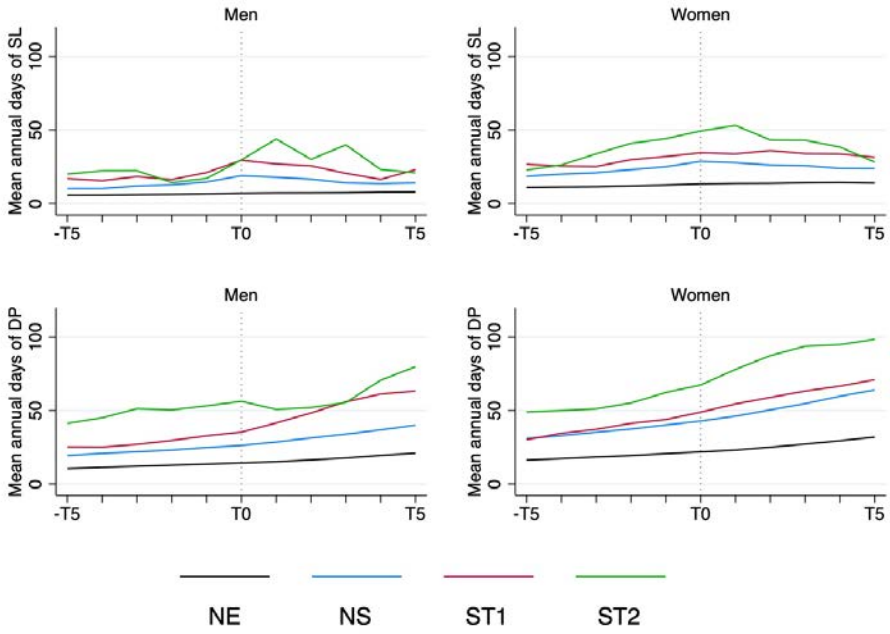

***Figure 13**. Differences in mean annual days of SL and DP between men and women, in relation to follow-up time (-T5 to T5). Adjusted for DEGURBA, level of education, country of birth, age, and calendar year.*

In Study IV, the impact of MBD and MSD was considered. Overall, the surgically treated pwTMJD had higher numbers for SL and DP regardless of the presence of comorbidity. The highest numbers of SL over the 10-year follow-up time were found in the S cohort for dorsopathies, osteopathies and chondropathies, mental disorders due to substance abuse, schizophrenia disorders, mood affective disorders, neurotic disorders, and behavioral disorders with onset occurring in childhood. For DP, the highest numbers were also found in the S cohort for systemic connective tissue disorders and osteopathies and chondropathies. All MBD had more than 100 mean annual days of DP in the S cohort. However, for DP in Group III, the S cohort had just as many mean annual days during the entire follow up as the NE cohort (66.9 days). Otherwise, for Groups I, II, and III, the overall mean days of work disability were 2–3 times higher among pwTMJD than for the general population. In Group IV, the difference between the unexposed and exposed cohorts was smaller, but pwTMJD in the S group still had 30–50% more mean annual days than the unexposed subjects. The mean annual days of SL and DP over the different MBD and MSD diagnostic categories and stratification of Groups I–IV are seen in Table 14 and 15; these numbers are also depicted in Figure 14 and Figure 15.

Table 14. Mean annual days of SL in Groups I–IV and in all diagnostic categories of MBD and MSD.

	Sick leave					
	NE		NS		S	
Group	Mean	95% CI	Mean	95% CI	Mean	95% CI
Group I	6.9	[6.9–7.0]	12.7	[12.4–13.0]	20.2	[18.9–21.4]
Group II	16.0	[15.8–16.2]	24.9	[24.3–25.5]	34.9	[33.0–36.8]
Group III	21.8	[21.5–22.2]	28.5	[27.3–29.7]	41.4	[36.7–46.0]
Group IV	35.1	[34.5–35.7]	43.4	[42.1–44.8]	49.0	[45.2–52.8]
MSD						
M00-M25	19.4	[19.2–19.7]	29.6	[28.7–30.4]	37.9	[35.7–40.0]
M30-M36	24.1	[23.1-25.1]	39.5	[36.5–42.5]	36.3	[30.4–42.1]
M40-M54	24.8	[24.4–25.1]	35.6	[34.6–36.7]	43.9	[40.1–46.9]
M60-M79	20.9	[20.6–21.2]	31.3	[30.5–32.1]	38.7	[36.1–41.2]
M80-M94	22.1	[21.4–22.8]	31.3	[29.2–33.5]	40.0	[34.2–45.8]
M95-M99	26.5	[25.3–27.8]	35.5	[32.2–38.7]	38.6	[30.5–46.6]
MBD						
F00-F09	22.3	[21.5–23.2]	32.2	[29.1–35.2]	39.0	[30.4–47.7]
F10-F19	24.1	[23.5–24.7]	35.9	[33.8–38.0]	47.0	[40.9–53.1]
F20-F29	20.9	[20.0–21.7]	35.4	[31.8–39.0]	44.4	[34.4–54.5]
F30-F39	34.5	[34.0–35.0]	44.3	[42.7–45.9]	50.2	[45.3–55.0]
F40-F48	29.2	[28.8–29.6]	38.0	[36.9–39.2]	47.5	[43.8–51.3]
F50-F59	23.1	[22.5–23.7]	32.3	[30.5-34.2]	40.0	[34.8–45.2]
F60-F69	28.6	[27.8–29.3]	36.8	[34.6–39.1]	46.3	[39.9–52.6]
F70-F79	5.3	[4.3–6.3]	8.7	[4.8–12.7]	22.7	[0.7–44.7]
F80-F89	18.4	[17.5–19.3]	30.1	[26.9–33.3]	34.9	[27.4–42.5]
F90-F98	26.6	[25.9–27.3]	34.0	[31.9–36.0]	52.8	[46.2–59.5]
F99	24.0	[23.3–24.8]	37.7	[35.0–40.3]	42.8	[35.9–49.7]

Table 15. Mean annual days of DP in Groups I–IV and in all diagnostic categories of MBD and MSD.

