# Back and Neck Pain: A Comparison Between Acute and Chronic Painful TMD

A Manuscript-based Thesis


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## DEDICATION

I would like to dedicate this work to my lovely mother Jackline Hanna and the soul of my grandmother Ester Benyamin for their love, support, and prayers.

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| | |
|---|---|
| TMD | Temporomandibular Disorders |
| IASP | International Association for the Study of Pain |
| ACTION | Acute to Chronic Transition |
| NHIS | National Health Interview survey |
| CI | Confidence Interval |
| OR | Odds Ratio |
| RDC/TMD | Research Diagnostic Criteria for Temporomandibular Disorders |
| DC/TMD | Diagnostic Criteria for Temporomandibular Disorders |
| NIH | National Institute of Health |
| OHRQoL | Oral Health-Related Quality of Life |
| OHIP | Oral Health Impact Profile |
| CMD | Craniomandibular disorders |
| ADL | Activities of Daily Living |
| GOHAI | General/Geriatric Oral Health Assessment Index |
| OPPERA | Prospective Evaluation and Risk Assessment |
| CPSQ | Comprehensive Pain and Symptom Questionnaire |
| TMJ | Temporomandibular joint |
| LBP | Low Back Pain |
| M | Male |
| F | Female |
| TP | Tender points |
| SCM | Sternocleidomastoid |
| TRAP | Trapezius |
| GCPS | Graded Chronic Pain Scale |
| PHQ-8 | Patients Health Questionnaire-8 |
| GAD-7 | Generalized Anxiety Disorders-7 |

## ABSTRACT

**Background:** Painful temporomandibular disorder (TMD) is a serious public health problem. Chronic painful TMD is resistant to treatment and has substantial economic and social impacts. The accurate distinction between acute and chronic painful TMD is important to deliver proper and effective care to patients. However, we do not know how acute and chronic painful TMD differ regarding painful comorbidities.

**Objectives:** The aims of this study were to compare the likelihood of back and neck pain between acute and chronic painful TMD as defined by (i) pain duration and (ii) pain-related disability.

**Methods:** Acute (≤ 3 months) and chronic (> 3 months) painful TMD participants were recruited from four hospitals/clinics in Montreal and Ottawa, Canada in accordance with the Diagnostic Criteria of TMD. The presence of back and neck pain was assessed using a self-reported checklist. Chronic painful TMD based on pain-related disability (chronic-disability) was defined as having grade III or IV on the Graded Chronic Pain Scale. Patient Health Questionnaire-8 and Generalized Anxiety Disorder-7 were used to self-report depression and anxiety symptoms, respectively. Univariate and multivariable logistic regression analyses were employed.

**Results:** This study enrolled 487 adults with painful TMD: acute (n = 118, 24.22%) and chronic (n = 369, 75.77%). Relative to acute painful TMD, the chronic group had almost twice the odds of reporting back or neck pain (odds ratio (OR) = 1.84, 95% confidence intervals (CI) = 1.21 - 2.78). More specifically, neck pain was the comorbidity significantly associated ($OR_{neck\ pain}$ = 2.17, 95% CI = 1.27 - 3.71, $OR_{back\ pain}$ = 0.96, 95% CI = 0.57 - 1.64). Reporting both was not associated with chronic painful TMD (OR = 0.93, 95% CI = 0.46 - 1.88).

Participants with chronic-disability were twice as likely to report neck pain (OR = 1.95, 95%CI = 1.20 - 3.17), but not back pain (OR = 1.13, 95%CI = 0.69 - 1.82) compared to those without. All analyses were adjusted for age, sex, anxiety, and depression symptoms.

**Conclusions:** The association of neck pain with chronic painful TMD suggests that central dysregulation mechanisms are implicated in the process of painful TMD chronification. The similar association of chronic-disability with neck pain highlights the relevance of considering disability when defining chronic painful TMD.

**RÉSUMÉ**

**Contexte:** Les désordres temporo-mandibulaire (DTM) douloureux sont un grave problème de santé publique. Les DTM douloureux chroniques sont résistantes au traitement et ont des impacts économiques et sociaux substantiels. La distinction précise entre les DTM douloureuses aiguës et chroniques est importante pour fournir des soins appropriés et efficaces aux patients. Cependant, nous ne savons pas en quoi les DTM douloureuses aiguës et chroniques diffèrent en ce qui concerne les comorbidités douloureuses.

**Objectifs:** Les objectifs de cette étude étaient de comparer la probabilité de douleurs au dos et au cou entre les DTM douloureuses aiguës et chroniques définies par (i) la durée de la douleur et (ii) le handicap lié à la douleur.

**Méthodes:** Des participants à un DTM douloureux aigu (≤ 3 mois) et chronique (> 3 mois) ont été recrutés dans quatre hôpitaux/cliniques à Montréal et à Ottawa, au Canada, conformément aux critères de diagnostic du DTM. La présence de douleurs au dos et au cou a été évaluée à l'aide d'une liste de contrôle autodéclarée. Les DTM douloureuses chroniques basées sur une incapacité liée à la douleur (chronique-incapacité) ont été définies comme ayant un grade III ou IV sur l'Echelle de Douleur Chronique Graduée. Questionnaire de Santé du Patient-8 et Trouble d'Anxiété Généralisée-7 ont été utilisés pour l'auto-évaluation des symptômes de dépression et d'anxiété, respectivement. Des analyses de régression logistique univariées et multivariées ont été utilisées.

**Résultats:** Cette étude a inclus 487 adultes atteints d'DTM douloureuse : aiguë (n = 118, 24,22 %) et chronique (n = 369, 75,77 %). Par rapport aux DTM douloureuses aiguës, le groupe chronique avait presque deux fois plus de chances de rapporter des douleurs au dos ou au cou

(rapport de cotes (RC) = 1,84, 95% intervalles de confiance (IC) = 1.21 - 2.78). Plus précisément, la douleur au cou était la comorbidité significativement associée ($RC_{\text{douleur au cou}}$ = 2.17, 95% IC = 1.27 - 3.71, $RC_{\text{douleur au dos}}$ = 0.96, 95% IC = 0.57 - 1.64). Le signalement des deux n'était pas associé aux DTM douloureux chronique (RC = 0.93, 95% IC = 0.46 - 1.88).

Les participants atteints d'une chronique-incapacité étaient deux fois plus susceptibles de signaler des douleurs au cou (RC = 1.95, 95% IC = 1.20 - 3.17), mais pas de douleurs dorsales (RC = 1.13, 95% IC = 0.69 - 1.82) par rapport à ceux qui n'en ont pas. Toutes les analyses ont été ajustées en fonction de l'âge, du sexe, des symptômes d'anxiété et de dépression.

**Conclusions:** L'association de la cervicalgie avec les DTM douloureux chroniques suggère que les mécanismes centraux de dérégulation sont impliqués dans le processus de chronification des DTM douloureux. L'association similaire du chronique-incapacité et la cervicalgie met en évidence la pertinence de la prise en compte du handicap dans la définition des DTM douloureux chroniques.

## PREFACE

This thesis has followed a manuscript-based thesis style. As per McGill University standards, the manuscripts included in theses should be logically coherent and should have a unified theme. The manuscript in this thesis discusses a novel project on the comparison of back and neck pain between acute and chronic painful TMD. Following a brief introduction of the topic in the first chapter, the second chapter provides previous and current knowledge in the field of painful temporomandibular disorders and their association with back and neck pain. Chapter three includes the objectives of the study. The methodology of the study was presented in chapter four and the manuscript in chapter five. Chapter six presents a comprehensive discussion including some methodological considerations. Finally, the last chapter presents a succinct conclusion of this work.

Multiple authors have contributed to the thesis work. Explicit appreciation of each author's contribution is mentioned in the following section.

## CONTRIBUTION OF AUTHORS

**Manuscript:**

Back and Neck Pain: A Comparison Between Acute and Chronic Painful TMD

**Jack Botros**, MSc candidate, Contributed to recruiting participants, carrying out the statistical analysis, and writing the manuscript.

**Mervyn Gornitsky**, Professor Emeritus, McGill University, has clinical and research experience in orofacial pain and saliva studies and he supported this project by performing the clinical examination of patients and revising the manuscript.

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**Ana Miriam Velly,** Associate professor, Faculty of Dentistry, McGill University. She conceived this investigation, designed and supervised this study, carried out the statistical analysis, and contributed to manuscript writing.

## CHAPTER1. INTRODUCTION

Painful temporomandibular disorder (TMD) is a serious public health problem. It is a common musculoskeletal condition affecting the muscles of mastication and/or the temporomandibular joint.[1] Signs include tenderness of the muscles of mastication on palpation, pain upon opening and/or limitation of jaw opening.[2,3] It affects 5 to 12% of the general population with an annual cost estimated at $4 billion in the United States.[4] TMD has a negative impact, not only on the healthcare system, but also on the individual's quality of life as well as social and mental health.[5-8]

Temporomandibular disorder causes chronic or recurring pain. Several treatment modalities have been suggested for TMD pain according to its phase. Ranging from physiotherapy, diet modification, oral appliances, and anti-inflammatories in the simple and acute cases to antidepressants, trigger point injection, and psychological consultation in the complex and chronic cases.[9] However, regardless of the treatment received almost two thirds of patients continue to have recurrent or chronic TMD pain.[10] In addition, one in three TMD patients will continue to suffer from the same or worse pain at follow-up.[11]

As the pain persists, it becomes more resistant to treatment,[12] and its economic, social and functional implications continue to grow. The process of chronification of pain in general and TMD pain in particular has not been clearly understood. Despite the proposed mechanisms to explain this process,[13-15] the exact difference between acute and chronic TMD pain is still unknown. In this context, Gatchel *et al.* investigated the difference in psychological symptoms between acute and chronic TMD participants using a 6-month cut-off. They found that acute TMD patients reported anxiety more frequently than the chronic patients, while the chronic patients reported affective disorders more frequently.[16] Similarly, Garofalo *et al.* found that pain

intensity and the diagnosis of myalgia were associated with the transition from acute to chronic TMD pain at 6-month follow-up.[17,18]

More recently, the International Association for the Study of Pain (IASP), in an attempt to draw a line of demarcation between acute and chronic pain, has released its latest definition of chronic pain. Chronic pain was defined as: “pain that lasts or recurs for longer than 3 months”. They have also included significant emotional distress (e.g., anxiety, anger, frustration, or depressed mood) and/or significant functional disability (interference in activities of daily life and participation in social roles) as criteria for chronic primary pain. However, the 3-month threshold, was chosen arbitrarily and was dependant on its acceptability in the medical field.[19]

The accurate differentiation between acute and chronic TMD pain is of substantial significance in clinical as well as research settings. The management of TMD pain differs based on whether it is acute or chronic.[9] Identifying the difference will also help determining the potential risk factors implicated in the transition from acute to chronic painful TMD. This, in turn, can help clinicians to prevent this transition with its associated impacts on the individuals, society and healthcare system.

Painful comorbidities such as back and neck pain have been identified in the literature to be associated with painful TMD,[20-23] as well as risk factors of its development.[24-26] Therefore, in this study we compare the frequency and likelihood of back and neck pain between acute and chronic painful TMD. This study is an analysis of the baseline data of Acute to Chronic transition (ACTION) project that aims to identify the risk factors for the transition from acute to chronic painful TMD.

## CHAPTER 2. BACKGROUND

### 2.1 Prevalence of painful TMD

The prevalence of TMD pain has been assessed by multiple studies. The prevalence estimates vary across studies due to different assessment methodologies, populations, and assessed pain duration or frequency. In this section, we summarize the studies that evaluated painful TMD prevalence among adults in the general population (table 2.1).

