The impact of insomnia in the persistence of pain-related temporomandibular disorders: a six-month cohort study

A Manuscript-based thesis

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Dedication

I would like to dedicate this humble work to my beloved parents Niher Sarcar and Mini Sarcar for their support and love. Both have worked very hard and sacrificed their time for me and my brother, Tejeshwar. I would also like to dedicate this work to Divya who would be soon becoming a member of our family.

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List of abbreviations

PTMD:	Pain-related temporomandibular disorder
TMD:	Temporomandibular disorder
RDC:	Research Diagnostic Criteria
DC:	Diagnostic Criteria
ISI:	Insomnia Severity Index
CPI:	Characteristic Pain Intensity
RR:	Relative Risk
CI:	Confidence Interval
adj:	adjusted
c:	crude
IASP:	International Association for Study on Pain
TMJ:	Temporomandibular Joint
AAOP:	American Association of Orofacial Pain
OFHP SIG:	Orofacial and Head Pain Special Interest Group
IHS:	International Headache Society
ICOP:	International Classification of Orofacial Pain
ICHD:	International Classification of Headache Disorders
NHIS:	National Health Interview Survey
HR:	Hazards Ratio
OR:	Odds Ratio
GCPS:	Graded Chronic Pain Scale
ACR:	American College of Rheumatology
OPPERA:	Orofacial Pain Perspective Evaluation and Risk Assessment
FSS:	Fatigue Severity Scale
OSA:	Obstructive Sleep Apnea
EPP:	Epworth Sleepiness Scale

SCL:	Symptom Checklist
VAS:	Visual Analogue Scale
CMP:	Craniomandibular pain
CSP:	Cervical spine pain
CMI:	Craniomandibular Index
NRS:	Numeric Rating Scale
CSQ:	Coping Strategies Questionnaire
PSQI:	Pitt**s**burgh Sleep Quality Index
SRI:	Sleep-related Impairment
SD:	Sleep disruption
SDQ:	Sleep Disturbance Questionnaire
PSG:	Polysomnography
PPTh:	Pressure pain threshold
HPTh:	Heat pain threshold
SDN:	Standard deviation
CPM:	Conditioned Pain Modeling
CSI:	Central Sensitization Inventory
BDI:	Beck's Depression Index
DSM:	Diagnostic and Statistical Manual of Mental Disorders
BPI:	Brief Pain Inventory
PCS:	Pain Catastrophizing Scale
IVR:	Interactive Voice Response Assessment

Abstract

Background: Though most pain-related temporomandibular disorders (**PTMD**s) are mild and self-limiting, a significant frequency of patients experience persistent pain, presenting a great challenge in terms of management and often resulting in substantial disability. Individuals with PTMD commonly exhibit sleep-related comorbidities, with insomnia being a prevalent concern.

Objective: The aim of this multicenter cohort study was to assess whether insomnia contributed to the persistence of clinically significant PTMD defined by moderate to severe pain intensity within six months of follow-up.

Methods: Participants were enrolled from three clinics in Montreal and one in Ottawa. The diagnosis of PTMD was achieved through the utilization of either the Research Diagnostic Criteria (**RDC/TMD**) or the Diagnostic Criteria for Temporomandibular Disorders (**DC/TMD**). Insomnia at baseline visit was assessed using the Insomnia Severity Index (**ISI**). Persistence of clinically significant PTMD defined by moderate to severe pain intensity was measured using Characteristic Pain Intensity (**CPI**) scores within six months of follow-up period. Crude and multivariable logistic regression analyses were used to estimate the results.

Results: Out of the 456 PTMD participants, 447 answered the baseline questionnaires, 377 (84.3%) and 370 (82.8%) completed the three-month and six-month follow-up periods, respectively. Insomnia increased the likelihood of persistent clinically significant PTMD (CPI ≥ 50) in both the crude (OR_c= 1.63, 95%CI: 1.24—2.15, P= 0.0005) and multivariable (OR_{adj}= 1.60, 95%CI: 1.10 - 2.31, P= 0.01) analyses, within the six-month follow-up among the participants. Additional analysis showed that mild insomnia (OR_{adj}= 1.42, 95%CI: 0.94—2.12, P= 0.09),

moderate insomnia (OR_{adj}= 1.95, 95%CI: 1.23—3.08, P= 0.004) and severe insomnia (OR_{adj}= 2.43, 95%CI: 1.37—4.31, P= 0.002) contributed to the persistence of clinically significant PTMD in a dose-response manner.