	Disability pension					
	NE		NS		S	
Group	Mean	95% CI	Mean	95% CI	Mean	95% CI
Group I	9.3	[9.2–9.4]	16.6	[16.2–17.1]	28.5	[26.7–17.1]
Group II	27.9	[27.6–28.2]	45.9	[44.9–46.9]	58.1	[55.3–60.9]
Group III	66.9	[66.2–67.6]	70.3	[68.2–72.3]	66.9	[60.4–73.6]
Group IV	86.7	[85.7–87.7]	107.3	[105.0–109.6]	114.7	[108.7–120.7]
MSD						
M00-M25	37.4	[36.9–37.8]	63.6	[62.2–65.1]	75.7	[72.3–79.1]
M30-M36	66.9	[65.1–68.8]	117.1	[111.9–122.3]	139.4	[128.3–150.5]
M40-M54	53.5	[52.9–54.1]	82.1	[80.4–83.8]	100.3	[95.4–105.1]
M60-M79	41.3	[40.8–41.7]	66.0	[64.7–67.3]	83.5	[79.4–87.6]
M80-M94	54.3	[53.0–55.6]	87.4	[83.5–91.4]	108.1	[97.8–118.4]
M95-M99	49.6	[47.6–51.5]	88.3	[82.5–94.2]	91.2	[77.4–105.03]
MBD						
F00-F09	165.6	[163.4–167.7]	156.9	[150.8–163.1]	163.3	[147.1–179.4]
F10-F19	85.1	[83.9–86.3]	101.9	[98.1–105.6]	119.4	[109.3–129.4]
F20-F29	178.0	[175.8–180.2]	160.1	[153.2–167.1]	158.6	[141.6–175.6]
F30-F39	90.2	[89.2–91.1]	109.2	[106.6–111.8]	112.8	[105.4–120.1]
F40-F48	78.6	[77.8–79.3]	93.4	[91.5–95.4]	101.5	[95.6–108.3]
F50-F59	100.6	[99.3–101.9]	123.3	[119.7–127.0]	142.6	[133.3–152.0]
F60-F69	126.7	[125.1–128.3]	156.6	[152.3–160.9]	134.5	[124.0–145.0]
F70-F79	282.5	[278.0–286.9]	275.0	[262.1–287.8]	258.7	[212.4–305.1]
F80-F89	145.4	[143.1–147.8]	151.4	[144.7–158.1]	183.8	[169.0–198.6]
F90-F98	106.0	[104.6–107.5]	132.0	[127.9–136.0]	145.4	[134.8–155.9]
F99	129.7	[127.9–131.4]	150.2	[145.2–155.2]	163.5	[151.4–175.5]

GEE revealed a significant association between the exposure and the outcomes at almost all time points (-T5 to T5) and covariates. Whereas SL decreased after T0 for Groups I–III, Group IV did not display the same pattern. For DP, there was a steady increase starting at the beginning of the follow-up (-T5) to the end of the follow-up (T5).

In summary, pwTMJD were 2–3 times more reliant on SL and DP than the unexposed cohort from the general population. The strongest reliance was seen in female subjects who had undergone more than one surgical treatment. MBD and MSD comorbidity had a substantial impact on the mean annual days of SL and DP but not on the internal relation between the exposed and unexposed cohorts. However, for individuals with multimorbidity, the difference between the exposed and unexposed cohorts was smaller.

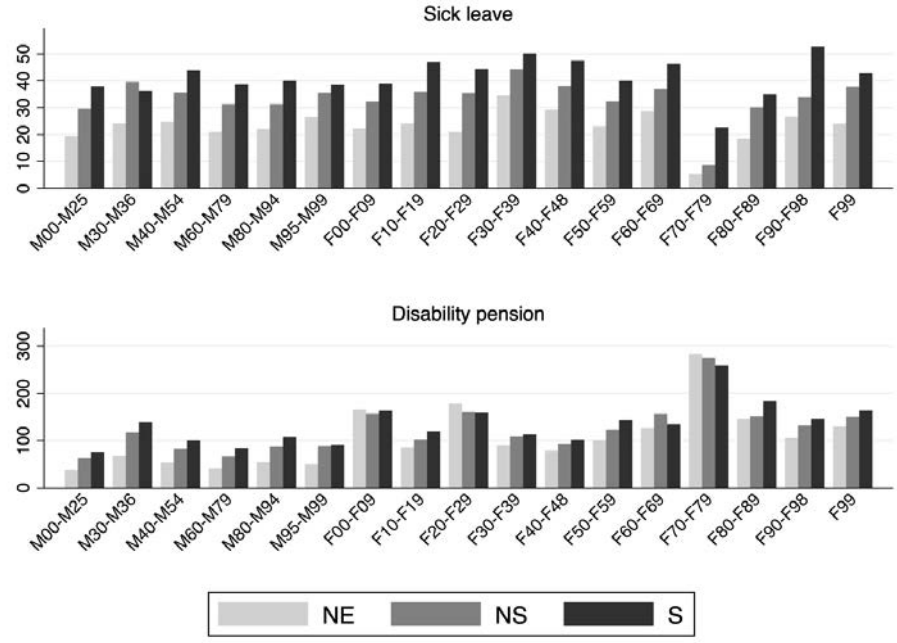

Figure 14. *Mean annual days of SL and DP accumulated over the 10-year follow-up, by diagnostic category.*

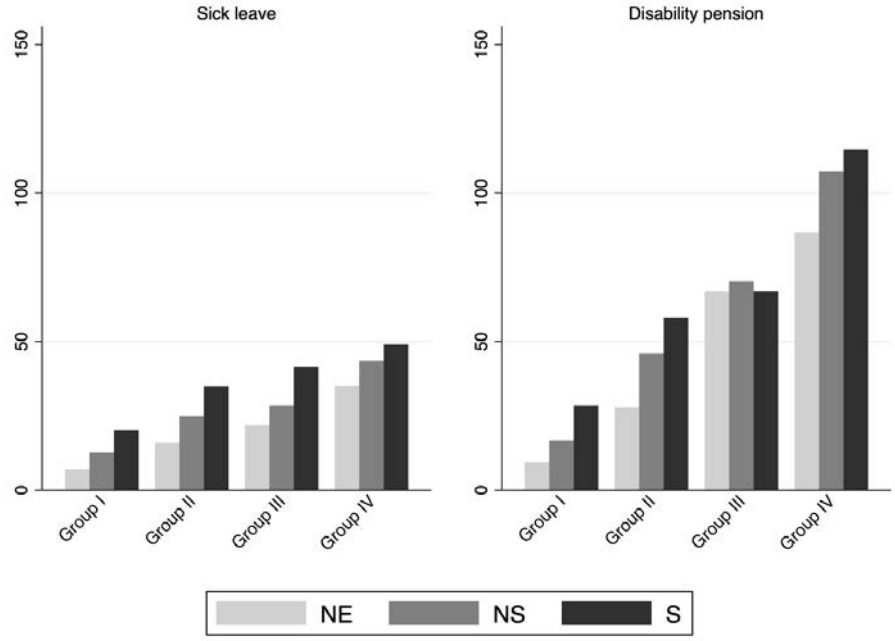

Figure 15. *Mean annual days of SL and DP, by Group I-IV.*

5 Discussion

This thesis assesses MBD and MSD as predictors of TMJD, investigates work disability among pwTMJD, and examines how comorbidities impact the trajectory of work disability. The complexity of TMD and subsequently TMJD, their coexistence with other conditions, potential risk factors, possible causal pathways, and the ongoing discussion regarding many of the aspects surrounding TMD/TMJD has been a true challenge to condense into a coherent text. The discussion highlights the findings of the included studies in relation to existing knowledge, their strengths, and, of course, their weaknesses.