Locker *et al.* randomly selected 1014 subjects from the voters' list in Toronto, Canada to enroll them in a survey assessing TMD pain-related symptoms, among others. These individuals were mailed a questionnaire asking about these symptoms in the past 4 weeks. Out of 1014 invited, 877 were eligible, and 67.7% of those responded. Reminders were sent to non-responder 2 and 4 weeks after the mailing. After 8 weeks, a random sample of those who did not respond was sent a short form of the questionnaire to collect data about non-responders. The age distribution of the sample was comparable to that of the city of Toronto population; however, females were overrepresented than males. The results show that the most prevalent TMD symptoms were pain in the jaw joint (9.6%) and pain in front of the ear (9.1%). The prevalence of jaw pain while chewing and jaw pain on opening wide was 8.0% and 6.4% respectively.[27]

Another study in Canada by Goulet *et al.,* invited 1675 adults living in the province of Quebec, Canada using the random dialing method. Of the subjects approached, 1508 were reached and only 1386 were eligible. The response rate was 64% (400 men, 497 women). The telephone interviews were conducted by trained interviewers and at the end of the study, 10% of the calls were repeated to validate the responses. The distribution of age, sex, living area, education level, and family income in the survey sample was similar to that in the general

population. Authors defined TMD pain as pain in the muscles of the jaw or the jaw joint. This study found that the prevalence of very often and quite often TMD pain was 7% (95% Confidence Interval (CI) = 5.1 - 8.8). Females had almost twice the prevalence (9%) compared to males (5%); however, TMD pain prevalence was not associated with age.[28]

In an analysis of the 2002 National Health Interview Survey (NHIS) of the USA, Isong *et al.* analyzed the data of 30,978 individuals. The data were collected through household-based self-reported questionnaires assessing TMD pain in the previous 3 months. The data collected also included the race, age, and sex of one adult per household. A final response rate of 74.4% was reached. TMD pain was defined as pain in the jaw muscles or the joint in front of the ear. The overall demonstrated prevalence was 4.6% with women showing a significantly higher prevalence of TMD pain (6.3%) than men (2.8%, $P< 0.001$). Non-Hispanic white females had a slightly higher prevalence (6.7%) of TMD pain than non-Hispanic black females (5.1%, $P = 0.014$). However, these racial differences were dependent on the age group.[29] Another analysis of the NHIS data from 2000 to 2005 by Plesh *et al.*, which included 189,977 subjects and used the same criteria to assess TMD pain, showed the same prevalence (4.6%).[21]

A study in Italy by Mobilio *et al.* invited 3400 adults (15-70 years) to participate in a survey estimating the prevalence of TMD symptoms. The Random-digit-dialling technique was used to recruit potential participants. Out of those invited, 2196 households were eligible to participate and 91.3 % (n=2005) of them accepted and were enrolled. Telephone interviews based on the Research Diagnostic Criteria of TMD (RDC/TMD) were used to assess TMD pain. A screen-out question was used to evaluate the eligibility of the household. When more than one individual was eligible in the same household, the person with the most recent birthday was selected. The characteristics of the study sample regarding age and gender distribution were

comparable to those of the general population. The overall prevalence of TMD pain was 4.9% (95% CI = 3.9 - 5.9) with females (6.5%, 95% CI= 4.9 - 8) having significantly higher prevalence than males (3.5, 95%CI = 2.5 - 4.7, P< 0.01).[30]

A survey in Finland, recruited 5,696 subjects from the birth cohort of 1966 to participate in a computer-aided survey assessing TMD pain, among others. Those who did not show up were mailed a copy of the same questionnaire. In this study, TMD pain was assessed using a question asking about pain in the jaw joint area at rest and during movement. This study showed that the prevalence of jaw joint pain at rest was 11.1% for men and 12.8% for women. The prevalence of pain with jaw movement was 10.9% and 13.4% for men and women, respectively. The risk difference between men and women for jaw joint pain during movement was statistically significant (2.6, 95% CI = 0.9-4.3).[31]

A cross-sectional study by Progiante *et al.* used the Research Diagnostic Criteria of TMD (RDC/TMD) to assess the prevalence of TMD in the Brazilian population. In this study, 1,775 subjects were randomly selected using a computer program (SPSS, IBM) from the public health dataset of Maringà, Brazil. Eligible subjects (n=1643) were invited through phone calls to participate in the study with an acceptance rate of 92.56%. Participants were invited to provide patient history and undergo a clinical examination according to Axes I and II of the RDC/TMD. The distribution of age, sex, marital status, race, level of income, and education was similar to that provided by the Brazilian Institute of Geography and Statistics for the city of Maringà which implies that the sample was representative of the population. Results showed that the most common type of TMD pain is myofascial pain (19.0%) followed by bilateral arthralgia (16.0%). The prevalence of myofascial pain with limited opening was 10.5% and unilateral arthralgia was 1.9%.[32]

In a study conducted by Gillborg and colleagues, 10,000 adults were recruited from the country of skåne in southern Sweden. Subjects aging from 20 to 89 years were randomly selected from the Swedish Government Personal Address Register. Eligible subjects (n = 9,690) were mailed a questionnaire assessing TMD pain, 63% of which responded (n = 6,123). Participants were deemed to have TMD pain if they reported pain in the face, jaw, temple, in front of the ear or in the ear, on opening the mouth, or chewing once a week or more often. The sex distribution among the sampled individuals as well as those who responded was comparable to that in the general population. The prevalence of TMD pain was estimated at 11.0% (95% CI = 10.2 - 11.8) and was 1.4 times higher among women than among men. Individuals younger than 50 years old had a significantly higher prevalence of TMD pain than those older.[33]

A study by Iodice *et al.* enrolled adults from the general population in the Campania region, Italy. Individuals were approached during their daily activities in public spaces (ie, supermarkets, cinemas, shopping centers, etc) for a face-to-face interview assessing TMD pain. Out of the 6180 subjects contacted, 4299 were enrolled (response rate = 69.6%). Participants were evaluated for TMD pain during the past month using a validated 3-item screening questionnaire and were scored according to Gonzalez *et al.* [34] with a cut-off score of 2 for positive screening of TMD pain. A comparison of the sample characteristics to those of the Italian population revealed a higher prevalence of females but an equal prevalence of subjects over 60 years old. Results showed that TMD pain prevalence was 16.3% (18.9% females and 12.4% males.[35]

In the Kingdom of Saudi Arabia, Nadershah recruited 500 participants (males = 250, females= 250) from adults presenting for a regular check-up at the ministry of health primary care centers. Participants were assessed for TMD pain using the 3-item screener developed by

Gonzalez *et al.*[34] A total score of 3 or more was deemed to indicate the presence of TMD pain. Results of this study showed that 35% were screened positive for TMD pain. Females demonstrated significantly higher prevalence of TMD pain (42%) than males (28%, P = 0.0008).[36]

A recent study by Qvintus *et al.* analyzed the Finnish health survey data collected from 2000 to 2012. Adults living in northern and southern Finland were invited to participate in the study (n = 3469), and only 45% of which accepted (n = 1577). Enrolled participants underwent a standardized clinical oral examination by 4 dentist-nurse teams for the diagnosis of different TMD signs including TMJ and masticatory muscle tenderness on palpation. A clinical interview as well was conducted to assess TMD pain symptoms using the questions developed by Nilsson *et al.*[37] This 2-question screener instrument evaluated TMD pain that occurred at least once a week. This study showed that the prevalence of TMJ and masticatory muscle tenderness was 2.7% and 4.3% respectively. In addition, 8% of the sample reported pain in the temples, face, TMJ, or jaws once a week or more. Pain when opening the mouth wide or chewing at least once a week was manifested by 5.8%. Females demonstrated a statistically significant association with TMD pain signs but not symptoms. Subjects who were considered to have TMJ or muscle tenderness were also more likely to report TMD pain symptoms once a week or more. [38]

## 2.2 Economic and social impact of TMD

### 2.2.1 Economic impact of chronic TMD

The impact of TMD in general and chronic TMD pain, in particular, goes beyond the individuals affected by it to represent a financial burden on healthcare systems and governments. The National Institute of Health (NIH) estimated the cost of TMD at $ 4 billion in the USA.[4] In this section, studies assessing the economic impact of TMD will be summarized.

A case-control study by White *et al.* compared the use and the cost of health and dental services for TMD patients to those of matched subjects. This study enrolled 8,801 members of Kaiser Permanente Northwest Division who had at least 1 TMD-related visit or procedure between January 1990 and December 1995. Controls were identified electronically and matched on 14 attributes including age and gender. The average number of TMD clinic visits for cases was 3.26. On overage, dental visits for TMD subjects were more frequent (mean = 7.46) than for controls (mean = 5.28, $P < 0.001$). In addition, TMD cases had 1.7 times more drug dispensing ($P = 0.0001$), 1.7 times more outpatient visits ($P = 0.0001$), 1.4 times more inpatient admissions ($P = 0.0001$), and 1.5 times more radiological procedures ($P = 0.0001$) than controls. Compared to the comparison group, TMD patients had 1.6 times higher average costs. In addition, they used more healthcare services than their matched controls. The mean cost of healthcare services for TMD subjects for the period of the study was $15,996.26 and for comparison, subjects was $10,173.79 ($P = 0.0001$).[39]

Shimshak *et al.* conducted a matched case-control study where they examined the administrative database for a major healthcare insurance company in Massachusetts, USA. To be considered as cases, members of the insurance company had to be enrolled during the years 1989 and 1990 and had received a claim related to TMJ disorder diagnosis according to the 9$^{th}$ International Classification of Disease (ICD-9). Controls were selected from the same database from those who had not received a TMD-related claim. One-to-one matching of the controls to the cases was performed according to age, gender, relationship to subscriber (dependent, spouse, or subscriber), and employer group, yielding 1,819 matched pairs. Results show that the total payments for cases was $10.8 million (mean = $5,945/person) and for controls was $5.4 million (mean = $2,973/person, $P < 0.001$). The number of inpatient admissions for the TMD population

(n = 598) was 1.6 times that in the control population (n = 367). Additionally, pharmacy claims show that the TMD group had almost double the drug utilization costs of the control group.[40]

Another case control by Shimshak and DeFuria used the database of a large New England insurance database to compare healthcare utilization patterns between TMD and non-TMD patients. Enrollees during the calendar year 1994 who had been diagnosed and treated for TMD according to the ICD-9 were considered as cases. Cases had at least 1 inpatient or patient TMD-related claim in 1994. Those who did not have TMD-related claims were deemed controls. The number of cases and controls enrolled was 1,713 and 532,485, respectively. This study showed that TMD patients had 33% higher admission rate per 1000 and 81% higher inpatient claim costs per capita than patients without TMD, regardless of their age and sex. Admissions per 1000 and inpatient costs per capita were 13% and 46% respectively even after TMD claims were excluded. Cases had 70% higher outpatient claims and 100% higher cost per capita when compared to non-TMD controls. Similarly, TMD cases still showed 57% higher rates of outpatient service utilization per 1000 and 79% higher cost per capita even when TMD-related claims were excluded from the analysis.

A cross-sectional study by Alanen and Kirveskari enrolled 599 male shipyard workers in Finland to investigate the association of TMJ dysfunction and sick leaves. Evaluation of stomatognathic dysfunction was performed through a clinical examination, and information about sick leaves was obtained from the workers' sickness fund records. Subjects were considered to have TMJ dysfunction only if pain or tenderness were elicited during clinical examination. On average, the dysfunction groups had 15.6 days of sick leaves, while the no dysfunction (control) group had 10.8 days ($P < 0.001$).[41]

Another study in Finland investigated the association between TMD treatment need, sick leaves, and use of healthcare services. Potential participants (n = 478) underwent 2 TMD clinical examinations at 12-months intervals. A questionnaire was sent to them asking about sick leaves and healthcare services utilization in the past 12 months. Of them, 441 completed and sent the questionnaires back. To analyze TMD treatment needs, participants were categorized into three groups: acitve-, passive-, or no-treatment need. Participants were considered in the active-treatment-need group, if they needed TMD professional care, regardless of other dental care. They were deemed in the passive-treatment-need group only if the TMD care was indicated in association with other dental treatments. The no-treatment-need group was composed of those who are TMD-free. Results show that active-treatment-need group had significantly more sick leave weeks for any reason (mean = 6.32) than that on the passive-treatment-need (mean = 1.81) and 10 times as high as the no-treatment-need group (mean = 0.69, $P < 0.001$). Additionally, the active group visited a general practitioner (GP, mean = 1.79) or a psychiatry specialist (SP, mean = 0.25) more frequently than those in the passive- (mean $_{GP}$ = 1.30, mean $_{SP}$ = 0.01), and the no-treatment-need groups (mean $_{GP}$ = 0.92, mean $_{SP}$ = 0.00, $P < 0.001$).[42]

### 2.2.2 Impact of chronic TMD on the quality of life

In this section, studies investigating the effect of TMD in general and chronic painful TMD in particular on the quality of life in adults are summarized.