Conclusion: These results indicate that insomnia increases the likelihood of persistent clinically significant PTMD within six months of follow-up period, and therefore should be considered as an important factor when evaluating and developing treatment plans for patients with PTMD.

Résumé

Contexte: Bien que la plupart des troubles temporo-mandibulaires liés à la douleur (**PTMD**) soient légers et se résorbent d'eux-mêmes, une fréquence significative de patients souffre d'une douleur persistante, représentant un défi majeur en termes de prise en charge et entraînant souvent un handicap substantiel. Les personnes atteintes de PTMD présentent généralement des comorbidités liées au sommeil, l'insomnie étant une préoccupation prévalente.

Objectif: L'objectif de cette étude de cohorte multicentrique était d'évaluer si l'insomnie contribuait à la persistance du PTMD cliniquement significatif défini par une intensité de douleur modérée et sévère dans les six mois de suivi.

Méthodes: Les participants ont été recrutés à partir de trois cliniques à Montréal et d'une à Ottawa. Le diagnostic de PTMD a été établi grâce à l'utilisation des Critères de Diagnostic de Recherche (**RDC/TMD**) ou des Critères Diagnostiques des Troubles Temporomandibulaires (**DC/TMD**). L'insomnie lors de la visite initiale a été évaluée à l'aide de l'Indice de Sévérité de l'Insomnie (**ISI**). La persistance du PTMD cliniquement significatif, définie par l'intensité de la douleur, a été mesurée à l'aide des scores de l'Intensité Caractéristique de la Douleur (**CPI**) dans les six mois de la période de suivi. Des analyses de régression logistique brutes et multivariées ont été utilisées pour estimer les résultats.

Résultats: Sur les 456 participants atteints de PTMD, 447 ont répondu aux questionnaires initiaux, 377 (84.3%) et 370 (82.8%) ont complété respectivement les périodes de suivi de trois et six mois. L'insomnie a augmenté la probabilité de persistance du PTMD cliniquement significatif (CPI ≥ 50) dans les analyses brutes (OR_c= 1.63, 95%CI : 1.24—2.15, P= 0.0005) et

multivariées (OR_{adj}= 1.60, 95%CI : 1.10—2.31, P= 0.01) sur une période de six mois parmi les participants. Une analyse supplémentaire a montré que l'insomnie légère (OR_{adj}= 1.42, 95%CI : 0.94—2.12, P= 0.09), l'insomnie modérée (OR_{adj}= 1.95, 95%CI : 1.23—3.08, P= 0.004) et l'insomnie sévère (OR_{adj}= 2.43, 95%CI : 1.37—4.31, P= 0.002) ont contribué à la persistance du PTMD cliniquement significatif de manière dose-dépendante.

Conclusion: Ces résultats indiquent que l'insomnie augmente la probabilité de troubles de stress post-traumatique persistants cliniquement significatifs dans les six mois suivant la période de suivi, et devrait donc être considérée comme un facteur important lors de l'évaluation et de l'élaboration de plans de traitement pour les patients atteints de PTMD.

Preface

This thesis fulfills the requirements for the degree of Master of Science (Dental Sciences), and its objectives stem from the authors' keen interest in unraveling the intricate relationship between sleep disturbances and pain. Following the manuscript-based format mandated by the Graduate and Postdoctoral Studies at McGill University, this thesis endeavors to expand upon the existing literature by exploring the role of insomnia in the persistence of pain-related temporomandibular disorders. After a concise abstract, Chapter one sets the stage with an introduction to the thesis, followed by a subsequent chapter delving into the existing literature on temporomandibular disorders and insomnia. Chapter three outlines the aims and hypotheses, paving the way for a detailed exploration of the methodology in Chapter Four. The subsequent chapter presents the manuscript, followed by an extensive discussion and conclusion.

In the sections that follow, due acknowledgment is explicitly given to each contributor's invaluable contribution to this thesis.

Contribution of the authors

Manuscript: The impact of insomnia in the persistence of pain-related temporomandibular disorders: a six-month cohort study

Avinash Sarcar, MSc Candidate, McGill University: contributed to recruiting participants, interpretation of the results and writing the manuscript.

Sherif M Elsaraj, Faculty Lecturer, Jewish General Hospital: Contributed to the original concept of the research protocol and participated in clinical examination and patient recruitment.

Zovinar der Khatchadourian, Assistant Professor, Faculty of Dental Medicine and Oral Health Sciences, McGill University: Collaborated by performing clinical examination of patients.

Firoozeh Samim, Assistant Professor, Faculty of Dental Medicine and Oral Health Sciences, McGill University: Collaborated by performing clinical examination of patients and reviewed the manuscript.