5.1 Predicting TMJD

Study II and Study III used case-control designs to assess the probability of being diagnosed or surgically treated for TMJD among individuals with MBD and MSD. The results strongly suggest that many MBD and principally all MSD can predict future TMJD, and that there are particularly strong associations with TMJD that require surgical treatment. There are important perspectives from which the results must be discussed.

5.1.1 Study II

Most studies investigating the association between MBD and TMD have focused on depression, anxiety, catastrophizing, and somatization, which have been assessed by numerous instruments including DC/TMD.[102,103,114] Even mild catastrophizing has been associated with increased pain intensity in patients with TMD.[189] While Study II does not address psychosocial status and pain disability made possible using DC/TMD, its registry-based approach has the advantage of including a large number of subjects, thereby including both common and uncommon possible risk factors. Depression is very common in the general population and is often episodic, with a course of remission, recovery, relapse, and recurrence.[190] Yet, 20-30% of depressive disorders show tendencies of chronicity.[191] In Study II, the possibility of differentiating depressive episodes from persistent or chronic depression is limited to the two codes, M32 and M34, not unlike the methods used by Liao et al. and Lin et al.[115,117] Liao et al. found that the hazard ratio for TMD in their depression cohort was 2.21, and Lin et al. found that the hazard ratio for chronic depression to be slightly lower, 1.64. The findings in Study II agree with these two studies, as depressive episode had higher ORs in all strata than persistent mood affective disorders. Other anxiety disorders (F41) was also one of the diagnoses with the highest ORs and with almost twice the prevalence among cases compared to controls.

Reaction to severe stress was also a strong predictor for TMJD, in all subgroups, which is in line with other findings where there is a suggested overlap in the pathway of analgesia, hyperalgesia, descending pain inhibition, and stress.[192] Salivary markers for cortisol and cortisone have been of interest in connection to higher levels of stress among TMD patients. Staniszewski et al. found that the levels of morning salivary cortisone and cortisol was higher among TMD patients compared to healthy controls, suggesting an upregulation in the hypothalamic-pituitary-adrenal axis. Comorbid anxiety, depression,

and pain catastrophizing might contribute to this upregulation.[105] On the contrary, Nilsson et al. did not find any difference in morning salivary levels of cortisol between TMD cases and healthy controls.[193] As pain itself may act as a stress factor in patients already suffering from acute or chronic pain, it is perhaps not surprising that maladaptive or exaggerated responses to pain could form a vicious nexus of stress-induced pain, emphasizing the importance of evaluating non-pain-related stress in the treatment of painful TMD.[169,194]

5.1.2 Study III

The associations between MSD and TMD found in Study III are in line with many other studies' findings.[81,133–151,195] Although the indications of existing associations are not altered by the results of the study, the design, and the comprehensiveness of the material add valuable insights in the search for possible causal links. Many of the earlier observational and epidemiological studies on risk factors for TMD and TMJD development have been of cross-sectional or case-control design, based on convenience samples. However, it seems that large scale registry-based studies are claiming their place in the field of TMD research, with strong indications of a causal relationship between MSD and TMD. For a long time, it has been known that widespread pain elsewhere in the body is a predictor of TMD and that conditions such as low back pain are strongly associated with TMD development.[22,196,197] The findings of Study III on the association of TMJD with conditions such as RA, low back pain, and JIA concur with the findings of contemporary large registry-based cohort studies.[137,142,145,150] The approach to confirm the outcome of TMD differs between the studies: whereas Lin et al. and Byun et al. use ICD-9-CM and ICD-10, respectively, to define TMD, Lee et al. and Ma et al. use RDC/TMD and DC/TMD. However, it is unclear how these instruments were used to determine diagnoses for such a vast number of subjects. On the other hand, the approach to solely use an ICD code as the definition of TMD or TMJD poses other obstacles, which will be discussed later.

Unlike other similar studies, Study III investigates all diagnoses contained within the MSD chapter of ICD-10. That is, other studies mostly focus on one or possibly a few conditions, which are assessed as possible risk factors. The approach to assess fewer conditions is most likely more comprehensible and provides a more straightforward basis of discussion for possible causal pathways. However, an interesting outcome of assessing all MSD diagnoses is that more uncommon conditions also are included, conditions that might not be probable or interesting enough to form a research project around by themselves. As a result, in this study, the inclusion of these rarer conditions has raised some interesting questions. For example, gout, which is the most common inflammatory arthritis, is well-described in the literature but very rare in the TMJ.[198–201] In Study III, the association between gout and TMJD was insignificant for ST2 but was significant for ST1 with an OR of 3.3 (CI 1.4–8.0) and for NS with an OR of 1.3 (CI 1.1–1.7). The question of whether a common condition such as gout can increase the risk of TMJD is interesting and might warrant further research. Another example is ankylosis, typically classified under M24 and with an OR of 8.1 (CI 5.4-12.0) in ST2. Interestingly, ankylosis of the TMJ is usually classified under K07.6, indicating that ankylosis classified elsewhere anatomically, seemingly increases the

risk of ankylosis in the TMJ or might induce other pathologies that require surgical TMJ treatment. ICD-10 M12 include Pigmented villonodular synovitis (M12.2), which is a rare and locally destructive disease that has been reported in the TMJ.[202] This is yet another interesting example of a rare condition that in this thesis shows an OR of 1.8–4.9. Furthermore, Synovial Chondromatosis (SC) (M67/M71), which is an unusual benign neoplasm where only 3% of the tumors are found in the TMJ, is also represented in the findings of Study III.[203,204] Although uncommon in the TMJ, it has been reported in numerous case reports with subsequent surgical treatment.[203,205-207] The OR for M67 and M71 in Study III are 1.6–3.3 and 1.7–4.7 respectively, indicating that SC outside of the TMJ is indeed a risk factor for developing TMJD or that the risk for SC in the TMJ is increased. It is possible, however, that the surgical treatment of TMJ in these rare conditions, such as SC, in fact refers to a neoplasm or another condition located in the TMJ. This would cause a temporal bias as the outcome variable would be misclassified as an exposure. However, an association is also seen in the NS group, reinforcing the possible hypothesis that these conditions may in fact cause subsequent TMJD, perhaps mediated by stress.