A cross-sectional study by John *et al.* enrolled 416 TMD patients in Leipzig, Germany aging 14 years or more. Potential participants were included if they had at least 1 diagnosis according to the RDC/TMD protocol. The oral health-related quality of life of these participants was assessed using the Oral Health Impact profile-49 (OHIP-49) instrument and was compared

to the Oral Health-Related Quality of Life (OHRQoL) of other subjects sampled from the general population (n = 919 < 40 years old, n = 1,117 ≥ 40 years old). The average OHIP score of TMD patients regardless of their diagnosis (42.9) was almost triple (more impaired) than those from the general population (15.8). The OHIP scores were the highest for myofascial pain (mean = 49.7) in males and for myofascial pain with limited mouth opening (mean = 55.6) in females. Jaw disability and GCPS score were both correlated with higher OHIP scores ($r_{GCPS} = 0.49$, $r_{jaw\ disability} = 0.39$; $P < .05$). [43]

Another cross-sectional study by Barros *et al.* was conducted in Brazil where they enrolled 78 TMD patients (≥ 15 years old) clinically examined and interviewed by calibrated clinicians. Patients included in the study were examined in accordance with the RDC/TMD axis I, then they completed an OHIP-14 questionnaire to assess their OHRQoL. About 99% of the sample reported some degree of impact on their quality of life according to the OHIP scores. The presence of painful TMD including group I diagnoses (myalgia, myofascial pain, and myofascial pain with referral), and groups III diagnoses (arthralgia, arthritis, arthrosis) showed a statistically significant impact on the quality of life compared to their absence (P = 0.013, P < 0.001 respectively). In contrast, Group II diagnoses (disc displacement) did not show any significant impact (P = 0.74). [7]

A case-control study in Finland by Miettinen *et al.* recruited 149 subjects, 79 of which were TMD cases and 70 were controls. Inclusion criteria for the cases were the presence of 1 or more RDC/TMD diagnoses, 20 years of age or more, and lack of general diseases that may affect the TMJ complex. Controls were recruited from dental students at the University of Oulo, Finland. All patients underwent clinical examinations and filled in questionnaires including the OHIP-14. Ninty one percent of the TMD cases versus 33% of the controls had at least one

problem in the OHIP questionnaire reported as occasionally, fairly often, or very often ($P < 0.001$). On average cases scored higher on the OHIP scale (mean = 15.7, SD = 10.5) than controls (mean = 3.0, SD = 5.5). The mean OHIP score was associated was higher RDC/TMD Axis II subscale scores. [44]

Another case-control study included 387 subjects: 187 TMD patients and 200 controls. The TMD group consisted of patients referred to a TMD clinic, while TMD-free individuals presented to the conservative dental department of a primary dental clinic were deemed controls. Patients were considered cases if they were 18 to 50 years old and diagnosed with TMD according to the RDC/TMD protocol. All participants underwent a clinical examination and filled out a questionnaire including the OHIP-14 instrument to evaluate their OHRQoL. Results showed that TMD cases had worse average OHIP-14 scores (mean = 12.50, SD = 8.14) compared to the controls (mean = 9.58, SD = 10.00, $P = 0.002$). The TMD pain-related symptoms were significantly associated with a worse OHIP-14 score. These symptoms include increasing levels of pain upon opening ($P = 0.008$), the presence of preauricular pain ($P = 0.005$). [5]

A study included 80 TMD patients of age range 18-60 years who had TMD diagnosis established by the RDC/TMD and orofacial pain in the past 6 months. Craniomandibular index (CI) was used to evaluate TMD severity and OHIP-14 for the impact on the quality of life. All participants were examined by a trained examiner. Participants having the 3 diagnoses (muscle disorders, disc displacement, and joint disorders) according to the RDC/TMD showed the highest mean OHIP score ($12.83 \pm 4.3$,) followed by those having groups I and II ($11.79 \pm 5.3$), I and III ($10.78 \pm 5.1$) and II and III ($8.7 \pm 6.51$). Additionally, a higher mean score of OHIP was associated with a higher TMD severity as scored by CI. [45]

Schierz *et al.* conducted a case-control study in Germany that enrolled 416 participants diagnosed with TMD (≥16 years old) using RDC/TMD protocol by an experienced dentist in TMD. These cases were compared to a sample of the general population (n = 2026) taken from a national survey. The OHRQoL was evaluated using OHIP-14 for both groups. Participants with TMD showed higher mean OHIP scores (mean = 14.0; 95% CI: 13.0 – 14.9) than those from the general population (mean = 4.1; CI: 3.8 – 4.4). For all items of OHIP-14 except one, TMD patients showed a higher prevalence of (of ‘‘fairly often’’ and ‘‘very often’’ responses) compared to the general population ($P < 0.01$). [46]

A systematic review searched the literature for the relationship between quality of life (QoL) and TMD. Studies were included if they investigated QoL or OHRQoL in relation to TMD or Craniomandibular disorders (CMD). Out of 12,665 articles and 1316 reviews found through an electronic search via Medline/PubMed, 12 satisfied the inclusion criteria and were included in this review. Instruments used to assess OHRQoL in the included studies were Activities of Daily Living (ADL), the General/Geriatric Oral Health Assessment Index (GOHAI), and the Oral Health Impact Profile (OHIP). Studies that used OHIP (n = 7), showed that TMD patients had higher scores (i.e., worse OHRQoL) than those without TMD. Only 5% of TMD patients did not experience any impact on their QoL (OHIP = 0).[47]

| Table 2.1 Summary of painful TMD prevalence | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Reference, year** | **Country** | **Sample size** | **Age** | **Response rate %** | **Assessment** | **Duration/ Frequency** | **Prevalence % (95% CI)** | |
| Locker *et al.*, [27] 1988 | Canada | 594 | 18+ | 67.7 | Mailed questionnaire | 4 weeks | Pain in the jaw joints | 9.6 |
| | | | | | | | Pain in the jaw while chewing | 8.0 |
| | | | | | | | Pain in the jaw joint while opening the mouth wide | 6.4 |
| | | | | | | | Pain in the face just in front of the ear | 9.1 |
| Goulet *et al.*, [28] 1995 | Canada | 897 | 18+ | 64 | Telephone interview | Quite often or very often | 7 (5.1 - 8.8) | |
| Isong *et al.*, [29] 2008 | USA | 30,978 | 18+ | 74.4 | Self-reported questionnaire | 3 months | 4.6 | |
| Rauhala *et al.*, [31] 2000 | Finland | 5,696 | 33 | - | Computer-aided or mailed questionnaire | 1 year | At rest (males) | 11.1 |
| | | | | | | | At rest (females) | 12.8 |
| | | | | | | | On movement (males) | 10.9 |
| | | | | | | | On movement (females) | 13.4 |
| Plesh *et al.*, [21] 2011 | USA | 189,977 | 18+ | - | Self-reported questionnaire | 3 months | 4.6 | |
| Mobilio *et al.*,[30] 2011 | Italy | 2005 | 15-70 | 91.3 | Telephone interview | 1 month | 4.9 (3.9 - 5.9) | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Progiante *et al.,*[32] 2015 | Brazil | 1,643 | 20-65 | 92.56 | RDC/TMD protocol | Variable | Myofascial pain | 19.0 |
| | | | | | | | Myofascial pain with limited opening | 10.5 |
| | | | | | | | Unilateral arthralgia | 1.9 |
| | | | | | | | Bilateral arthralgia | 16.0 |
| Gillborg *et al.,* [33] 2017 | Sweden | 6,123 | 20-89 | 63 | Mailed questionnaire | ≥ Once a week | 11 (10.2 - 11.8) | |
| Iodice *et al.,* [35] 2019 | Italy | 4299 | 18+ | 69.6 | Face-to-face interviews | 1 month | 16.3 | |
| Nadershah , [36] 2019 | Saudi Arabia | 500 | 18+ | - | Self-reported questionnaires | 1 month | 35 | |
| Qvintus *et al.,* [38] 2020 | Finland | 1577 | 18+ | 45 | Clinical examination, clinical interview | Current | TMJ tenderness | 2.7 |
| | | | | | | | Muscle tenderness | 4.3 |
| | | | | | | ≥ Once a week | Temples, face, TMJ, or jaws pain | 8.0 |
| | | | | | | | On chewing or opening pain | 5.8 |

RDC/TMD = Research diagnostic criteria of temporomandibular disorders, TMJ = Temporomandibular joint

## 2.3 TMD association with back and neck pain

### 2.3.1 The association between TMD and back pain

Back pain is one of the most commonly encountered comorbid conditions with TMD pain in both adult and adolescent populations. Observational studies show the association between these two conditions. Cohort studies as well demonstrate the association of back pain with the incidence of TMD pain. A summary of these studies is presented in table 2.

In a case-control study analysis of the baseline data of the Prospective Evaluation and Risk Assessment (OPPERA) study, Ohrbach *et al.* included 1,633 controls and 185 cases with chronic TMD pain. They assessed back pain using the Comprehensive Pain and Symptom Questionnaire (CPSQ). Using this questionnaire, participants were asked about the presence of current back pain and the number of back pain episodes in the last 12 months. Chronic TMD cases were diagnosed according to the Research Diagnostic Criteria of TMD (RDC/TMD). Chronic TMD pain was defined as pain that lasted for at least 6 months including at least 5 days in the preceding month and diagnostic findings on clinical examination. This study demonstrated that 29% and 25.5% of the participants with current TMD pain also reported current back pain and 11 or more episodes of back pain in the preceding year respectively compared to the controls (current back pain = 12.6%, ≥11 episodes = 9.1%). TMD cases were 3.0 times as likely to have current back pain and 5.2 times as likely to have 11 or more episodes of back pain in the previous year as the controls ($P < 0.0001$).[20]

Sanders *et al.* in a prospective cohort study (OPPERA), followed up 2,722 TMD-free participants for 3 years. Out of the recruited participants at baseline, 16% completely dropped out of the study, while 58% were partially lost to follow-up (i.e., did not complete all intended follow-

up questionnaires). Participants with Back pain were assessed at baseline using the CPSQ and TMD absence was clinically confirmed by calibrated examiners according to the RDC/TMD. Subjects with current back pain were almost at a 2-fold increased risk of developing TMD pain compared to those without back pain. The annual incidence of first-onset TMD in participants with current low back pain (5.92%) and participants having 11 or more episodes of back pain in the previous year (5.26%) was almost twice that seen in participants without low back pain (2.92%).[25]

Plesh *et al.* in an analysis of the National Health Interview Survey included a total of 189,977 individuals from the United States. The data analyzed were collected through face-to-face interviews and surveys from 2000 to 2005. This cross-sectional study used self-reported questionnaires to evaluate back pain in the last 3 months in TMD participants. This analysis revealed that 63.9% of TMD pain cases also reported low back pain compared to 26.3% of the controls. The results showed as well an increased likelihood for back pain in TMD patients (OR = 5.0, $P < 0.001$).[21]

Conversely, a matched case-control study, which enrolled 96 back pain patients and 192 controls, tested the hypothesis of an association between back pain and TMD pain. Back pain cases were recruited from a vocational rehabilitation institute; thus, they were examined by a physician. TMD pain was evaluated through a clinical examination in accordance with the RDC/TMD as well as Helkimo's anamnestic (Ai) and clinical (Di) dysfunctional indices. Results showed that 34% of spinal pain cases met the RDC/TMD diagnostic criteria, compared to 1% among the controls (OR = 75.7, 95% CI = 14.6 - 392.2, $P < 0.0001$). The same study also found that the frequent symptoms of the jaw-face region (pain in the jaw-face, fatigue in the jaws, TMJ sounds, difficulties in opening the mouth wide or TMJ locking) according to Helkimo's Index (Ai I and Ai II) were more prevalent (47%) in back pain cases than in controls (12%) (OR = 7.3, 95% CI = 3.9 - 13.7, $P < 0.0001$). Back

pain cases as well showed more likelihood to report the clinical signs of jaw dysfunction according to Helkimo (Di I, II, and III) than controls (OR = 9.4, 95% CI = 4.4 - 20.1, P < 0.0001).[48,49]

A cross-sectional study analyzed the data of a nationally representative survey conducted in Finland including 8028 adults. The study enrolled 6227 subjects (79% of the original sample) who underwent an oral examination by calibrated specialists. Questionnaires were mailed to them to assess painful conditions including back pain. In addition, participants were asked through an interview if they had back pain during the preceding month. This study demonstrated that the prevalence of back pain was higher among participants with TMJ pain on palpation (8.9%) and those with masticatory muscle pain on palpation (10.9%) versus their control groups (2.9%, P < 0.007 and 6%, P < 0.001 respectively). Participants with TMJ pain on palpation ($OR_{Male}$ = 2.3, $OR_{Female}$ = 3.0) and masticatory muscle pain ($OR_{Male}$ = 1.8, $OR_{Female}$ = 2.3) were found to have an increased likelihood of back pain.[50]

Visscher *et al.* conducted an analysis of the Netherlands Twin Registry which included a web-based pain questionnaire. Out of 27,892 individuals invited to participate, 11,948 accepted (response rate 43%), and 11,648 were enrolled in the study. Both TMD and back pain were assessed through a self-reported questionnaire asking about the pain experienced during the previous year. Only 57.6% of participants without TMD pain reported back pain, while 75% and 86.2% of those with occasional and usual TMD pain reported back pain, respectively. Logistic regression analysis showed a likelihood of 2.2 for TMD pain patients to report back pain compared to the controls.[51]

A multi-site matched case-control study recruited 122 chronic TMD female cases and 121 controls from Saudi Arabia, Sweden, and Italy. The TMD cases were included if they had TMD pain fulfilling the RDC/TMD criteria for at least 3 months. The controls had to be pain-free in the

TMJ and the masticatory muscles, not using any medication for oro-facial pain, and age-matched with a case in the respective site. The participants were asked whether they had back pain in the previous 6 months using a self-administered questionnaire. Although no significant difference was found in the prevalence of back pain among cases and controls in the 3 sites collectively (P = 0.38), back pain was more prevalent among the TMD cases than the controls in Sweden and Italy (P = 0.02).[52]

In a 3-year prospective cohort study conducted on adolescents, LeResche *et al.* recruited 1,674 (out of 1,996 invited, response rate = 49%), TMD-free adolescents, at the age of 11 who were selected from a healthcare database in Washington state. At baseline, adolescents were asked if they had ever had facial or back pain (among others) through an interview. Then they were followed up every three months using mailed questionnaires. Eventually, after 36 months another phone interview was conducted and participants who reported first-onset TMD were invited for a clinical examination. Only those who completed at least the 3-month follow-up (n=1310) were included in the analysis. The results showed that 29.2% versus 7.3% of participants with back pain and those without back pain respectively had first onset of TMD pain. The risk of developing TMD pain was 3.9 times higher for adolescents who experienced back pain at baseline versus those who did not experience back pain.[53]