Ana Miria Velly, Associate Professor, Faculty of Dental Medicine and Oral Health Sciences, McGill University: Conceived this investigation, designed the study, carried out statical analyses and revised the manuscript.

Chapter 1. Introduction

Temporomandibular Disorders (**TMD**s) represent a spectrum of musculoskeletal and neuromuscular conditions (1, 2), with pain emerging as the predominant concern for patients seeking relief (3, 4). With the prevalence of 5% to 12% among the general population, TMDs stand as the leading cause of chronic orofacial pain, ranking only second to back pain in the realm of chronic musculoskeletal discomfort (5). While most individuals experiencing TMDs may find their symptoms to be mild and self-limiting (2, 6, 7), a significant portion, face a different reality. For these individuals, the pain associated with TMDs persists (8-21), gradually becoming less responsive to treatments (22). This persistence of pain-related temporomandibular (**PTMD**s) poses a considerable challenge to healthcare (23-25) and, more importantly, casts a shadow over the affected individuals' quality of life (26-29).

Studies have demonstrated that persistence of PTMDs are associated with an array of biopsychosocial factors (8, 9, 11-21). Additionally, it has also been noted that sleep disturbances like obstructive sleep apnea have also impacted persistence of PTMD (11).

Insomnia is a sleep-wake disorder that exhibits strong associations with a diverse range of physical and psychological health conditions (30). The relationship between PTMD and insomnia including symptoms of insomnia, have been demonstrated by several studies (11, 31-45). While studies suggest that insomnia symptoms may raise the risk of TMD (45) and that insomnia can also impact the pain intensity in TMD patients (33, 35, 37, 40-42), it is still uncertain whether insomnia increases the likelihood of persistent PTMD, particularly clinical significant PTMD when moderate to severe pain intensity is used as a criterion to measure persistence of PTMD.

This is particularly relevant given the prevalence of insomnia symptoms among TMD patients (31).

Chapter 2. Comprehensive review of literature

2.1 Temporomandibular disorders

TMDs comprise a diverse range of musculoskeletal and neuromuscular conditions of the orofacial region that involves the temporomandibular joint (**TMJ**) complex, the masticatory muscles and skeletal structures (1, 2). Common symptoms observed in patients with TMD included pain in the facial and head regions, limited jaw mobility, the presence of TMJ sounds, and ontological symptoms like otalgia and hyperacuity (46-48). The predominant signs observed in TMDs are tenderness experienced during palpation, clicking sound of TMJ and limitation of jaw opening (47, 48). The severity of TMD symptoms ranges from mild, self-limiting discomfort to severe debilitating dysfunction (2, 6, 7, 49).

2.2 Pain-related temporomandibular disorders

The International Association for Study on Pain (**IASP**) defines pain as an adverse sensory and emotional encounter connected with, or resembling the experience linked to actual or potential damage to bodily tissues (50). Pain is likewise the symptom most commonly reported by patients when seeking treatment (3, 4). Hence for this study the term pain-related temporomandibular disorder (**PTMD**) was used to describe pain pertaining specifically to TMD.

2.3 Diagnostic criteria and classification for temporomandibular disorders

The Research Diagnostic Criteria for Temporomandibular Disorders (**RDC/TMD**) is a standardized dynamic concept developed in 1992 by Dworkin and LeResche (51) based on the biopsychosocial model of pain (51, 52). The primary aim of the RDC/TMD was to create a research diagnostic tool that were valid and reliable for the most common TMDs. RDC/TMD

consisted of a dual axes approach: 1. *Axis I*, which included clinical diagnosis that identified structural dysfunctions in the muscles and joints, and 2. *Axis II* encompassed the evaluation of disability related to pain, pain severity, pain location and other psychological factors like distress that could have an impact on prognosis and management (51).

In 2012, the Diagnostic Criteria for Temporomandibular Disorders (**DC/TMD**), comprehensively developed from the Validation Projects of RDC/TMD (53-58) was drafted with an intent to provide a valid and reliable protocol for immediate application in research as well as clinical settings. Similar to the RDC/TMD, the DC/TMD included *Axis I* and *Axis II* diagnostic criteria. Based on *Axis I*, TMD diagnoses were categorized into four groups: 1. Temporomandibular Joint Diseases, 2. Masticatory Muscles Disorders, 3. Headaches related to TMD, and 4. Associated structures. The validity (sensitivity and specificity > 0.80) and inter-examiner reliability (Kappa ≥ 85) of the DC/TMD were excellent in relation to myalgia, myofascial pain with referral and arthralgia. Among the intracapsular conditions, disc displacement without reduction with limited opening showed good validity (sensitivity and specificity ≥ 0.80) (54).