5.1.3 The effect of sex

It is well known that pwTMJD are predominantly female with ratios reported to 2:1 in general populations, and up to 8:1 in clinical settings.[93] In the studies included in this thesis, the ratio was 2.7:1 in the entire study population, 2.6:1 in NS, 3.3:1 in ST1, and 5.3:1 in ST2. As described in the literature review, one possible explanation for this is that women are more health care seeking, which drives the ratio towards a more skewed difference between the sexes and explains what is seen in the surgically treated subgroups.[69,208,209] However, an important question to consider is the female majority in many of the MBD and MSD that are investigated as possible risk factors in this thesis. If they are true causal factors for the development of TMJD, it might be fair to assume that the skewed male to female ratio in the risk factors also drives the tilted ratio among TMJD subjects. Examples of this can be found in RA and SLE where more women are afflicted during pre-pubertal and reproductive years.[210,211] Depressive episodes also have higher prevalence among women than men, and chronic depression afflicts twice as many women than men.[190,191] Although RA, SLE, and depression does not account for the entire spectra of MBD and MSD, the difference in gender might partially be explained by the demographic patterns of the diseases, which are responsible for, or contributes to, the development of TMJD.

5.2 Consequences of TMJD – sick leave and disability pension

Study I and Study IV are cohort studies that assessed the impact of TMJD on the need for SL and DP and further investigated the impact of comorbidities on the trajectory of the work disability. The results strongly suggest that there is a vast increase in mean annual days of SL and DP among pwTMJD compared to the general population. In addition, the results show that comorbidities had a large impact on work disability but the internal relation between the exposed and the unexposed cohorts remained. The not very surprising exception was for the strata with both MBD and MSD comorbidity (Group IV), where the results show a smaller difference between the exposed and unexposed cohorts, although the pwTMJD had more mean annual days of work disability. Multimorbidity has been shown to have great impact on work life outcomes such as more frequent spells of SL and negative impact on RTW.[212–214] Only a few studies conducted in the 1980s and 1990s have investigated SL and DP among pwTMJD.[167,168,215–217] Some of these studies sampled subjects from industrial or dock workers, limiting the generalizability of the results. Nevertheless, the results are in line with the findings in Study I and IV: pwTMJD had higher mean annual days of SL and DP, indicating an increased work disability among these patients.

A study investigating the covariation between back pain and common mental disorders and their impact on SL and DP found that genetic variations could play an important role in the need of SL and especially in DP.[218] TMD pain seems to be influenced by several genes associated with glucocorticoid and serotonin receptors, and it has been speculated that genetic predisposition together with other conditions play an important role in the development of chronic TMD.[104] Moreover, Werner et al. show that SL among patients with low back pain is strongly influenced by mental health and other comorbidities, findings that coincide with the findings regarding Group IV in Study IV.[219] Other factors such as occupation and sex have been seen as risk factors for SL and DP.[220] For DP, living alone, living in rural areas, and experiencing long durations of stress-related mental disorders and comorbid somatic disorders have been established as risk factors.[221] The results in Study I and IV also show slightly higher numbers of SL and DP days for pwTMJD living outside of large cities, which might be caused by the availability to dental and/or health care.

In Study IV, the β-coefficient for sex was much lower for DP in the group with MBD comorbidity (Group III) than in the other groups, with a value close to zero. This is in line with findings in a previous study on SL and DP among twins with mental disorders, where the estimates were similar between the sexes.[222] The finding suggests that the effect of MBD trumps the difference in work disability between the sexes seen among pwTMJD. However, this study is unable to determine whether this is due to lower success rate in the treatment of pwTMJD with these diagnoses, whether patients, regardless of sex, with these disorders are more affected by TMJD, or whether concurrent of MBD completely outweighs the effect of sex on SL and DP among pwTMJD. Lower level of education is strongly associated with DP, particularly for individuals with musculoskeletal disorders.[223] The results of this study agree with these earlier findings, although higher education was

protective in the group with no comorbidities, it had a diminishing effect, with the lowest impact in the group with both MSD and MBD comorbidity (Group IV). In Group III, the overall mean annual days of DP in the S cohort equaled those in the NE cohort, and the S cohort with MBD comorbidity was less dependent on DP than the other cohorts five years before inclusion (-T5) but had the highest mean annual days five years after inclusion (T5), emphasizing the importance of incorporating time in the interpretation. Similar results have been found in patients undergoing lumbar decompression surgery where mental health disorders were risk factors for both long-term SL and DP after surgical intervention.[224] These findings emphasize the need for thorough diagnostics and treatment of mental disorders before TMJ surgery, which should be included in the diagnostic and therapeutic panorama of these patients. It is also important to stress that increased work disability does not necessarily reflect the surgical outcome, which is measured in variables unknown in this thesis such as improvement in maximum inter-incisal opening and TMJ pain and disability.

5.3 Methodological considerations

There are many strengths of the studies included in this thesis. The most prominent advantages and added value of the studies are the large study sample due to the population-based design and the properties of the included registries. The unique prerequisites of the Swedish registries offer high quality data and rigorous longitudinal information. The large TMJD population and the size of the matched group offered opportunities to detect differences in even rare conditions. This unique approach adds to the knowledge of TMJD using methods only available in a handful of countries. The richness of the used registries allowed for adjustments of several possible confounders, based on data of high validity. Nonetheless, there are always methodological and epidemiological considerations that need to be discussed.

5.3.1 Causal inference

Causality is the idea that a cause (exposure) partly or completely contributes to the creation of an effect (outcome) and is the focus of many epidemiological studies. There is essential value in understanding the difference between causation and association. A causal relation does indeed require an association between an exposure and an outcome, but an association does not automatically suggest a causal relationship.[225] Hill's criteria for causation have long been used as the standards when inferring a causal effect between an exposure and an outcome. The criteria include strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy.[226] More modern approaches on causal inference have since been developed with crucial contributions from Rubin, Robins, and Pearl.[227-229] These approaches to causal inference include a counterfactual perspective that implies a potential outcome that would happen if the included exposed subjects would have been unexposed, which, of course, is impossible to answer, emerging in the fundamental problem of causal inference.[230] To mitigate this, some methods mimic the counterfactual, such as constructing a comparison group of unexposed that mirrors the exposed group (matching) or randomization of the exposure. These methods attempt to minimize

selection and confounding bias, which can distort the relationship or the association between the included variables. Other means of controlling for confounding include stratification and using multivariate regression models.[231]