A recent multi-city cross-sectional study by Khan *et al.* recruited adolescent students from Brazil, Canada, and France (n = 1432) aged between 14 and 17 years old. Participants were recruited from schools in Canada and France and homes in Brazil. They were asked about frequent (≥ once a week) TMD pain, the presence, and the frequency of back pain through self-reported questionnaires. The response rate was 89% in Canada, 32.3% in France, and 51.5% in Brazil. Adolescents with TMD pain demonstrated more likelihood (OR = 1.54) to exhibit back pain at

least once a week than those without painful TMD. In addition, the study showed that adolescent boys experiencing TMD pain were more likely to report back pain than adolescent girls experiencing TMD pain($OR_{boys} = 1.36$, $OR_{girls} = 1.93$).[54]

The relationship between TMD and back pain was found to be reciprocal rather than unidirectional. Several papers addressed this perspective. A nested case-control study within a 2-year prospective cohort study included 280 dental students. Students were examined at baseline, year 1, and year 2 of the study following the RDC/TMD protocol. They also filled out questionnaires assessing their spinal pain at each visit and its frequency using a 5-grade scale (never; once or twice a month; once a week; several times a week; and daily). Spinal pain was defined as reported frequent (≥ once a week) pain in the neck, shoulders, and/or back. Twenty five percent of the students dropped out from the study, 69% of which dropped out during the first year. The authors concluded that TMD signs at baseline increased the likelihood of spinal pain (OR = 2.6). On the other hand, spinal pain reported at baseline increased the likelihood of TMD pain (OR = 2.9).[24]

Moreover, Wiesinger *et al.* investigated the Reciprocal dose-response-like relationship between spinal pain and TMD. The aforementioned case-control study had a total of 616 subjects and used two different designs: one with spinal pain as an independent variable and the other with TMD pain as an independent variable. The participants were recruited from the employees of four companies and patients at a vocational rehabilitation center. Both TMD and back pain symptoms were collected through questionnaires together with their frequency (never; not now, but previously; once or twice a month; once or twice a week; several times a week; daily), duration (< 1 month; 1 month–1 year; 1–5 years; > 5 years) and intensity. The results demonstrated an increase in the prevalence of frequent spinal pain with increasing the

severity/frequency of TMD from 30% in the control group to 68% in the group with frequent and severe TMD symptoms. The OR of reporting frequent spinal pain also increased with increasing the severity/frequency of TMD from 2.8 (95% CI: 1.4 - 5.7) in the infrequent TMD group to 5.1 (95% CI: 1.9 - 13.4) among those with frequent severe TMD symptoms. On the contrary, the prevalence and OR of TMD symptoms increased in a dose-response pattern with increasing the frequency of spinal pain showing a significant Cochran-Armitage Test for Trend ($P < 0.001$).[55]

### 2.3.2 The association between TMD and neck pain

Evidence showed that TMD and neck pain are associated. Studies conducted in different populations demonstrate this association, A summary of these studies is presented in table 3.

A cross-sectional study recruited 60 TMD pain patients where they were examined by a maxillofacial surgeon according to the RDC/TMD protocol. Participants were also examined by a physiatrist for cervical spine-related symptoms including pain. Patients aged ≤ 18 years, having rheumatic diseases or postural disorders, history of trauma or surgery, or undergoing orthodontic treatment were excluded. This study found that 46.7% (n = 28) of TMD pain had also neck pain. The same study demonstrated that the mean TMD-related pain scores among participants with neck pain (63.7 ± 18.6) are significantly higher than pain scores in participants without neck pain (50.1 ± 21.8, $P < 0.05$).[56]

A case-control study by Hagberg *et al*. employed 80 (56 women, 24 men) patients with CMD as cases from the patients attending the department of clinical oral physiology, Huddinge whose clinical forms were already available, and 174 controls of randomly selected men and women in the country of Stockholm, Sweden. Neck pain was assessed ‘right now’ and during the

past 12 months using questions from the Nordic questionnaire. None of the invited subjects refused to participate. Sixty six percent of CMD patients reported neck pain in the past 12 months. The percentage of neck pain (women: 46% Men: 26%) in CMD subjects was higher than in controls (women: 29%, men: 13%). In addition, women with CMD were found to be 1.6 as likely to present neck pain compared to the controls with a border-line significance (95% CI = 1.00-2.49).[57]

Another case-control study included 40 female volunteers. Participants in the TMD group (n = 20) were included if they demonstrated one or more diagnoses of TMD according to the RDC/TMD protocol, while the control groups (n = 20) were included if they did not have the signs and symptoms of TMD according to the same criteria. Volunteers were excluded if they had dental problems. History of facial, TMJ, or cervical trauma, using analgesic and anti-inflammatory drugs or using braces. The results showed that 65% of the female participants in the TMD group had cervical pain, compared to 30% in the control group. The same study concluded that patients with TMD pain are 2.16 times as likely to have cervical pain as the controls ($p<0.05$). [58]

Plesh *et al*. conducted an analysis based on the NHIS. The NHIS is a United States nationwide household survey that included 189,977 adults. The data analyzed were collected through face-to-face interviews and questionnaires from 2000 to 2005. This cross-sectional study used self-administered questionnaires to assess neck pain in the last 3 months in TMD participants. This analysis found that 54.2% of those who reported TMD pain reported neck pain as well versus 13% of those who didn't report TMD pain (OR = 7.9, $P \leq 0.001$).[21]

This is consistent with a case-control study conducted by Visscher *et al*., who recruited 147 cases with CMD from patients referred to the Academic Centre for Dentistry Amsterdam, and 103 controls from the friends and relatives of the recruited patients. Participants were examined for CMD by a calibrated dentist and for cervical spine pain by calibrated physical therapists.

Additionally, participants underwent an oral interview by the same examiners including questions about orofacial and neck pain. Most of the TMD cases (91%) were chronic (> 6 months). Out of the participants who presented craniomandibular pain, 58% also suffered from cervical spinal pain compared to 13% of the participants who did not present craniomandibular pain ($P<0.05$) [59]

Similar results were demonstrated by a cross-sectional study on females among a Sami population in Sweden which invited 751 women to participate. Frequency of pain was also described in 5 categories (Never; No, not now but had it previously; Yes, at most once or twice a month; Yes, once a week; Yes, several times a week; Yes, daily). A symptom that occurs once a week or more often was considered frequent. Orofacial pain and dysfunction were classified according to the anamnestic dysfunction index (Ai) by Helkimo. Participants were mailed the questionnaires assessing TMD and neck pain and data were analyzed. Sixty five percent of the invited subjects (n = 487) answered and returned the questionnaires. The analysis showed that 29 out of 67 females who reported frequent TMD symptoms also reported frequent neck pain. Females with frequent TMD pain were 3 times as likely to report frequent neck pain .[60]

In a population-based, case-control study on adolescents in Sweden, Nilsson *et al*. included 350 adolescents attending the public dental service with self-reported TMD pain, and 350 healthy adolescents aged between 12 and 19 years. Cases and controls were sent a questionnaire to assess TMD and neck pain 2 to 4 weeks after their annual check-up. Participants were asked if they had TMD pain symptoms once a week or more often. The questionnaires also include a body drawing for participants to mark where they experience recurrent pain. The results demonstrated a higher prevalence of neck pain (45.9%) among adolescents with TMD pain than among controls (18.3%). Additionally, Adolescents presenting with TMD pain were found to be 3 times more likely to report neck pain than those without TMD pain ($OR = 4.0$, $P < 0.001$)[61].

Similarly, another cross-sectional study included 1432 adolescents (14-17 years old) from three cities: Montreal (Canada), Nice (France), and Arceburgo (Brazil). Self-reported questionnaires were mailed to their homes or delivered to their schools to assess TMD and neck pain. Pain that occurred more than once a week was considered frequent. Frequent neck pain was more prevalent among participants with TMD pain (99 out of 134) than among controls (134 out of 875). Adolescents with painful TMD were found to be more likely to experience neck pain at least once weekly regardless of their sex (Boys: OR = 1.95, 95% CI = 1.29-2.95, girls: OR = 2.13, 95% CI = 1.12 - 4.07, $P < 0.05$).[54]

Furthermore, TMD pain has been associated with cervical muscles tenderness. A case-control study compared 31 TMD pain cases seeking care at a TMD clinic to 30 controls including students, staff members, and patients attending other departments. Participants were examined by trained examiners for both TMD and cervical pain. This study concluded that TMD pain subjects exhibited significantly more tender points upon palpation of the Trapezius, Sternomastoid, and other neck muscles compared to controls with OR ranging from 3.82 to 6.92 for different muscles.[23]

Likewise, Ohrbach *et al*. in the OPPERA baseline case-control study analyzed the data of 1,633 controls and 185 cases with chronic, painful TMD recruited between 2006 and 2008. OPPERA is a multi-site study where TMD cases were diagnosed according to the RDC/TMD criteria. The neck muscles were examined on both sides using 2 lbs of pressure to assess cervical tenderness to palpation. Results showed that TMD cases had a significantly higher mean (mean = 5.99) of neck sites tender to palpation compared to controls (mean = 1.18). In addition, participants with TMD pain were more likely to report more sites of neck tenderness than controls ($P < .0001$).[20]

**Table 2.2 Summary of painful TMD association with back pain**

| Reference | Study design | Sample size | Age | TMD assessment | Back pain assessment | % (n) in TMD cases /controls (P < 0.05) | Adjusted Odds ratio (95%CI) |
|---|---|---|---|---|---|---|---|
| Ohrbach *et al.* [20] | case-control study | Controls = 1,633<br>Cases = 185 | 18 - 44 | RDC/TMD protocol | Comprehensive Pain and Symptom Questionnaire (self-reported) | Current LBP: 29.0 (53)/12.6 (204) | Current LBP: 2.9 (2.0 - 4.3) |
| | | | | | | ≥11 LBP episodes in last year: 25.5 (47)/9.1 (147) | ≥11 LBP episodes in last year: 5.2 (3.2 - 8.4) |
| Plesh *et al.* [21] | Cross-sectional study | 189,977 | 18+ | Self-reported Questionnaire | Self-reported Questionnaire | 63.9/26.3 | 5.0 (4.7 - 5.2) |
| Nilsson *et al.* [61] | Population-based case-control study | Controls = 350<br>Cases = 350 | 12 - 19 | Self-reported Questionnaire | Self-reported Questionnaire | 43.5/23.6 | 1.17 (0.75 - 1.84) |
| Sipilä *et al.* [50] | Cross-sectional study | 6,227 | 30+ | Clinical examination, mailed questionnaire | Mailed questionnaire, Personal interview | TMJ pain on palpation: 8.9 (31)/2.9 (35) | M = 2.2 (1.4 - 3.6)<br>F = 3.0 (2.2 - 4.1) |
| | | | | | | Masticatory muscle pain: 10.9 (90)/6.0 (128) | M = 1.8 (1.4 - 2.5)<br>F = 2.3 (1.9 - 2.7) |
| Khan *et al.*[54] | Cross-sectional | 1,714 | 14 - 17 | Self-reported and mailed questionnaires | Self-reported and mailed questionnaires | 51 (229)/24.2 (236) | 1.54 (1.15 - 2.05) |
| LeResche *et al.* [53] | 3-year cohort study | 1,310 | 11 | Phone interviews, RDC/TMD protocol | Phone interviews, mailed questionnaires | 29.2 (26)/ 7.3(62) | 3.90 (2.2 - 6.8) |
| Marklund *et al.* [24] | Nested case-control study | Controls = 213<br>Cases = 49 | 18 - 43 | RDC/TMD protocol | Self-reported questionnaires | - | 2.9 (1.3 - 6.2) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Sanders *et al.* [25] | 3-year cohort study | 3,263 | 18 - 44 | RDC/TMD protocol | Comprehensive Pain and Symptom Questionnaire (self-reported) | Current LBP = 5.92/2.92 (per annum) | Current LBP: 1.91 (1.41 - 2.58) |
| | | | | | | ≥11 LBP episodes in last year = 5.26/2.92 (per annum) | ≥11 LBP episodes in last year: 1.92 (1.30-2.83) |
| Wiesinger *et al.*[55] | Case-control study | Controls = 137 Cases = 129 | 20 - 65 | Self-reported questionnaires | Self-reported questionnaires | Controls= (30) | 1 |
| | | | | | | Infrequent TMD = (52) | 2.8 (1.4 - 5.7) |
| | | | | | | Frequent mild TMD = (57) | 3.3 (1.8 - 6.2) |
| | | | | | | Frequent severe TMD = (68) | 5.1 (1.9 - 13.4) |
| Macfarlane *et al.*[62] | 20-year cohort study | 1,018 | 11 - 12 | Clinical examination, mailed questionnaires | Mailed questionnaires | Sometimes = 23 (47)/ 16.5 (14) | 1.56 (0.82 - 2.97) |
| | | | | | | Often (once a week) = 34.8 (16)/ 16.5 (14) | 2.72 (1.05-7.04) |
| Visscher *et al.* [51] | Cross-sectional study | 11,648 | 18+ | Self-reported questionnaires | Self-reported questionnaires | No TMD pain = 57.6 | 1 |
| | | | | | | Occasional TMD pain = 75.0 | 2.2 (1.9-2.6) |
| | | | | | | TMD pain a lot of time = 86.2 | |
| Al-Harthy *et al.* [52] | Matched case-control study | Controls = 121 Cases = 122 (females) | 18 - 75 | RDC/TMD protocol | Self-reported questionnaires | Saudis = 71.8 (28) / 59.5 (22) | P = 0.38 |
| | | | | | | Swedes = 60.0 (24) / 32.5 (13) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | Italians = 66.7 (28) / 38.6 (12) | |
| Hagberg et al. [57] | Case-control study | Controls = 174<br>Cases = 80 | 20 - 68 | Clinical records | Self-reported Questionnaire | F = 32 (41) / 28 (79) | F = 1.14 (1.04-3.61) |
| | | | | | | M = 14(21) / 23(87) | M = 0.62 (0.20-1.90) |
| LBP = Low Back Pain, TMJ = Temporomandibular Joint, RDC/TMD = Research Diagnostic Criteria of Temporomandibular disorders, F= Female, M = Male | | | | | | | |