Classification is a process of systematic categorization of various conditions based on established criteria of etiology, pathophysiology and/or diagnosis. Throughout the years, a variety of systems have been established to classify TMDs.(59) The expanded taxonomy for TMD is an combination of the DC/TMD and the American Association of Orofacial Pain (**AAOP**) taxonomy and included 37 conditions which were categorized into four major disorders namely: 1. Temporomandibular joint disorders, 2. Masticatory muscle disorders, 3. Headache attributed to TMD and 4. Disorders involving associated structures (60).

Furthermore, TMDs were also classified based on the cause and duration of pain. The collaborating group consisting of the Orofacial and Head Pain Special Interest Group (**OFHP SIG**) of the IASP, the International Network for Orofacial Pain and Related Disorders Methodology (**INfORM**), the AAOP, and the International Headache Society (**IHS**) developed the International Classification of Orofacial Pain, 1st edition (**ICOP –1**), to enhance the clinical and research management of orofacial pain. The ICOP adopted a structure incorporating both the diagnostic criteria of DC/TMD and the International Classification of Headache Disorders, 3rd edition (**ICHD – 3**) for classifying PTMDs based on pain characteristics. PTMDs were broadly classified as pain that was muscle-related; termed as myofascial orofacial pain, and pain arising from the joint as TMJ pain. These conditions or disorders were further subcategorized into primary and secondary pain. The term 'secondary' was used when the pain was clearly associated with the effects of other diseases, trauma, or other factors. 'Primary' was favored over the use of idiopathic pain or nociplastic pain as their pathophysiology was related to central pain centres (61). 'Acute' and 'chronic' were used to classify the pain conditions based on the duration of pain. According to the IASP, the pain which tends to recur or persist more than three months were referred to as being chronic (61, 62).

2.4 Epidemiology of pain-related temporomandibular disorders

2.4.1 Prevalence of pain-related temporomandibular disorders

Prevalence refers to the proportion of individuals within a population who exhibit a particular characteristic during a specified time frame. Prevalence may be reported in three ways: 1. When estimated at a specific point in time, point prevalence is reported, 2. Period prevalence refers to the proportion that exhibits the specified characteristic at any point during

a given time interval and 3. Lifetime prevalence indicates the proportion of the population, who have experienced the specified characteristic at some point in life (63).

A cross-sectional study using mailed questionnaires was carried out in a sample population of 1265 individuals aged 18 – 75 years with a response rate of 80.3%. Von Korff *et al*. (64), observed that 6-month period prevalence of self-reported facial pain among the general population in Seattle, United States (**US**) was estimated to be 12%. It was also noted that nearly half of the participants who complained of facial pain experienced recurrent episodes. Results also showed the prevalence was greater among participants aged below 55 years and facial pain were more prevalent among females.

A telephone survey was conducted by Locker *et al*. (65), among the general population in Toronto to estimate the prevalence of TMD symptoms. The participants were identified using a random digit dialing technique and 677 individuals were recruited for the study with a participation rate of 67.7%. The participants were above 18 years of age and the prevalence of PTMD at rest or function was 12.9%. The results also showed that those reporting pain had a greater likelihood of presenting other symptoms of TMD like joint sounds and pain in front of the ears ($P < 0.0001$). Furthermore, females were found to have a two-fold higher likelihood of experiencing ear pain and muscle tenderness on awakening compared to males. Pain in the TMJ were present more among individuals under the age of 44 years but the results were not significant.

Goulet *et al*. (66), carried out a survey to assess the prevalence and pattern of jaw pain among the French-speaking general population of Quebec. The response rate for the telephone

interview was 64% and 897 respondents above 18 years were included in the study. This survey observed that 7% (95% Confidence Interval (**CI**): 5.10 - 8.80) of the sample had frequent self-reported symptoms of jaw pain. The female gender showed a higher prevalence of jaw pain compared to males among all the age groups, and the urban population presented with increased jaw pain symptoms. The results also revealed that increased pain frequency was related to greater pain intensity. A major finding was that if the prevalence was estimated from standpoints of both severity and frequency, at least 5% of the population would have significant jaw pain. More than 20% of the participants who reported jaw pain also reported other symptoms of TMD.