If an association between an exposure and an outcome is found, different explanatory models are considered. One simple deduction is that the exposure in fact directly or indirectly causes the outcome. However, there are other possible explanations to an association found in a study, such as random error and systematic error. Systematic error, or bias, is a concern in any observational study and may bidirectionally falsify the association between an exposure and an outcome, both to be over- and underestimated. Systematic error is divided into three main types: information bias, selection bias, and confounding. Figure 16 depicts possible explanations for a found association.[232]

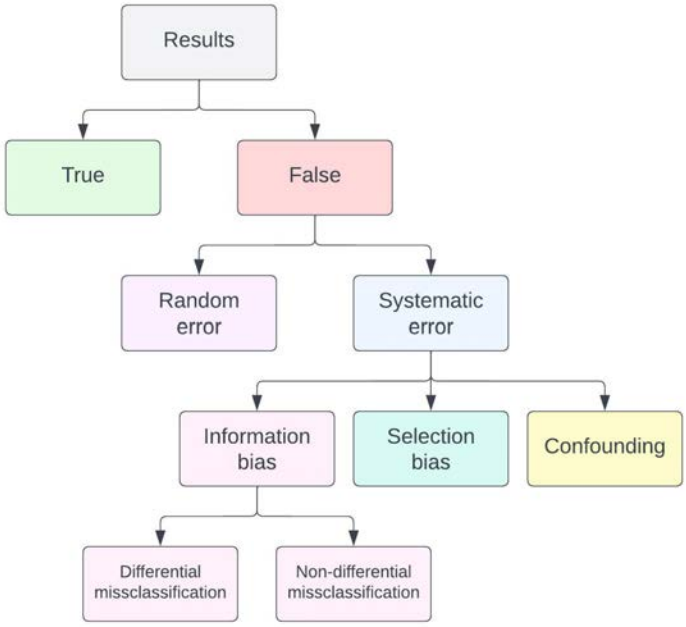

***Figure 16**. Possible explanations for an association between the exposure and the outcome.*

5.3.2 Information bias

Information or misclassification bias arise when data on the exposure and/or the outcome is erroneous and may be attributed to several factors, such as incorrect measurement (measurement bias) of the variables. Information bias may also be attributed to recall bias and interviewer's bias, which is connected to the design of the study. Information bias may be further classified into non-differential and differential. Non-differential misclassification is equally distributed over all study groups and is associated with a random measurement error, which may lead to bias towards the null. Bias towards the null can hide a true association between two variables. Differential misclassification, on the other hand, is associated with a non-random misclassification, and status of exposure

affects the measurement of the status of outcome or vice versa. This can both hide and create an association between two variables.[233-235]

Information bias or misclassification of either the exposure, outcome, or covariates is a concern also in registry-based research and the studies included in this thesis are no exception to this. In Study II and Study III, there is a possible risk of misclassification of both the exposure and the outcome. The risk of misclassification is highly associated with the validity of the registries used. However, the validity and PPV of the NPR have been reported to be high, and there are few, if any, reasons to believe that any misclassification would be differential or unequally distributed between cases and controls.[173] There is, however, a concern regarding the validity of the K07.6 diagnosis as we cannot control for the medical professional who made the diagnosis or which criteria were used in the examination of these subjects. Presumably, most K07.6 diagnoses are not registered with a preceding screening method using a validated instrument such as DC/TMD. The use of the NPR also reduces the number of diagnoses contained within the TMJD spectrum into a single code, limiting the possibilities of differentiating between subcategories such as DDwR, DDwoR, and ankylosis. Another matter is temporal bias or ambiguity–i.e., the notion that the exposure precedes the outcome. This issue is commonly associated with cross-sectional and ecological studies and may completely alter the direction of the association.[236,237] In the registries used in this thesis, the data are prospectively collected in real-time, which decreases the risks of such bias. However, one issue must be addressed. There might be subjects who are in fact diagnosed with TMJD within the dental care system before they are admitted to a hospital and receive an K07.6 code registered in the NPR. This could potentially alter the temporal relation between the exposure and outcome and the direction of the association would be false or even reversed–i.e., reverse causation. Examples of a bidirectional association have been seen between AS and TMD.[147]

Similar issues arise in Study I and Study IV, where the exposures depend on the validity of the NPR and the outcomes on the validity of the LISA registry. Although the risk of misclassification of exposures remains, the misclassification of the outcomes could be argued to be close to zero and there is no reason to assume differential misclassification. This is due to the high completeness of data in the LISA registry.[174] However, for the exposed subjects, the timing of T0 could be subject to temporal ambiguity if the true incidence of TMJD in fact occurred before the recording in the NPR and this may very well affect the trajectory of the outcome measures. In a scenario where the temporality of the exposure and the outcome is erroneous, it is plausible that TMJD would act as a mediator, effect modifier, or confounding factor.

Another question that must be addressed is the possibility of misclassification of unexposed or controls, as these cohorts may include subjects who have received a TMJD diagnosis within the dental care system but not within the health care system. This would lead to a misclassification of pwTMJD as unexposed subjects or controls. On the other hand, this would most probably lead to an underestimation of the associations in both the case-control studies and the cohort studies, causing bias towards the null.

5.3.3 Selection bias

Selection bias occurs when the study population does not represent the target population and can be a result of how the population was sampled. This implies that the participants in the study might represent a different association between the exposure and outcome than for the rest of the population–i.e., the people not included in the study. It may also be the result of competing risks, health care access, duration of the exposure, incidence, prevalence, overmatching, and inclusion bias.[236] Discussion regarding selection bias in registry-based research have revolved around improper patient selection for the included registries.[238]

The studies in this thesis include all Swedish citizens diagnosed with TMJD in a hospital setting or surgically treated for the condition between 1998 and 2016. One of the many strengths of the Swedish registries is that the completeness of the data minimizes and to some extent even excludes selection bias.[239] This is accurate for the patients who are surgically treated, as all surgical procedure codes are recorded in the NPR. It is fair to assert that these patients have truly received a surgical treatment, in many ways a very binary variable, and that they represent a subgroup that constitutes around 1% of the entire TMD population.[44] We know both the type and number of surgical interventions they have undergone during the follow-up period. However, subjects registered with TMJD in the NPR but with no subsequent surgical treatment may present with a risk for selection bias, at least in relation to what population we are drawing conclusions on. There is most likely a difference between subjects who are treated for TMJD within the dental care system and those who are diagnosed with TMJD within the health care system. It would be careless to infer the results of the non-surgical cohort in this thesis on the entire TMD population. So, who are included in the non-surgical cohort? How are they different from pwTMJD who never receive a K07.6 diagnosis within the health care system? At this point, we depend on mere speculations, but other variables, measurable or unmeasurable, might cause this group of individuals to be more health care seeking. The typical TMJD symptoms might not be the main reason for seeking professional medical help and K07.6 might be a diagnosis that is given based on described symptoms of the patients, while not being rooted in any robust examination. What we do know is that the non-surgical cohort is in fact given an ICD code for TMJD and that this group in many ways mimics the surgically treated groups but with overall weaker associations in all studies. In addition, there might be financial reasons to primarily seek medical care for TMJD-related symptoms, as the costs for medical and dental care differs largely.