**Table 2.3 Summary of painful TMD association with neck pain**

| Reference | Study design | Sample size | Age | TMD assessment | Neck pain assessment | % (n) in TMD cases /controls (P < 0.05) | Adjusted Odds ratio (95%CI) |
|---|---|---|---|---|---|---|---|
| Benlidayi *et al.*[56] | Cross-sectional study | 60 | 19+ | RDC/TMD protocol | Clinical examination | 46.7 (28) | - |
| Storm & Wänman [60] | Cross-sectional study | 487 (Females) | 21 - 70 | Mailed questionnaire, Helkimo index | Mailed questionnaire | - | 3.2 (1.9 - 5.3) |
| Ohrbach *et al.* [20] | case-control study | Controls = 1,633<br>Cases = 185 | 18 - 44 | RDC/TMD protocol | Clinical examination | - | 3.5 (3.0 - 4.1) |
| Plesh *et al.* [21] | Cross-sectional study | 189,977 | 18+ | Self-reported Questionnaire | Self-reported Questionnaire | 54.2/13 | 7.9 (7.5 - 8.4) |
| Visscher *et al.* [59] | Cross-sectional study | 250 | Mean age = 34 | Clinical examination | Clinical examination | 58/13 | - |
| De Laat *et al.* [23] | Case-control study | Controls = 31<br>Cases = 30 | 15 - 67 | Clinical examination | Clinical examination | TP SCM L = 23.3 /6.7 | 4.26 |
| | | | | | | TP SCM R = 46.7 /13.3 | 5.69 |
| | | | | | | TP TRAP L = 43.3/ 16.7 | 3.82 |
| | | | | | | TP TRAP R = 6.7 /26.7 | 5.50 |
| Hagberg *et al.* [57] | Case-control study | Controls = 174<br>Cases = 80 | 20 - 68 | Clinical records | Self-reported Questionnaire | F = 46 (50)/29 (79) | F = 1.58 (1.00 - 2.49) |
| | | | | | | M = 26 (19)/13 (82) | M = 1.96 (0.77 - 4.98) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ries & Bérzin [58] | Case-control study | Controls = 20<br>Cases = 20 (Females) | 18 - 41 | Clinical examination | Clinical examination | 65 (13)/30 (6) | 2.16 |
| Sipilä *et al*. [50] | Cross-sectional study | 6227 | 30+ | Clinical examination, mailed questionnaire | Mailed questionnaire | Masticatory muscle pain = 13.7 (133)/5.2 (115) | M = 2.6 (2.0 - 3.6)<br>F = 2.3 (1.9 - 2.7) |
| Nilsson *et al*. [61] | Population-based case-control study | Controls = 350<br>Cases = 350 | 12 - 19 | Self-reported Questionnaire | Self-reported Questionnaire | 45.9/18.3 | 4.00 (2.73 - 5.87) |
| Khan *et al*.[54] | Cross-sectional | 1714 | 14 - 17 | Self-reported and mailed questionnaires | Self-reported, and mailed questionnaires | 42.6 (134)/11.3 (99) | 1.99 (1.41 - 2.82) |
| Macfarlane *et al*.[62] | 20-year cohort study | 1018 | 11 - 12 | Clinical examination, mailed questionnaires | mailed questionnaires | Sometimes = 34.6 (44)/ 12.9 (23) | 3.58 (2.17 - 5.90) |
| | | | | | | Often (once a week) = 44.0 (11)/ 12.9 (23) | 5.29 (2.48 - 11.29) |

LBP = Low Back Pain, TMJ = Temporomandibular Joint, RDC/TMD = Research Diagnostic Criteria of Temporomandibular disorders, F = Female, M = Male, TP = Tender points, SCM = Sternocleidomastoid, TRAP = Trapezius, L = Left, R = Right

## CHAPTER 3. STUDY OBJECTIVES AND HYPOTHESES

Considering the aforementioned context, the literature lacks high quality studies investigating the difference between acute and chronic painful TMD, particularly according to the new definition of chronic pain by the IASP.[19] Thus, the overarching goal of this case-control analysis is to compare the likelihood of back and neck pain among acute relative to chronic painful TMD based on pain duration (≤ 3 months versus > 3 months) and pain-related disability (high disability versus low disability).

### Specific aims and null hypotheses

**Aim 1.1:** To compare the likelihood of back pain between acute and chronic painful TMD defined by pain duration.

**Null hypothesis 1.1:** There is no difference in the likelihood of back pain between acute and chronic painful TMD defined by pain duration.

**Aim 1.2:** To compare the likelihood of neck pain between acute and chronic painful TMD defined by pain duration.

**Null hypothesis 1.2:** There is no difference in the likelihood of neck pain between acute and chronic painful TMD defined by pain duration.

**Aim 2.1:** To compare the likelihood of back pain between acute and chronic painful TMD defined by pain-related disability.

**Null hypothesis 2.1:** There is no difference in the likelihood of back pain between acute and chronic painful TMD defined by pain-related disability.

**Aim 2.2:** To compare the likelihood of neck pain between acute and chronic painful TMD defined by pain-related disability.

**Null hypothesis 2.2:** There is no difference in the likelihood of neck pain between acute and chronic painful TMD defined by pain-related disability.

# CHAPTER 4. METHODOLOGY

## 4.1 Overview

In this section, the methodology of the current baseline case-control analysis comparing the acute and chronic cohorts of the ACTION project is described. The ACTION project is a multi-site prospective cohort study investigating the risk factors for the transition of acute to chronic painful TMD.

The ACTION project was approved by the McGill Institutional Review Board in Montreal, Canada (approval number: A12-M113-14A) and by the Dental Specialists Group in Ottawa, Ontario (approval number: 240-400). All participants agreed to participate in this study and signed the consent form.

## 4.2 Study population

All the participants were recruited between August 2015 and March 2021. Enrollment in this ACTION prospective cohort study continued afterwards and is still going on, and the new data will be analyzed for future publications.

Individuals with painful TMD were eligible to participate if they were aged between 18 and 85 years and were diagnosed with painful TMD (muscle and/or joint pain) according to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD). This instrument employs both patients' history and clinical examination to reach a diagnosis and it can be used for clinical as well as research settings. The DC/TMD has been demonstrated to have high validity and reliability particularly for painful TMD (sensitivity $\geq 86$, specificity $\geq 98$). As reported by Schiffman *et al.* this protocol showed excellent sensitivity and specificity, specifically for myalgia (0.90, 0.99), myofascial pain with referral (0.86, 0.98), arthralgia (0.89, 0.98), and disc

displacement without reduction with limited opening (0.8, 0.97) respectively. Moreover, the inter-examiner reliability for the DC/TMD has been demonstrated to be very high for myalgia (Kappa=0.94), myofascial pain with referral (Kappa=0.85), and arthralgia (kappa=0.86).[3] Patients were excluded, however, if they had another orofacial pain or cancer, had no access to a telephone, did not speak English or French, or were unable to provide an informed consent.

Individuals who met the eligibility criteria were recruited from the Jewish General Hospital general dental clinic, the Faculty of Dentistry of McGill University oral diagnosis clinic, Montreal General Hospital, and the Dental Specialists Group TMD-specialized clinic.

### 4.3 Classification of acute and chronic painful TMD

#### 4.3.1 Classification of acute and chronic painful TMD based on pain duration

When defined by pain duration, painful TMD was classified according to the recent chronic pain definition by the International Association for the study of Pain (IASP): "pain that lasts or recurs for longer than 3 months". [19] Therefore, painful TMD lasting for 3 months or less was considered acute, and that lasting for more than 3 months was deemed chronic.

#### 4.3.2 Classification of acute and chronic painful TMD based on pain-related disability

When defined by pain-related disability, painful TMD was classified using the Graded Chronic Pain Scale (GCPS). According to this scale, painful TMD was classified into one of four grades (I-IV). The GCPS evaluates pain-related disability hierarchically with more disability is expressed as a higher grade. According to this scale, disability is graded by its impact on activities, unemployment, healthcare utilization, medications, depression, and self-perceived health status. It comprises 4 grades: Grade I, low disability - low pain intensity (<50%); Grade II, low disability - high pain intensity (≥50%); Grade III, high disability - moderately limiting;

Grade IV, high disability - severely limiting.[63] Grades III and IV (i.e., high disability) were deemed chronic-disability TMD, while grades I and II (i.e., low disability) were considered non-chronic-disability TMD.

The GCPS has been proven to be a valid and reliable instrument. The original publication of the GCPS shows a good Cronbach's alpha of 0.71.[63] In addition, more recent clinical trial data showed even higher internal consistency of the scale (Cronbach's alpha = 0.90).[64,65] The concurrent validity of the GCPS has also been shown to be good. Increased GCPS grade was associated with an increased impact of TMD on daily life, frequency of pain-related visits, frequency of opioid use, unemployment, and depression.[63,64]

## 4.4 Assessment

### 4.4.1 Assessment of back and neck pain

The targeted pain conditions were non-specific back and neck pain. Therefore, no diagnostic criteria were used to assess them. A self-reported checklist was used to assess both back and neck pain with the question: "Do you have …?" on top. Participants had two choices: "Yes" and "No" to choose from.

### 4.4.2 Assessment of potential confounders

Confounding is a distortion of the exposure-outcome association due to its mutual association with another factor.[66] This distortion can lead to either overestimation or underestimation of the true association between exposure and outcome. In our study, the possible confounders were age, gender, anxiety, and depression.

For the assessment of potential confounders, Generalized Anxiety Disorders (GAD-7) and Patient Health Questionnaire (PHQ-8) were used to screen for anxiety and depression

symptoms, respectively. The GAD-7 questionnaire has 7 statements to which the participant responds by a score from zero to three indicating the frequency these statements apply to them. The total score sums up to a range from 0 to 24. The scoring cut-offs for the GAD-7 assessing anxiety symptoms were: 0-4 indicates minimal, 5-9 mild, 10-14 moderate and 15–21 indicates severe anxiety symptoms.[67]

The GAD-7 is a highly valid instrument for assessing anxiety symptoms. A systematic review and meta-analysis demonstrated that GAD-7 has high accuracy for identifying GAD. Sensitivity and specificity were found to be 0.83 (0.71 - 0.91) and 0.84 (0.70 - 0.92) respectively. In addition, GAD-7 is accurate in identifying any anxiety disorder. Sensitivity and specificity ranges were (0.77 - 0.92) and (0.74 - 0.83) respectively.[68]

Similarly, the PHQ-8 questionnaire consists of 8 statements to which the participants respond by a score from zero to three. Thus, the total score ranges from 0 to 24. The cut-offs for the PHQ-8 assessing depression symptoms were: : 0-4 indicates minimal, 5-9 mild, 10-14 moderate and 15–24 indicates severe depression symptoms.[69] The PHQ-8, as well, has been proven to have high validity for detecting depression symptoms. A recent systematic review and meta-analysis published in 2019 concluded that PHQ-8 has excellent sensitivity and specificity among studies that used semi-structured interviews (sensitivity = 0.86, 95% CI = 0.80 - 0.90, specificity = 0.86, 95% CI = 0.83 - 0.89). Likewise, sensitivity and specificity among studies that used fully structured interviews were found to be high (sensitivity = 0.77, 95% CI = 0.66 - 0.85, specificity = 0.78, 95% CI = 0.71 - 0.84).[70] In the present study the cut-off used to detect both anxiety and depression symptoms was 5. Furthermore, age and sex were considered as socio-demographic factors.

### 4.5 Statistical analysis

Student-t and Chi-square tests were used to assess statistical differences between the acute and chronic painful TMD groups for continuous and categorical variables, respectively.