Isong *et al*. (67), used data from the 2002 National Health Interview Survey (**NHIS**) and estimated the difference in the prevalence of self-reported TMD (reported pain) between non-Hispanic white and non-Hispanic black populations in the US. The results also showed age and gender-stratified 3-month period prevalence of PTMD in the two populations. A total of 17,498 females and 13,480 males were included as participants in the study. The overall 3-month period prevalence of PTMD was 4.6% in the general population. It was quite evident from the results that the prevalence of PTMD was twice more in females (6.3%) when compared to males (2.8%). Non-Hispanic white race/ethnicity had a slightly greater prevalence. There were differences in prevalence between genders when age was included in the analysis. The analysis showed that age, gender and race effects were greatly associated with the prevalence of PTMD and the two-way interactions between the variables were quite significant ($P<0.001$).

Janal *et al*. (68), assessed the 6-month period prevalence of facial pain and myofascial TMD excluding tooth ache and sinus pain among 19,586 female participants weighted to mimic

the 2000 census using a telephone survey; the estimated period prevalence of facial pain was 10.1%, and the point prevalence was 5.1%. The period prevalence of myofascial TMD was reduced to 6.0% when pain had to be present for more than 2 weeks and further decreased to 4.4% by excluding headaches. The results also showed am inverse proportionality between facial pain and age as well as income. Hispanic women showed higher prevalence compared to non-Hispanics. The analyses were weighed as there were more chances of selection bias. RDC/TMD was used as the examination tool for diagnosing myofascial TMD and an overall prevalence of 10.5% (95% CI: 8.5% – 13%). Black race (OR_{adj}= 2.18, 95%CI: 1.18—4.03) and age category less than 50 years (OR_{adj}= 0.49, 95%CI: 0.25—0.98) increased the odds of presenting with myofascial TMD. It was also observed that although facial pain screening was a sensitive indicator for myofascial PTMD diagnosis, screening failed to identify half of the true cases.

A cross-sectional study was conducted on a Swedish population(69). The response rate stood at 63%; 3480 females (57%) and 2643 males (43%) aged between 18 and 89 years. The prevalence of self-reported PTMD which occurs once a week or more was estimated as 11% (95% CI: 10.2% - 11.80%). The prevalence was greater among individuals below the age of 50 years, and females showed 1.3 -times (OR: 1.32, 95% CI: 1.07 – 1.64) greater odds of presenting with PTMD compared to males. It was also noted that the prevalence was 10.1% among individuals born in Sweden.

2.4.2 Incidence of pain-related temporomandibular disorders

Incidence refers to the number of new cases or conditions that arises. Incidence in a population can be expressed as a proportion, cumulative incidence or rate, incident density. The

term incident rate refers to the new cases in a specific time divided by total time each person is at risk. Cumulative incidence is the proportion of new cases that occurs in a disease-free population over a specified time period (70).

Slade *et al*. (71), assessed the incidence of PTMD in the US using a multicentre prospective cohort study which had a mean follow-up period of 2.8 years per person. The dropout rate was 16% (n=3,258) and 2,737 participants aged between 18 and 44 years completed at least one follow-up questionnaire. The incidence of TMD was estimated as 3.9% per annum (95% CI: 3.50% - 4.30%) after adjusting for loss to follow-up, and 260 individuals developed first onset TMD. Almost 97.30% of the incident cases complained of painful symptoms and among them almost 75.09 % (n=190) were diagnosed as having myalgia or arthralgia based on the RDC/TMD criteria. After adjusting for demographics and loss to follow-up, it was also estimated from the analysis that participants aged between 24 and 44 years had 40% greater risk of TMD (Hazards Ratio (**HR**) rangers from 1.38 – 1.46) when compared to people between 18 and 23 years. Variations in incidence based on gender was not statistically significant but females appeared to have a higher risk when compared to males (HR= 1.22, 95% CI: 0.94–1.57, P= 0.13).

A three-year longitudinal study (71) involving 1016 participants (dropout rate= 15%) aged between 18 -65 years who did not have PTMD at baseline were followed to estimate first onset PTMD incidence. The results of this cohort study showed that 6.5% of the sample developed first onset PTMD over the three-year period (72). Similar results were obtained from a four-year longitudinal study in Japan which included 672 participants aged above 20 years.

The overall dropout rate for that study was 40% and the four-year cumulative incidence of PTMD was 6.1%.

2.4.3 Factors associated with persistent pain-related temporomandibular disorders

Studies enlisting the association between several factors and persistence of PTMD have been enlisted in Table 1 and the study findings are elaborated in the following sections.