5.3.4 Confounding

Confounding arises when a confounding factor is associated with the exposure and outcome among both exposed and unexposed subjects, which can occur in all epidemiological studies. Confounding can be mitigated by designing the study using matching or randomization or during the analysis phase, if the confounding variables have been measured appropriately.[232]

Directed Acyclic Graphs (DAGs) are models that visualize possible causal pathways and are powerful instruments in causal inference.[229,240] DAGs can be used not only to depict how an exposure might cause an outcome but also how other variables and possible confounders might interact with this relation. This is an effective way of examining which pathways should be adjusted for in the analysis phase. Figure 17 describes examples of causal diagrams and possible pathways to explain an association between two variables.

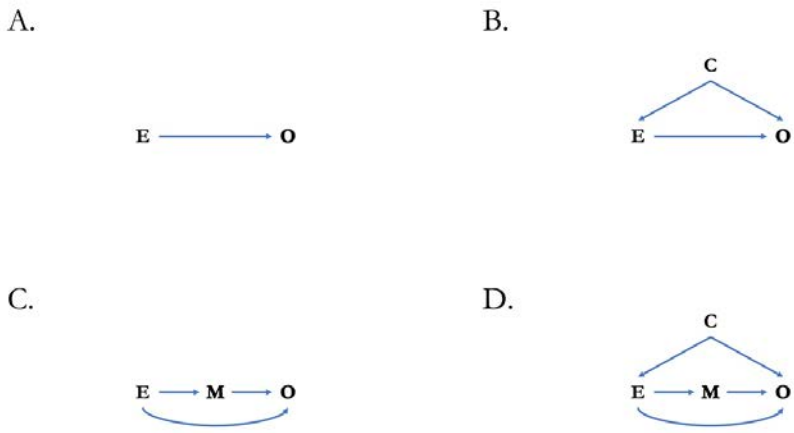

***Figure 17**. Examples of causal pathways that can be described by DAGs.*

In all the studies, possible confounding factors are included in the regression models. The covariates considered confounders contain very little missing data and the completeness of the data is a strength. Nonetheless, some perspectives are better visualized by the aid of DAGs, that also may be used to incorporate residual confounding, which is always a matter of concern and must be take into account when inferring on possible causal pathways. Figure 17A depicts a direct effect of the exposure (E) on the outcome (O) and one can claim that there is a direct causal effect. Figure17B depicts how a common variable, confounder (C), causes both the exposure and the outcome. Figure 17C depicts both a direct and an indirect effect of the exposure to the outcome through a mediator (M). Figure17D depicts a direct and indirect causal effect of the exposure on the outcome, and the presence of a confounding factor, which should be considered when drawing conclusions about associations found in the experiment.[232]

5.3.4.1 Study II and III

Study II and III investigate the association between MBD, MSD and TMJD. Strong associations between many of the diagnoses and TMJD were found. Figure 18 depicts possible explanations for the associations found in these studies. A true causal relation is depicted in Figure18A, whereas Figure18B depicts a confounder such as stress, which impacts both mental and physical health.[241] Stress is measurable in many ways, for example, by using self-reporting, questionnaires, interviews, or stress-related biomarkers.[242] Stress should be considered a confounder if it is causal for either MBD or MSD as well as TMJD, which is supported by the literature.[104,241]

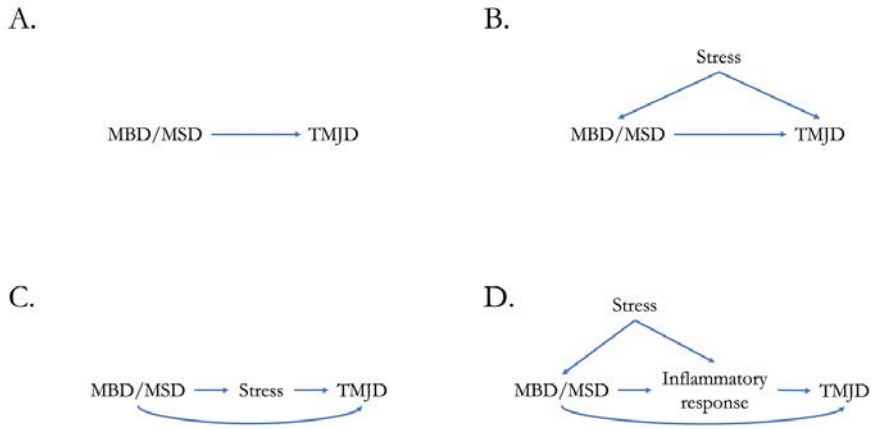

***Figure 18**. Possible pathways between MBD/MSD and TMJD, which are either mediated or confounded by stress.*

Indeed, MBD and/or MSD could cause stress, which is causative of TMJD. This association would make stress a mediator in the development as seen in Figure 18C. Stress is also known to cause peripheral and systemic inflammation, which might also be caused by MBD and MSD, causing the inflammatory response to act as a mediator in the development of TMJD, and stress as a confounder (Figure 18D).[240,243] Stress could, of course, be replaced by another variable or a set of variables that have a complex system of interaction, which is most likely the case and also in line with the ideas of the biopsychosocial model of Engel et al. and Suvinen et al.[62,63] An example of a causal diagram that describes multiple causal pathways is seen in Figure 19, where catastrophizing, gender, socioeconomic factors, and stress interact in a complex causal nexus.[24,107,189,240]

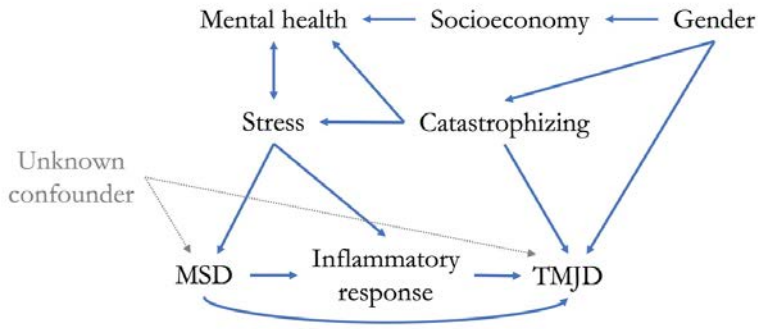

***Figure 19**. Possible causal pathways to explain the findings in Study II and III.*

5.3.4.2 Study I and IV

For Study I and IV, a similar approach in assessing causal pathways between TMJD, SL and DP with the influence of other variables can be proposed (Figure 20). TMJD could be the true cause of increased SL/DP (Figure 20A), but it could also be a mediator (Figure 20C).