Univariate and multivariable unconditional nominal logistic regression models were employed to assess the primary (aims 1.1 and 1.2) and the secondary (aims 2.1 and 2.2) aims of the study. The multivariable logistic models also included age, sex, anxiety, and depression symptoms as potential confounders.

A secondary analysis was performed to assess whether both comorbidities (i.e., the presence of back and neck pain) or either of them (i.e., the presence of back or neck pain) was associated with the independent variables (i.e., chronic painful TMD based on pain duration or disability). Univariate and multivariable unconditional nominal logistic regression analyses were used to assess these associations. The multivariable analyses were adjusted for age, sex, anxiety, and depression symptoms.

The odds ratios (OR), as well as the 95% confidence intervals (95%CI), were estimated. Statistical software package SAS (version 9.4) was used to perform the analyses with the significance level for type I error set at 0.05. The statistical power of this study was 83% and 88% to detect an OR as low as 2.0 for back and neck pain, respectively. This power was calculated putting into consideration the sample size used (369 chronic painful TMD patients 118 acute) and the prevalence of back (64%) and neck pain (55%) among chronic TMD pain patients (controls).[21]

## CHAPTER 5. MANUSCRIPT

# Back and neck pain: A comparison between acute and chronic painful TMD

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## 5.1 Introduction

Painful temporomandibular disorder (TMD) is a prevalent orofacial pain condition that affects 5-12% of the general population.[4] This term is used to refer to an umbrella of painful disorders affecting the masticatory muscles (e.g., myofascial pain), and/or the TMJ (e.g., arthralgia) or the surrounding structures.[1] Chronic TMD represents a heavy burden on the healthcare system and economy.[40,71] It has negative impacts on the patients' quality of life and functioning.[5,6,8]

Despite the wide range of treatments proposed to manage chronic TMD pain,[9] pain usually persists or worsens at follow-up in almost one third of the patients.[11] The risk factors, as well as the mechanisms implicated in the persistence of pain, have not yet been clearly identified.. Some mechanisms have been proposed for painful TMD chronification such as central sensitization and the inhibition of pain down-regulation mechanisms.[13,15,72] However, these mechanisms do not aid in differentiating between acute and chronic cases. Determining the mechanisms should be complemented with clear signs that help clinicians to distinguish chronic cases from acute ones. This distinction is critical to delivering accurate and personalized management strategies for patients.[9]

Recently, the International Association for the Study of Pain (IASP) has updated the definition of chronic pain as "pain that lasts or recurs for longer than 3 months". It also included functional disability and emotional distress as significant factors associated with chronic pain.[19] This suggests that pain duration only is not enough to classify pain into acute and chronic. Other factors might be considered to make this classification. Evidence shows that painful comorbidities, particularly back and neck pain, are not only highly associated with chronic painful TMD,[20-23] but also increase the risk of its development.[25,26]

Therefore, the aims of the present study were to compare the likelihood of back and neck pain between acute and chronic painful TMD defined by (i) pain duration (≤ 3 3months versus > 3 months); and (ii) pain-related disability (high disability versus low disability).

## 5.2 Methods

The current case-control analysis comparing the acute and the chronic cohorts of the ACTION project is described below. The ACTION project is a multi-site prospective cohort study investigating the risk factors for the transition of acute to chronic painful TMD as well as its persistence.

The ACTION project was approved by the McGill Institutional Review Board in Montreal, Canada (approval number: A12-M113-14A) and by the Dental Specialists Group in Ottawa, Ontario (approval number: 240-400). All participants agreed to participate in this study and signed the consent form.

### 5.2.1 Study population

Participants of the current study were recruited between August 2015 and March 2021 from four sites: (i) the Jewish General Hospital general dental clinic; (ii) the Faculty of Dentistry of McGill University oral diagnosis clinic; (iii) Montreal General Hospital; (iv) the Dental Specialists Group TMD-specialized clinic.

To be included in the study, patients should be diagnosed with painful TMD (muscle and/or joint pain) in accordance with the DC/TMD protocol and aged between18 and 85 years. The DC/TMD was proved to have high validity and reliability particularly for painful TMD.[3] Exclusion criteria were: (i) the presence of another orofacial pain or cancer. The presence of another orofacial pain, cancer, or their treatments may cause similar signs and symptoms to painful TMD, thus, increasing the chance of misclassification bias; (ii) no access to a telephone;

(iii) inability to speak English or French; (iv) inability to provide an informed consent. All eligible patients presenting to the recruitment sites were considered for enrollment and were invited to participate.

### 5.2.2 Classification of painful TMD

#### 5.2.2.1 Classification painful TMD based on pain duration

When defined by pain duration, painful TMD was classified according to the recent chronic pain definition by the International Association for the Study of Pain (IASP): "pain that lasts or recurs for longer than 3 months".[19] Therefore, painful TMD lasting for 3 months or less was considered acute, and that lasting for more than 3 months was deemed chronic.

#### 5.2.2.2 Classification of painful TMD based on pain-related disability

When defined by pain-related disability, painful TMD was classified using the Graded Chronic Pain Scale (GCPS). According to this scale, painful TMD was classified into one of four grades (I-IV). The GCPS evaluates pain-related disability hierarchically with more disability is expressed as a higher grade. According to this scale, disability is graded by its impact on activities, unemployment, healthcare utilization, medications, depression, and self-perceived health status. It comprises 4 grades: Grade I, low disability - low pain intensity (<50%); Grade II, low disability - high pain intensity (≥50%); Grade III, high disability - moderately limiting; Grade IV, high disability - severely limiting.[63] Grades III and IV (i.e., high disability) were deemed chronic-disability TMD, while grades I and II (i.e., low disability) were considered non-chronic-disability TMD.

### 5.2.3 Assessment

#### 5.2.3.1 Assessment of back and neck pain

Non-specific back and neck pain were evaluated. Therefore, no diagnostic criteria were used to assess them. Both back and neck pain were screened using a self-reported checklist. Participants were asked if they had these conditions and they had two choices: “Yes” or “No”.

#### 5.2.3.2 Assessment of potential confounders

Age, sex, anxiety, and depression symptoms were considered potential confounders. GAD-7 and PHQ-8 were used to assess anxiety and depression symptoms, respectively. Both questionnaires have several statements to which participants respond by a score from zero to three according to the frequency these statements apply to them. The total scores of GAD-7 and PHQ-8 are 21 and 24, respectively. These instruments were proven to have high specificity and sensitivity.[67-70] In our study, a cut-off of 5 was used to detect the presence of anxiety or depression symptoms. In addition, age and sex were deemed socio-demographic variables.

### 5.2.4 Statistical analysis

Student-t and Chi-square tests were used to assess statistical differences between participants with acute and chronic painful TMD for continuous and categorical variables, respectively.

Univariate and multivariable unconditional nominal logistic regression models were employed to compare the likelihoods of neck and back pain between acute and chronic painful TMD as defined by pain duration (aim 1) and pain-related disability (aim 2). The multivariable logistic models also included age, sex, anxiety, and depression symptoms as potential confounders or effect modifiers.

A secondary analysis was performed to assess whether the presence of the two comorbidities (i.e., both back and neck pain) or one comorbidity (i.e., either of them) was associated with the independent variables (i.e., chronic painful TMD defined by pain duration or disability). Univariate and multivariable unconditional nominal logistic regression analyses were used to assess these associations. The multivariable models were also adjusted for the covariates previously described.

The odds ratios (OR), as well as the 95% confidence intervals (95%CI), were estimated. Statistical software package SAS (version 9.4) was used to perform the analyses with the significance level for type I error set at 0.05. Considering the sample size used (369 chronic painful TMD patients 118 acute) and the prevalence of back (64%) and neck pain (55%) among chronic painful TMD patients,[21] this study had a statistical power of 83% and 88% to detect an OR as low as 2.0 for back and neck pain, respectively.

## 5.3 Results

### 5.3.1 Description of the sample

Table 1 compares the characteristics of the sample between the acute and chronic painful TMD pain groups. This study enrolled 487 adults with painful TMD, 118 of which had acute painful TMD (24.22 %) and 369 had chronic (75.77%). The percentage of females in the chronic painful TMD group (n = 288, 78.05 %) was significantly higher than that in the acute group (n = 81, 68.64%, P = 0.038). The mean age was similar between both groups (mean $_{\text{Acute}}$ =42.82, standard deviation (SD) = 16.63 , mean $_{\text{Chronic}}$ = 42.36, SD = 16.35). Participants recruited from Ottawa represented 23% (n = 112) of the total sample, while those recruited from Montreal accounted for 77% (n = 375). Chronic painful TMD participants had statistically higher frequency of both back (n = 179, 48.51%) and neck pain (n = 185, 50.41%) compared to those

with acute ($n_{back\ pain}$ = 42, 35.90%, P = 0.017, $n_{neck\ pain}$ = 37, 31.36%, P < 0.001). The majority of both groups was classified as grade II according to the GCPS ($n_{Acute}$ = 35, 29.66%, $n_{Chronic}$ = 133, 36.05%). Depression symptoms, but not anxiety, were significantly more prevalent among the chronic painful TMD (n = 296, 80.22%) relative to the acute group (n = 76, 64.96%, P < 0.001).

### 5.3.2 Chronic TMD defined by pain duration

Table 2 demonstrates the association between back and neck pain, and chronic compared to acute painful TMD based on pain duration (≤ 3 months versus > 3 months) using crude and adjusted logistic regression models. Participants with chronic painful TMD had twice the likelihood to report neck pain (OR = 2.17, 95%CI = 1.27 - 3.71) compared to those with acute painful TMD, regardless of their age, sex, anxiety , and depression symptoms. On the other hand, the presence of back pain did not show a significant association in the adjusted analysis (OR = 0.96, 95%CI = 0.57 - 1.64). Furthermore, depression symptoms (OR = 2.08, 95%CI = 1.21 - 3.58) and female sex (OR = 2.08, 95%CI = 1.21 - 3.58) were the confounder variables associated with chronic TMD pain  The adjusted ORs for age, sex, and anxiety were not statistically significant.

#### 5.3.2.1 Secondary analysis

We assessed whether participants with chronic compared to acute painful TMD had a higher likelihood to present the two comorbidities (i.e., back and neck pain) or only one (e.i., either back or neck pain). The group distribution is presented in figure 1.

Multivariable logistic regression analysis showed that relative to the acute group, those with chronic painful TMD were more likely to report neck or back pain (OR = 2.34, 95%CI =

1.47 - 3.73), than none. The likelihood to present both painful comorbidities, however, was not statistically significantly different between acute and chronic painful TMD groups (OR = 1.47, 95%CI = 0.71 - 3.05). Furthermore, we did not find a difference between the odds to present both comorbidities or only one (OR = 0.63, 95%CI = 0.30-1.33). These models included the covariates sex, age, anxiety, and depression symptoms.

### 5.3.3 Chronic-Disability TMD

Table 3 shows the crude and adjusted ORs of the logistic regression analysis assessing the association between neck and back pain comorbidities, and chronic painful TMD defined by disability (GCPS grades III-IV). Similar to the results presented in table 2, participants with chronic-disability TMD were twice as likely to report neck pain (OR = 1.95, 95%CI = 1.20 - 3.17) compared to those with non-chronic-disability TMD, regardless of the participant's age, sex, anxiety, depression, presence of back pain, and the acute-chronic pain status defined by pain duration. The covariates associated with the study outcome were anxiety (OR = 2.43, 95%CI = 1.51 - 3.90), depression symptoms (OR= 1.85, 95%CI = 1.04 - 3.29), and acute-chronic pain status defined by pain duration (OR = 0.51, 95%CI = 0.32 - 0.81). Conversely, participants in the group with chronic-disability TMD did not show an increased likelihood to report back pain (OR = 1.13, 95%CI = 0.69 - 1.82) versus those in the non-chronic-disability group.

#### 5.3.3.1 Chronic-disability TMD secondary analysis

Multivariable logistic regression analysis showed that relative to the non-chronic-disability TMD group, those with chronic-disability TMD were twice as likely to report any of the two comorbidities (OR = 2.17, 95%CI = 1.40 - 3.37), than none. The OR to present the two painful comorbidities was not statistically significant (OR = 1.14, 95%CI = 0.55 - 2.38). Finally,

we did not find a difference between the odds to present both comorbidities or only one (OR = 0.53, 95%CI = 0.26 - 1.07). These analyses were adjusted by sex, age, anxiety and depression symptoms, and acute-chronic pain duration status.