2.4.3.1 Demographic factors

Females have a higher proportion of presenting with persistent PTMD compared to males, and studies have also shown that the likelihood of females experiencing PTMD are more than males (11, 21, 44) (refer Sections 2.4.3.9 ,2.4.3.4, 2.4.3.10.3, respectively for methodology). Age is also observed as a putative factor for persistence of PTMD, and it is noted that the likelihood of persistent pain is more as the age increases (21) (refer Section 2.4.3.3 for methodology).

2.4.3.2 Bruxism and trauma

A nested case-control study within a two-year cohort was conducted by Marklund *et al*. (20), with 280 dental students to investigate the risk factors related to the persistence of TMD. Bruxism, which included grinding and/or clenching was assessed using self-reported questionnaires at baseline visit. The persistence of TMD was defined as having symptoms and signs of TMD at baseline, one-year and two-year follow up examinations and was reported as 12% but was not statistically significant. The persistent TMD cases were matched with the participants who did experience TMD during the entire follow-up period (n=247). Notably, participants who reported experiencing bruxism had significantly higher odds of experiencing

persistent TMD (Odds Ratio $_{crude}$ (**OR_C**)= 2.30, 95% CI: 1.10–4.90). The chances for misclassification of bruxism and absence of multivariate analysis and index date could have been limitations of this study.

2.4.3.3 Variations in dental occlusion

The study designed by Marklund *et al*. (20) (refer Section 2.4.3.2 for methodology), assessed if occlusal factors could have association with persistence of TMD. The results revealed that the presence of deep bite (OR_C= 2.90 95%CI: 1.20–7.80), mandibular instability at the intercuspal position defined by the inability to have a firm occlusal grip (OR_C= 4.70 95%CI: 2.00–11.10) and unilateral contact in retruded contact position (OR_C= 3.10 95%CI: 1.20–7.80) profoundly increased the odds of persistence of TMD. A possible limitation could be that the dentists were not blinded.

2.4.3.4 Fibromyalgia and widespread pain

A prospective cohort study enrolling 572 participants aged between 18 and 65 years with chronic PTMD was conducted by Velly *et al*. (17), to assess if fibromyalgia and widespread pain predicted the onset and persistence of clinically significant chronic PTMD Graded Chronic Pain Scale (**GCPS**) Grades II-IV) at an 18-month follow-up. To conduct this study, chronic PTMD participants were allocated into two cohorts; 262 participants with non-significant pain (GCPS Grade I) to assess the onset of clinically significant chronic PTMD, and 310 participants with clinically significant pain (GCPS Grade II–IV) to evaluate chronic PTMD persistence and progression. The study had a 15% dropout rate (n= 485) and approximately 30% continued to have clinically significant pain (GCPS II—IV) after the 18-month follow-up period. Fibromyalgia

was assessed using the criteria set by the American College of Rheumatology (**ACR**) and widespread pain was self-reported. After adjusting the model for potential confounders, participants with clinically significant PTMD exposed to fibromyalgia had almost 2.5 times greater odds of having persistent or progressive pain (OR_{adj}= 2.48, 95% CI: 1.16 – 5.29, P= 0.02). Furthermore, participants with widespread pain (with or without fibromyalgia) had more than two times odds of developing clinically significant chronic PTMD (OR_{adj}= 2.29, 95% CI: 1.03 - 5.09, P= 0.04) and approximately twice the odds of having persistent clinically significant chronic PTMD (OR_{adj}= 1.73, 95% CI: 1.02 – 2.92, P= 0.04).

A 2-year prospective cohort study involving 397 TMD patients aged between 18 and 74 years were interviewed at 1-year and 2-year follow-up intervals to investigate if widespread pain increased the risk of developing and maintaining dysfunctional TMD pain (GCPS grades II–IV). John *et al*. (19), found that the results were quite similar to the study by Velly *et al*. (17), in showing that widespread pain increased the odds of dysfunctional TMD pain onset by two times (OR_{adj}= 1.90, 95%CI: 1.20 - 2.80, P= 0.003) among the females. No significant associations were found when analyzing the male gender (OR_{adj}= 1.00, 95%CI: 0.40—2.80, P= 0.95).

A four-year population-based prospective cohort study design involving 424 (dropout rate= 79%) participants aged between 18 and 65 years was conducted by Macfarlane *et al*. (21), to identify the factors that contributed to the outcome of orofacial pain. Widespread pain was assessed based on criteria set by the ACR and self reported questionnaires were used to assess pain and other covariates. After four years of follow-up, 54% of the sample reported persistent orofacial pain. Analyses by backward stepwise regression showed that widespread body pain doubled (RR_{adj}= 1.99, 95%CI: 1.41 - 2.81) the risk of orofacial pain persistence.