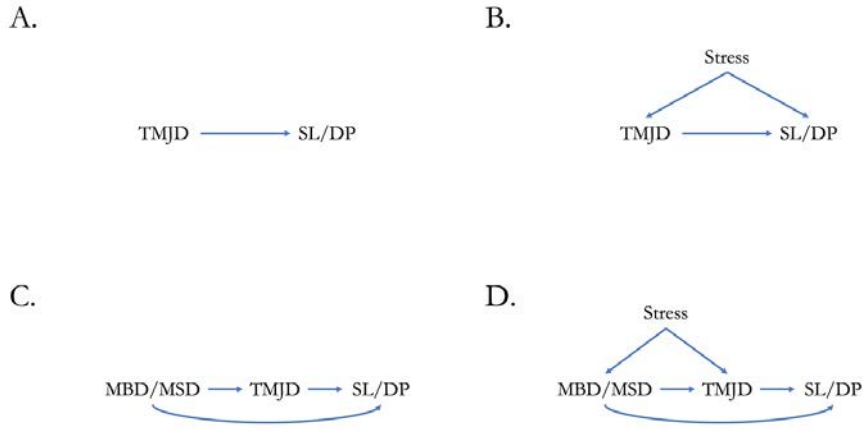

***Figure 20**. Possible causal pathways between TMJD and SL/DP.*

Stress has been found not only to be a predictor of psychological and physiological disorders but also of increased work disability.[221,244] Frequent presenteeism, or working while sick, is also predictive of disability pension.[245] Additionally, SL itself is a strong predictor for DP, creating a multifaceted interconnection between exposure, outcome, and covariates.[246] An example of a DAG that depicts possible causal pathways for the association between TMJD and SL/DP is seen in Figure 21. In Study I, a variety of possible confounding factors were included in the regression model. In Study IV, stratification on comorbidity was added to further investigate the role of concurrent conditions. While a multivariate analysis based on extensive registry data was used, residual unknown confounding is inevitable. Furthermore, it could be discussed whether earlier sick leave should have been included in the model as an adjustment variable.

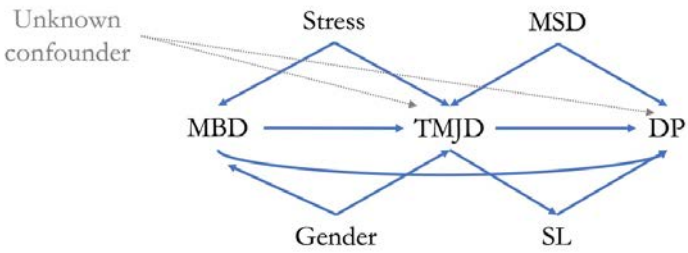

***Figure 21**. Possible causal pathways to explain the findings in Study I and IV.*

5.3.5 Random error

Random error occurs due to chance, it is associated with all types of research and cannot be removed. Random error is associated with the individual and inter-individual variability, the size of the sample, and the size of the association (stronger associations or larger differences are less likely to be explained by randomness). Random error is highly unpredictable but can be moderated by using adequate statistical analysis and larger study populations. The value of probability or P-value is one way to assess the likelihood that the results can be attributed to chance or random error. Similarly, confidence intervals reflect a range of values in which the true value is contained, determined with a certain probability.[232]

For the studies included in this thesis, results with $P<0.05$ were considered statistically significant. That is, there is a 5% chance that the results can be explained by chance. In most research, 0.05 is the gold standard for the P-value; however, this can be argued to be an arbitrary number, so a value of $P<0.05$ should not automatically be considered relevant. This is because the P-value is a continuous measure and there is no palpable difference between a P-value of 0.03 and 0.07.[232]

The population size, P-values, and confidence intervals in the studies of this thesis are used to moderate random error, but residual random error cannot be refuted completely.

5.3.6 Internal and external validity

Validity determines to what degree the research is measuring what it is intended to measure. Internal validity refers to whether the research question can be answered correctly in relation to the research population and requires absence of major biases and adequate statistical precision. External validity or generalizability refers to the validity for populations other than the research population, such as the general population or a larger group of patients, if only a subset of patients is investigated in the research.[232]

The studies included in this thesis have high internal validity as the subjects included in the studies represent the entire population of individuals diagnosed with K07.6 or surgically treated for TMJD between 1998 and 2016. All patients who fulfilled these criteria were included. The biggest concern is the pwTMJD diagnosed in a hospital setting with no subsequent surgical treatment. These patients represent a subset of the entire TMD population which therefore might affect the generalizability. It is not entirely clear how pwTMJD who are diagnosed within the health care system with no subsequent surgical treatment, differ from those who are diagnosed and treated within the dental care system. This difference affects which patients the results can be inferred on. It would be careless to simply assume that patients who are diagnosed with K07.6 without subsequent surgical treatment represent patients with muscular disorders as much as to assume that they represent patients who are referred for surgery but for any number of reasons do not go through with surgical treatment. Therefore, it is important to interpret the results of the non-surgical subgroups with some caution, and not infer the results on the entire TMD population.

6 Conclusions

In this thesis, causes and consequences of TMJD were approached from an epidemiological perspective using registry-based data. This approach is unique for at least European literature and allows for the presentation of novel results and confirmation of earlier findings but in a population-based setting.

Study I showed that the mean annual days of SL and DP were 2–3 times higher among pwTMJD compared to the general population. pwTMJD were increasingly reliant on SL reimbursement five years before first diagnosis, with a peak at first time diagnosis or surgical treatment. Subsequently, the mean annual days of SL decreased over the following five years, whereas the mean annual days of DP increased. The results are the first of their kind in presenting data on work disability among pwTMJD in modern times and in a population-based sample.

Study II and **Study III** investigated the likelihood of developing TMJD among patients with and without MBD and MSD. The results show that many MBD and essentially all MSD can predict development of TMJD. These findings are not ground-breaking and have been confirmed by countless earlier studies; however, the methodological approach for this patient group is original and brings a new narrative for using registry-based population studies in approaching possible key elements in the development of TMJD. Although causal inference in observational studies might be a controversial topic, the methodological approach, the sample size, and the prospective nature and overall quality of the data suggest possible causal associations between MBD, MSD, and TMJD.

Study IV evaluated the impact of MBD and MSD comorbidity on the trajectory of SL and DP. In subjects with no comorbidities, the pwTMJD had 2-3 times more mean annual days of SL and DP than the general population. A similar relation was seen in patients with either MBD or MSD comorbidity. However, in subjects with both comorbidities, the differences between the pwTMJD and the general population were substantially smaller, although pwTMJD still had higher mean annual days of work disability.