**5.4 Discussion**

Several studies in the literature have already demonstrated that individuals with chronic painful TMD report back or neck pain more frequently than those without.[20-23] Additionally, both comorbidities increase the risk of painful TMD development.[25,26] However, to our best knowledge, this is the first study to compare the frequency and the likelihood of these two painful comorbidities between acute and chronic painful TMD. One cohort study assessed the association between TMD pain duration, widespread pain, and painful comorbidities including back and neck pain. In this study, results showed that increased TMD pain duration increased the odds of having painful comorbidities as well as pain beyond the orofacial region.[73] In our study, participants with chronic painful TMD were twice as likely to report either back or neck pain relative to acute. Specifically, neck pain was the painful comorbidity that showed significant ORs. Similarly, other studies found that the presence of painful comorbidities increased the risk of chronic post-operative pain and the odds of the transition from acute to chronic post-surgical pain.[74,75]

Kotiranta and colleagues in a recent study published in 2018 assessed the relationship between pain-related disability in TMD patients diagnosed according to RDC/TMD and comorbid pain conditions. This study found that TMD participants with high disability (3-6 disability points on the GCPS) presented a greater number of comorbidities (e.g. headache, back pain, neck pain, abdominal pain) relative to the non-disabled group (0 disability points).[76] In our current study, participants with GCPS grades III-IV (i.e., high disability) had double the odds to

present neck pain compared to those with low disability (grades I-II). Similarly, a headache study showed that chronic painful comorbidities accounted for one third of the disability difference between migraine participants and those without severe headaches.[77]

Our findings suggest that central dysregulation mechanisms[15,78] are implicated in the process of painful TMD chronification involving peripheral and central sensitization mechanisms. Central pain is characterized by being diffuse or multi-focal, thus associated with comorbid pain conditions.[72,79] This can explain why the chronic group had increased odds to report neck pain compared to the acute. Another suggested mechanism is trigeminocervical convergence.[80-82] The neurons in the trigeminal nucleus caudalis that extend to C2 and the lateral cervical nucleus are stimulated by trigeminal activation causing symptoms in both trigeminal and cervical regions. This mechanism could be activated as painful TMD becomes chronic leading to the observed association between chronic painful TMD and neck pain, but not with back pain. On the other hand, the absence of this association with back pain reflects its high prevalence in both study groups. However, it is still possible that back pain is more frequently reported in specific subgroups or subdiagnoses of chronic painful TMD compared to acute. Several studies proposed that different mechanisms are implicated in these subgroups,[83-85] thus leading to different associations with comorbidities.

Moreover, the association of chronic-disability with neck pain calls attention to the importance of including disability as a factor defining chronic painful TMD in addition to pain duration, which agrees with the latest IASP recommendations.[19] This accurate distinction will aid clinicians to better design the most suitable and effective management protocols that may involve a multidisciplinary team to address comorbidities associated with persistence or disability.

Interestingly, highly disabled participants seem to have acute rather than chronic painful TMD. This might be related to the treatment-seeking behavior of these acute cases and cannot be generalized. Participants with acute painful TMD who sought medical care reported high levels of disability more frequently than the chronic group. This agrees with a previous study that showed that treatment seekers were more likely to have a shorter duration of TMD pain and a higher disability score.[86] One reason for this association could be that painful TMD patients with a high disability usually seek care as early as possible in order to receive treatment. On the contrary, those without disability wait until the pain has already persisted past the acute/chronic threshold (i.e., 3 months).

The limitations of this study should be noted. First, temporality cannot be established in case-control studies. Due to the study design, whether exposures precede outcomes cannot be ascertained. Therefore, no causal relationships can be inferred. Second, self-report questionnaires were used in this study to evaluate anxiety and depression symptoms, back and neck pain, and disability. Though cost-effective and validated, these instruments are still liable to recall and misclassification biases. Third, sub-analyses to assess sex and site differences were not possible due to insufficient sample sizes in the respective subgroups. Fourth, variables such as ethnicity, socio-economic status, and educational level were not collected. As a result, it was not possible to assess their potential effects. Additionally, only the presence or absence of back and neck pain was assessed. Other determinants such as the duration or frequency of pain were not included.

The strengths of this study include: first, sufficient sample size was enrolled (118 cases and 369 controls) resulting in a power of 83% for back pain and 88% for neck pain to reject the null hypothesis that odds ratios equal one. This was calculated putting into consideration the detected odds ratios and the prevalence of neck and back pain among chronic painful TMD

patients (55% and 64% respectively).[21] Second, this study was a multi-site study conducted in four sites across two cities in two different provinces. The recruitment of participants at different sites not only reduces the chance of selection bias but also improves the external validity of the study. This, however, did not introduce any bias as the percentage of participants recruited from Montreal and Ottawa was similar in both study groups as shown in table 1. Third, we used a highly valid clinical instrument (DC/TMD) to diagnose participants in both groups. Anxiety and depression symptoms and disability were also assessed with validated and reliable questionnaires. In addition, the most updated IASP definition of chronic pain of the 3-month threshold was used to classify acute and chronic painful TMD based on pain duration. This reduces the chance of misclassification bias and enhances the validity of our results. Fourth, an analysis was conducted to compare the likelihood of back and neck pain when defining chronic painful TMD based on pain-related disability in accordance with the latest IASP recommendations.[19] This analysis yielded very interesting results.

In summary, our findings suggest the implication of central dysregulation and/or trigeminocervical convergence mechanisms in painful TMD persistence. These mechanisms are associated with regional comorbidity such as neck pain. Neck pain's similar association with high disability highlights the relevance of putting pain-related disability in consideration when defining chronic painful TMD rather than using only pain duration. These results emphasize the significance of comorbidity and disability detection in painful TMD patients.

Table 5.1 Comparison between acute and chronic painful TMD groups based on the sample characteristics

| | Category | Acute painful TMD [a] (n = 118) | Chronic painful TMD [b] (n = 369) |
|---|---|---|---|
| **Back pain, n (%)** [*] | No | 75 (64.10) | 190 (51.49) |
| | Yes | 42 (35.90) | 179 (48.51) |
| **Neck pain, n (%)** [*] | No | 81 (68.64) | 182 (49.49) |
| | Yes | 37 (31.36) | 185 (50.41) |
| **Age** | Mean (SD) | 42.82 (16.63) | 42.36 (16.35) |
| **Sex, n (%)** [*] | Male | 37 (31.36) | 81 (21.95) |
| | Female | 81 (68.64) | 288 (78.05) |
| **City, n (%)** | Montreal | 86 (72.88) | 289 (78.32) |
| | Ottawa | 32 (27.12) | 80 (21.68) |
| **Graded Chronic Pain Scale, n (%)** [*] | Grade I | 33 (27.97) | 110 (29.81) |
| | Grade II | 35 (29.66) | 133 (36.05) |
| | Grade III | 21 (17.80) | 54 (14.63) |
| | Grade IV | 29 (24.58) | 72 (19.51) |
| **Anxiety, n (%)** | No | 50 (42.74) | 130 (35.23) |
| | Yes [c] | 67 (57.26) | 259 (64.77) |
| **Depression [d], n (%)** [*] | No | 41 (35.04) | 73 (19.78) |
| | Yes [d] | 76 (64.96) | 296 (80.22) |

[a]: ≤ 3 months, [b]: > 3 months, [c]: GAD-7 score ≥ 5, [d]: PHQ-8 score ≥ 5, [*]: $P < 0.05$

Table 5.2 The association between neck and back pain, and chronic [a] relative to acute [b] painful TMD defined by pain duration.

| | | Crude | | Adjusted [c] | |
|---|---|---|---|---|---|
| | **Category** | **OR** | **95% CI** | **OR** | **95% CI** |
| **Back pain** | No | 1 | Reference | 1 | Reference |
| | Yes | 1.68* | 1.10 - 2.58 | 0.96 | 0.57 - 1.64 |
| **Neck pain** | No | 1 | Reference | 1 | Reference |
| | Yes | 2.23* | 1.43 - 3.45 | 2.17* | 1.27 - 3.71 |
| **Age** | | 1.05 | 0.66 - 1.67 | 1.00 | 0.99 - 1.01 |
| **Sex** | Male | 1 | Reference | 1 | Reference |
| | Female | 1.62* | 1.03 - 2.57 | 1.51 | 0.93 - 2.44 |
| **Anxiety** | No | 1 | Reference | 1 | Reference |
| | Yes [d] | 1.26 | 0.83 - 1.92 | 0.97 | 0.59 - 1.60 |
| **Depression** | No | 1 | Reference | 1 | Reference |
| | Yes [e] | 2.19* | 1.38 - 3.46 | 2.08* | 1.21 - 3.58 |

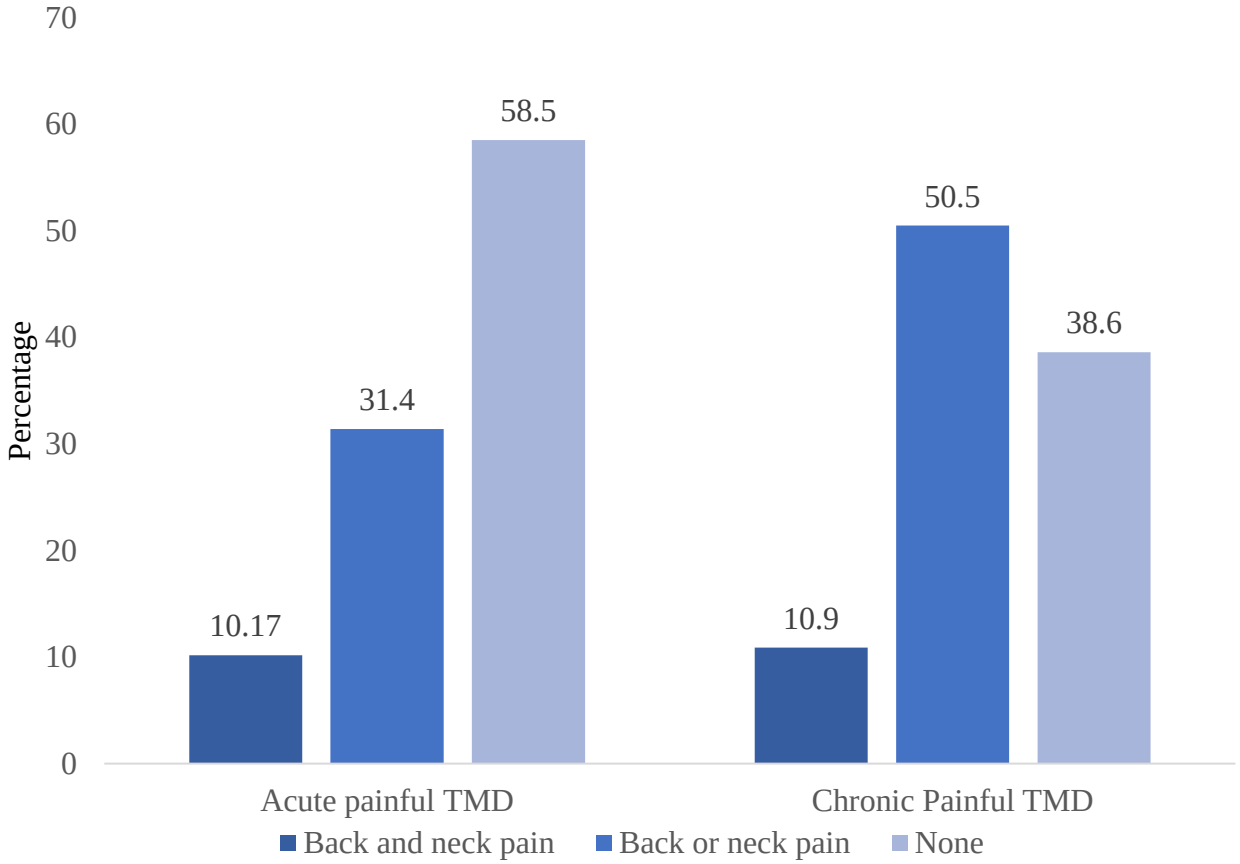
[a]: > 3 months, [b]: ≤ 3 months, [c]: Adjusted for age, sex, anxiety and depression symptoms, [d]: GAD-7 score ≥ 5, [e]: PHQ-8 score ≥ 5, *: $P < 0.05$

Table 5.3 The association between neck and back pain, and chronic [a] relative to non-chronic [b] painful TMD defined by pain-related disability.

| | | Crude | | Adjusted [c] | |
|---|---|---|---|---|---|
| | **Category** | **OR** | **95% CI** | **OR** | **95% CI** |
| **Back pain** | No | 1 | Reference | 1 | Reference |
| | Yes | 1.59* | 1.09 - 2.30 | 1.13 | 0.69 - 1.82 |
| **Neck pain** | No | 1 | Reference | 1 | Reference |
| | Yes | 1.82* | 1.25 - 2.65 | 1.95* | 1.20 - 3.17 |
| **Age** | | 0.99 | 0.98 - 1.00 | 0.99 | 0.98 - 1.00 |
| **Sex** | Male | 1 | Reference | 1 | Reference |
| | Female | 0.87 | 0.57 - 1.32 | 0.82 | 0.52 - 1.30 |
| **Anxiety** | No | 1 | Reference | 1 | Reference |
| | Yes [d] | 3.29* | 2.22 - 4.88 | 2.43* | 1.51 - 3.90 |
| **Depression** | No | 1 | Reference | 1 | Reference |
| | Yes [e] | 2.51* | 1.59 - 3.97 | 1.85* | 1.04 - 3.29 |
| **Acute/chronic painful TMD status** | Acute [f] | 1 | Reference | 1 | Reference |
| | Chronic [g] | 0.75 | 0.50 - 1.13 | 0.51* | 0.32 - 0.81 |

[a]: Graded Chronic Pain Scale (GCPS) = III-IV, [b]: GCPS = I-II, [c]: Adjusted for age, sex, anxiety, depression symptoms and acute/chronic painful TMD status, [d]: GAD-7 score ≥ 5, [e]: PHQ-8 score ≥ 5, [f]: > 3 months, [g]: ≤ 3 months, *: $P < 0.05$

Figure 1. Distribution of participants having both back and neck pain, either, or none of them in the acute [a] and chronic [b] painful TMD groups.