2.4.3.5 Pain characteristics

The study conducted by Macfarlane *et al*. (21) (refer Section 2.4.3.4 for methodology), also estimated if orofacial pain characteristics at baseline could impact the persistence of pain. From the multivariable analysis, it was observed that presence of pain at baseline (RR_{adj}= 1.33 95%CI: 1.01–1.76), pain duration lasting more than one hour (RR_{adj}= 1.43 95%CI: 1.06–1.92), pain disability defined by time take off work (RR_{adj}= 1.72 95%CI: 1.22–2.43) and use of pain medication and (RR_{adj}= 1.64 95%CI: 1.19–2.28) had a greater likelihood of presenting with persistent orofacial pain . Similar findings were observed from the John *et al*. study (19) (refer Section 2.4.3.4 for methodology), where pain intensity (OR_{adj}= 1.30, 95%CI: 1.10—1.50, P= 0.005) and presence of dysfunctional pain (OR_{adj}= 11.60, 95%CI: 3.70—37.00, P> 0.001) at baseline increased the odds of dysfunctional (GCPS II—IV) TMD among women.

A case-control study nested within a prospective cohort involving 72 persistent TMD cases were analysed from the Orofacial Pain Perspective Evaluation and Risk Assessment (**OPPERA**) study to identify factors that increased the likelihood of persistent PTMD in comparison to 75 transient pain-free controls. After adjusting for age, sex, race and study site, Meloto *et al*. (18), found that characteristic pain intensity (OR_{adj}= 1.50, 95% CI: 1.00--2.20, P= 0.03), increased pain frequency (OR_{adj}= 1.80 95% CI: 1.30–2.60) and extended pain duration in the previous one month (OR_{adj}=- 1.90 95% CI: 1.30–2.80, P= 0.0005) increased the likelihood of PTMD persistence. Furthermore, the dysfunction associated with the pain measured using the GCPS version 2.0 also increased the odds of persistent pain after six months (OR_{adj}= 1.30, 95% CI: 0.90–1.90).

Rammelsberg *et al*. (8), assessed the five-year longitudinal outcome of TMDs defined by RDC/TMD in 235 participants with and without PTMD at baseline. The attrition rate of the study was 36% (total n= 368). This study defined persistent pain as pain being present in all three follow-up periods, whereas recurrent cases were those who had myofascial pain at baseline and had pain during at least one of the follow-ups. It was observed that 110 (66%) of the 165 participants who had myofascial TMD at baseline continued to have persistent and recurrent TMD. The odds of presenting with persistent pain were greater among patients with frequent pain (OR_{adj}=1.79, 95%CI: 1.12–2.87,P= 0.01) and presence of other body (OR_{adj}= 1.81 95%CI: 1.00–3.29, P= 0.05) pain sites when compared with remitted TMD cases.

A prospective 3-month cohort study was conducted by Velly *et al*. (13), to assess the factors that contributed to transition of acute PTMD to chronic state. The study had a drop out rate of about 10% (total n= 121) and chronic PTMD was defined according to the current IASP definition of chronic pain (61). The study outcome as well as the predictors were assessed using the GCPS. Results revealed that Characteristic Pain Intensity (**CPI**) (OR_{adj}= 1.03, 95% CI: 1.01—1.05, P= 0.008), average pain intensity of TMD (OR_{adj}= 5.17, 95%CI: 1.59—16.84), dysfunction assessed by measuring the interference on activities (OR_{adj} ranges from 1.23—1.27, $P \leq 0.003$) and continuous nature of pain at baseline (OR_{adj}= 2.48, 95%CI: 1.04—5.90) increased the likelihood of PTMD transitioning to a chronic state. Similar results were obtained from the prospective studies by Velly *et al*. (11) (β_{adj}= 0.48, 95%CI: 0.32—0.65) (16) and Elsaraj *et al*. (12) (RR_{adj} ranges from 4.02—4.09, $P < 0.0001$) (refer Sections 2.4.3.9, 2.4.3.8, respectively for methodology), where it was concluded that dysfunctional PTMD (GCPS II—IV) increased the persistence of PTMD. Additionally from these studies (11, 12), it was also estimated that the

nature of PTMD at baseline based on the duration (acute versus chronic) also contributed to the persistence of PTMD (RR_{adj} ranges from 1.23—1.45, $P < 0.003$).