The collective findings indicate that pwTMJD represent a subgroup of TMD patients with strong developmental associations to MBD and MSD, and with high work disability and disease burden in comparison to the general population.

7 Points of perspective

One of the main challenges in this thesis was to address the heterogeneity of TMD and TMJD. There is a hint of frustration and discouragement when facing the fact that so much effort and progress have been made in defining the subcategories of TMJD, whereas the ICD-10 reduces the entire spectrum into one code. This was a challenge in this thesis as it required grouping several diagnoses together that may very well represent different associations and predictive models. This will also be a challenge in future registry-based research in the field of TMD and TMJD, but there are potential ways to develop better study designs and data collection platforms. The most interesting approach would be the establishment of a national registry for TMD patients, which could include both conservatively and surgically treated patients. Such a registry would provide the basis for differentiation between the subtypes of TMD and provide longitudinal data on outcome measures such as function, distress, and pain disability. It would also promote interdisciplinary collaboration, which is most likely one of the keys to improving the treatment outcome for these patients. The combination of data from a TMD quality registry with other national registries would offer immense research opportunities that would have been previously unimaginable. The possibility of extending K07.6 to also include subcategories of TMJD in future ICD versions is also encouraging.

It would be of interest to examine whether patients who are exclusively treated within the dental care system differ from patients who are diagnosed and treated within the health-care system. If TMD patients outside of the health care system display similar patterns of sick leave and disability pension, health economical calculations would be imperative. In the studies included in this thesis, the information on MBD and MSD was used to assert the impact of comorbidities on SL and DP. Another intriguing approach would be to use a comorbidity index–e.g., the Charlson Comorbidity Index adapted for Swedish registry-based research.[247] This would be an interesting way to look further into the effect of comorbidities. Furthermore, Study II and III look at diagnoses separately; however, it would also be interesting to see how and if clusters of diagnoses or increased numbers of a specific set of diagnoses interact with the development of TMJD. Perhaps certain diagnoses in combination pose higher risks, while other diagnoses may very well be protective. Moreover, there might be specific sets of predictors for the need of repeated surgery.

The question of causality is a controversial, but we can establish that there is an association between MBD, MSD, and TMJD, even in rare conditions. Future research should examine the possible causality nexus adjacent to this. Could more effective treatment of underlying MBD/MSD decrease the disease burden of TMJD? Or even reduce the incidence of TMJD? It is also important to address that the subjects included in this study have most likely been treated conservatively before being referred for surgery. This indicates that there may be patients with certain predispositions who are less likely to respond to conservative treatment and may very well need earlier surgical treatment, or perhaps adapted interventions to mitigate or prevent the need for surgical treatment.

8 Acknowledgements

I would like to express my deepest gratitude to everyone who has been a part of this journey and generously provided knowledge, expertise, and support. I wish to express special appreciation to those mentioned below.

Carina Krüger-Weiner, who undertook me as a doctoral student and who fought for this project to go through. You are an inspiration in the way you approach research, collaboration, and the implementation of research in clinical settings. I have learned a lot under your supervision while still being encouraged to develop my own ideas. Thank you for everything.

Aron Naimi-Akbar, who have spent countless hours teaching me how to code in STATA, how to analyze my results, and how to reason about the implications of our findings. You have inspired me and many of my peers with your knowledge and understanding of epidemiology and biostatistics; thank you for everything.

Annika Rosén, who was the first to introduce me to both research and oral and maxillofacial surgery. Thank you for taking me under your wings, and for teaching me to kill my darlings – even if it hurts.

Bodil Lund, for her generous supervision and guidance. Thank you for pushing and encouraging me to constantly find new perspectives and to always look for the bigger picture.

Johanna Adami, who has been a steady rock throughout my journey from an undergraduate student to a doctoral student. Thank you for all your swift and brilliant feedback ever since the very first meeting you had with me and Farid at VINNOVA.

Lars Fredriksson, thank you for always being optimistic and enthusiastic, for keeping me on my toes and for encouraging me to write my thesis as if I was inspired by Beethoven.

Britt Hedenberg-Magnusson, who has been patient, educational, and encouraging about my progress. Thank you for your guidance.

Irene Smedberg, my mentor, thank you for great discussions and support.

Pia Skott, for encouraging and promoting research among clinicians in Folktandvården Stockholm.

Pia Svedberg, for fruitful collaborations and valuable insights.

The research school for clinicians in epidemiology. Thank you for the admittance and a special thanks to the research school director **Anna Sandström**.

My friends, colleagues, and supervisors at the Eastman Institute. You are too many to mention but I want to give you all a heartfelt thank you for the positive and encouraging words during both my doctoral studies and residency.

My friends, colleagues and supervisors at the Karolinska University Hospital and Gävle Hospital. Thank you all for welcoming me with open arms and for everything you have taught me so far.

Former and present fellow doctoral students **Carina Pekkari**, **Niko Vähäsarja**, **Mattias Ulmner**, **Eva Nordendahl** and **many more**. Thank you for great discussions and instrumental input. I look forward to future collaborations.

My fellow residents at the Eastman Institute, Karolinska University Hospital, Linköping University Hospital, Örebro University Hospital and Gävle Hospital. Thank you for being amazing friends and colleagues. I am glad to share my residency with all of you.

The incredibly talented artist and doctor **Lucy Bai**, thank you for taking the time to illustrate the cover of my thesis. I look forward to working with you again in the future.

My extended family, **my brothers**, and **my little monkey**. Thank you for keeping me humble and for believing in me whenever I did not. I am thankful to have you all in my life, without you I am nothing.

My mother, **Annelie Fredricson**, my biggest supporter. For her dedication, wisdom, humility, endless kindness, and unconditional love. I am immensely proud of you and glad to have had my own mother as a doctoral colleague to discuss educational matters with during this long and sometimes difficult journey.

My father **Patricio Agurto Salinas**, for his perseverance and strive, for teaching me to live with passion and devotion, and to always face adversities with a smile. I will always be proud to be your son.

My big brother, **Mattias Salinas Blank**, for believing in my abilities like no one else. Thank you for being you.

My grandmother, **Kerstin Fredricson**, who I miss dearly and whose memory I will always keep close to my heart.

Research is impossible without funding. This research was funded by the Swedish Public Dental Services, Folktandvården Stockholm AB, the Steering Group for Collaborative Odontological Research at Karolinska Institutet and Stockholm City County, the Swedish Dental Society, and the Centre for Innovative Medicine, Region Stockholm. Without their support this work would never have happened, thank you.

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