[a]: ≤ 3 months, [b]: > 3 months

# CHAPTER 6. DISCUSSION

## 6.1 Summary of the results

Despite the rich literature in favor of the association between back and neck pain and chronic painful TMD, studies investigating the difference between acute and chronic painful TMD are lacking. To our best knowledge, this is the first study to compare the occurrence and the likelihood of back and neck pain between acute and chronic painful TMD as defined by pain duration or pain-related disability.

Our study found that participants with chronic painful TMD were more likely to present neck, but not, back pain when compared with those with acute. Moreover, when chronic painful TMD was defined by high disability, results showed that the highly disabled participants according to the GCPS had twice the odds to report neck pain relative to those with low disability. Nevertheless, our results did not show any increased odds for reporting back pain.

## 6.2 Comparison with similar studies

Studies comparing comorbidities in acute and chronic painful TMD in the literature are scarce. One study by Nguyen *et al.* 2019 investigated the relationship between pain duration and the presence of painful comorbidities in participants with painful TMD. This study included 198 adults attending the Occlusion Clinic at Chulalogkorn University, Bangkok, Thailand. Of these, 88 had chronic and 110 had acute TMD pain. Participants were diagnosed according to the DC/TMD and were classified into acute and chronic according to the recent IASP definition of chronic pain at a 3-month threshold.[19] Comorbidities identified were: fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, interstitial cystitis, frequent headache, chronic low back pain, and chronic pelvic pain. Results showed that for every 1-month of pain persistence,

the odds of having greater number comorbidities increased by 2.8% (OR = 1.028, 95% CI = 1.005 - 1.05, P = 0.008) adjusting for age. Additionally, a 1-month increase in pain duration increased the likelihood of pain beyond the orofacial region by 4.5% regardless of pain intensity and age (OR = 1.045. 95% CI = 1.024 - 1.066, P = 0.001).[73] Similarly, Dahan *et al.* in a cross-sectional study (n = 180) conducted in Montreal, Canada, and Boston, USA assessed TMD using RDC/TMD and five comorbid conditions: migraine, chronic fatigue syndrome, irritable bowel syndrome, interstitial cystitis, and restless leg syndrome. Findings showed that the number of comorbidities and the presence of chronic fatigue syndrome were associated with the duration of TMD pain ($P < 0.01$ for both).[87] The aforementioned studies show that longer TMD pain duration increases the likelihood of having comorbid pain conditions, which goes in agreement with the results of our study.

Although the OPPERA study assessed various comorbidities, no participants in this study had acute painful TMD at the time of clinical examination. According to Slade *et al.*, the mean time difference between the positive screening of a participant and the clinical confirmation was 18 months (interquartile range = 10 - 26 months). Therefore, by the time of the clinical diagnosis, all participants had chronic painful TMD.[88] This makes our study one of the unique studies including acute painful TMD participants using a 3-month cut-off.

Furthermore, the results of our study go in line with studies that investigated other types of chronic pain. A study by Althaus *et al.* found that the presence of comorbid preoperative pain elsewhere from the surgical site increased the risk of chronic postoperative pain by 1.8 times at 6 months follow-up.[74] A review by Glare *et al.* shows that medical comorbidities, disability, and preoperative pain are associated with the transition from acute to chronic postsurgical pain.[75]

On the other hand, disability has been associated with pain comorbidity by several studies. A study by Kotiranta *et al.* used RDC/TMD to diagnose TMD patients and GCPS to assess pain-related disability. Findings showed that highly disabled participants (3-6 disability points on the GCPS) demonstrated a higher number of pain comorbidities (headache, back pain, neck pain, joint pain, abdominal pain, chest pain, or fibromyalgia) compared to non-disabled ones (0 disability points).[76] Another study conducted by Saunders *et al.* on migraines found that chronic comorbid pain conditions accounted for a third of the role disability difference between migraineurs and those without severe headaches.[77]

### 6.3 Implications of the results

The increased odds of neck pain with chronic compared to acute painful TMD at a 3-month threshold suggests that central dysregulation mechanisms are implicated in the process of TMD pain chronification. Centralized pain is characterized by being regional (i.e., propagates to the surrounding region) or diffuse (i.e., generalized or multifocal) but not as well-localized as peripheral pain. In centralized pain, the central nervous system adaptation causes abnormal amplification of the ascending peripheral input as well as maintaining the perception of pain despite minimal or no nociception.[72] Central sensitization and dysregulated endogenous pain control mechanisms have been proposed as possible mechanisms for centralized pain.[15,78] As suggested by our results, painful TMD chronification is accompanied by comorbid pain (e.g., neck pain).

Another suggested mechanism is trigeminocervical convergence.[80-82] The neurons in the trigeminal nucleus caudalis that extend to C2 and the lateral cervical nucleus are stimulated by trigeminal activation causing symptoms in both the trigeminal and cervical regions. This mechanism could be activated as painful TMD becomes chronic leading to the observed

association between chronic painful TMD and neck pain, but not back pain. This lack of association with back pain suggests that chronic painful TMD, as shown by Bair *et al.*,[83] is comprised of different mechanistic or etiologic subgroups. Other studies as well proposed that different mechanisms are implicated in TMD subdiagnoses.[84,85] This might explain why chronic painful TMD in our study did not show a significant OR for back pain. One possible reason is that back pain is only related to one or more of these subgroups or subdiagnoses. It also highlights the high prevalence of back pain in both acute and chronic painful TMD.

The association between chronic-disability and neck pain reflects the impact of regional comorbid pain on the daily, recreational, and social activities of painful TMD patients. It demonstrates the relevance of including disability when classifying chronic painful TMD. This concurs with the latest IASP definition of chronic primary pain.[19]

The interesting association of high disability with acute painful TMD in comparison to chronic sheds the light on the care-seeking behaviors of acute cases. This indicates that patients with acute TMD pain who seek medical attention have more frequently high levels of pain-related disability relative to chronic. Similar results were found by Epker and Gatchel where treatment-seeking behavior was associated with a shorter duration of pain ($P < 0.001$) and higher disability score ($P = 0.01$).[86] A possible explanation is that highly disabled TMD patients tend to seek medical care as soon as possible (i.e., during the first 3 months) in order to relieve this disability. On the contrary, those with low disability do not seek treatment until their pain has become chronic.

The findings of this study encourage future research to investigate the impact of painful comorbidities on the risk of transition from acute to chronic painful TMD at 3 months. Additionally, more objective instruments such as conditioned pain modulation testing, laboratory

determination of serum neurotrophins and inflammatory mediators, functional imaging (e.g., fMRI, PET)[89] could be used to better understand the relationship between central sensitization events and the process of painful TMD chronification.

## 6.4 Methodological considerations

### 6.4.1 Bias

Bias can be defined as a systematic error that occurs in epidemiological research studies. This error can lead to an over- or under-estimation of the relationship between exposures and outcomes of interest depending on the direction of this bias. It occurs due to systematic errors in the study methodology that usually cannot be adjusted at the analysis stage. For this reason, care should be taken during the design phase of the study in order to avoid the introduction of biases and thus jeopardize the validity of its results.[90] The two main types of bias in epidemiological research are information bias and selection bias. In the following sections, causes of possible biases in our study and strategies to minimize them will be discussed.

#### 6.4.1.1 Information bias

Information bias occurs as a result of inaccurate methods of collecting information from participants in a study leading to incorrect evaluation of the relationship between exposures and outcomes. These inaccuracies may sometimes cause misclassification bias. This means that some cases are misclassified as controls and some controls are misclassified as cases. Misclassification can occur differentially or non-differentially between the study groups. Differential misclassification could result in an association that does not exist or the absence of an association that actually exists. However, non-differential misclassification leads to the dilution of the effect measure towards one.[91]

To minimize the chance of misclassification bias in our study, we used the most accepted and validated clinical instrument (DC/TMD) to diagnose both acute and chronic painful TMD. The latest definition of chronic pain at a 3-month threshold according to the IASP was used to classify acute and chronic painful TMD. In addition, disability, anxiety, and depression symptoms were assessed using highly valid and reliable instruments.

Recall bias is one of the sources of information bias, particularly in case-control studies. The inability of participants to accurately recall their exposure status could lead to an information bias. In general, cases are more likely to recall exposures related to their disease than healthy controls.[91] In the present case-control study, both groups have painful TMD (i.e., no health participants). Therefore, it is assumed that recall bias, if existent, will be non-differential across both study groups.

#### 6.4.1.2 Selection bias

Selection bias arises when the way cases or controls are selected results in an apparent association that does not exist, or to a non-existent association.[91] In case-control studies where cases and controls are selected from a hospital or a clinic, it is possible that an identified association between the exposure and the outcome is attributed to factors (e.g., referral patterns, neighborhood population) unique to that site. To reduce the chance of this type of bias, participants were recruited from four sites in two cities.

Moreover, selection bias in case-control studies may be caused by differences between individuals who accepted to participate and those who did not. If this bias exists, identified associations might be attributed to the differences between responders and non-responders rather

than the exposure status. In our study, the response rate is high (89%), thus the effect of selection bias due to non-response is negligible.

Berkson bias is a selection bias where the relationship between the exposure and the outcome is distorted due to the recruitment of participants at a hospital or a clinic.[92] For this type of bias to occur, both the exposure and the outcome should be associated with clinic/hospital attendance. Since participants from both groups were recruited at the same site, it is not likely that one group had a higher chance to attend the clinic/hospital more than the other.

#### 6.4.1.3 Bias due to confounding

The relationship between the exposure and the outcome might be biased by the presence of other factors (i.e., confounders) that are associated with both of them. The presence of confounders could lead to an over- or under-estimation of an effect measure.[90] In the present study, age, sex, anxiety, and depression symptoms were considered potential confounders. These potential confounders were included in the multivariable models. However, other potential confounders were not assessed such as socio-economic status, educational level, and ethnicity. Hence, we could not adjust for their potential effects.

### 6.5 Strengths

To our best knowledge, this is the first study comparing back and neck pain between acute and chronic painful TMD. The strengths of this study include: first, sufficient sample size was enrolled (118 cases and 369 controls) resulting in a power of 83% for back pain and 88% for neck pain to reject the null hypothesis that odds ratios equal one. This was calculated putting into consideration the detected odds ratios and the prevalence of neck and back pain among chronic painful TMD patients (55% and 64% respectively).[21] Second, this study was a multi-site study

conducted in four sites across two cities in two different provinces. The recruitment of participants at different sites not only reduces the chance of selection bias but also improves the external validity of the study. This, however, did not introduce any bias as both study groups had similar percentages recruited from Montreal and Ottawa as shown in table 1. Third, we used a highly valid clinical instrument (DC/TMD) to diagnose both cases and controls. Anxiety and depression symptoms and disability were also assessed using validated and reliable instruments. In addition, the IASP most updated definition of chronic pain of a 3-month threshold was used to define acute and chronic painful TMD.[19] This reduces misclassification bias and enhances the validity of our results. Fourth, following the IASP guidelines, our study also performed another analysis to compare the odds of back and neck pain when defining chronic painful TMD by high disability based on the GCPS. This analysis yielded very interesting results.

### 6.6 Limitations

The limitations of this study should be noted. First, due to the study design, whether exposures precede outcomes could not be determined as temporality was not assessed. Therefore, no causal relationships could be inferred. Second, self-report questionnaires were used in this study to evaluate anxiety and depression symptoms, back and neck pain, and disability. These instruments are highly valid and are used in research as well as clinical setting. However, they are still liable to recall and misclassification biases. Third, sub-analyses to assess sex, site, and age group differences were not possible due to insufficient sample sizes in the corresponding subgroups. Fourth, variables such as ethnicity, socio-economic status, and educational level were not evaluated, thus not included as covariates. This might have resulted in some residual confounding. Additionally, only the presence or absence of back and neck pain was assessed. Other determinants such as the duration or frequency of pain were not assessed.

# CHAPTER 7. CONCLUSIONS

The following could be concluded from the present study. First, chronic painful TMD differs from acute by being more associated with regional painful comorbidities (e.g., neck pain). Another suggested difference is the mechanism of pain, which could involve central and peripheral sensitization and/or trigeminocervical convergence mechanisms in chronic painful TMD. Future studies are encouraged to investigate the impact of painful comorbidities on the risk of transition from acute to chronic painful TMD. The identification of such risk factors will aid the development of management strategies to prevent this transition.

Second, pain-related disability is an important factor to be considered when defining chronic painful TMD together with pain duration. The detection of disability in painful TMD patients will allow the identification of complex cases that might need a multidisciplinary approach in pain management to address the associated comorbidities.

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