Garofalo *et al*. (14), conducted a six-month cohort study to assess the factors that contributed to chronic TMD. The results from this study involving 157 participants revealed that more that 50% (n= 87) of the sample presented with chronic TMD at the end of the study and, increased pain intensity at baseline(CPI > 15) had an impact on TMD chronicity (β= 0.03, P=0.02). Contrastingly, negative association was found between CPI and chronicity of TMD (β= -0.06, P< 0.001) by Epker *et al*. (15), among 204 acute TMD patients.

2.4.3.6 Clinical factors

Meloto *et al*. study (18) (refer Section 2.4.3.5 for methodology), estimated whether clinical variables could have an impact on the persistence of PTMD and a nested case-control study design was utilized. The results revealed that DC/TMD *Axis I* clinical variables like masticatory muscle pain (familiar or not) and TMJ pain (familiar or not) either from mobility or palpation increased the odds of persistent PTMD by 50% when compared to transient PTMD. The OR_{adj} of muscle pain ranged from 1.50–2.50 and that of joint pain were from 1.40–2.00. Headache on palpation (OR_{adj}= 1.50 95% CI: 1.10–2.20, P= 0.016) also revealed similar results. Furthermore, TMJ pain (familiar or not) accompanied by joint sounds almost doubled the odds of developing persistent PTMD (OR_{adj} ranges from 1.80–2.10)). Additional clinical findings like presence of crunching and grating along with any noises, pain during palpation of neck muscles and other body sides also showed statistically significant results in which the odds of developing persistent TMD were increased by at least 50%. It was also estimated that muscle related TMDs

contributed to the persistent state according to studies by Garofalo *et al*. (14) (β= 1.42, P= 0.02) and Epker *et al*. (15) (β= 0.78, P= 0.003) (refer Section 2.4.3.5 for methodology).

Ohrbach *et al*. (9), conducted a five-year longitudinal study which included 134 TMD participants. It was observed that in about 50% of the individuals, the pain was still persistent at five-year follow-up. Findings from this study showed that the changes in psychological and clinical measures were significantly associated with only remitted pain among participants. Changes in clinical and psychological measures were not associated with the change in average pain intensity among the persistent group (P > 0.05, hence they are not included in Table 1).

2.4.3.7 Psychological factors

An 18-month prospective cohort study evaluated whether catastrophizing and depression influenced the progression of pain in PTMD patients by Velly *et al* (16). The study involved an onset cohort (n= 230) and a progression cohort (n=250) of clinically significant pain (GCPS II—IV). Multivariable logistic regression analysis reveled that catastrophizing measured using the Coping Strategies Questionnaire (**CSQ**) contributed to the pain intensity (β= 3.79, 95%CI: 2.09—5.49), disability caused due to pain (β= 0.38, 95%CI: 0.25—0.50), onset of clinically significant pain (OR_{adj}= 1.71, 95%CI: 1.09—2.30) and progression of clinically significant pain (OR_{adj}= 2.16, 95%CI: 1.62—2.87). Additionally, it was also estimated that an increase in depression measured using the Beck's Depression Index (**BDI**) would elevate disability (β= 0.17, 95%CI: 0.03—0.31) caused due to pain. Findings from other studies also showed that psychological factors had a strong association with chronic TMD (17, 21) (refer Section for 2.4.3.4 methodology).

2.4.3.8 Fatigue

The impact of fatigue on the transition and persistence of PTMD was assessed in a prospective cohort study by Elsaraj *et al.* (12), involving 457 PTMD participants. The three-month follow-up period questionnaires were completed by 376 participants. Assessment of fatigue was done using the Fatigue Severity Scale (**FSS**) and pain persistence was measured based on the pain duration and dysfunction (GCPS II—IV). It was observed that fatigue increased the risk of persistent PTMD by 60% (RR_{adj}=1.62 95%CI: 1.13—2.33, P= 0.008) within a three-month follow-up period.

2.4.3.9 Sleep measures

A cohort study involving 456 PTMD participants was conducted by Elsaraj *et al*. (11), to assess if obstructive sleep apnea (**OSA**) influenced the transition and persistence of PTMD. The Epworth Sleepiness Scale (**EPP**) with the cut-off value of five was used to measure the extent of OSA and persistence of pain was defined by the presence of pain more than three months and having dysfunctional pain (GSPS II—IV). Insomnia was also measured, and analyses were performed by both including as well as excluding insomnia as a covariate. The results showed that presence of OSA had a borderline impact (RR_{adj}=1.11 95%CI: 0.99—1.25, P= 0.07) on the transition and persistence of PTMD when pain was defined by duration and OSA increased the risk of persistence by 40% (RR_{adj}= 1.40 95%CI: 1.00—1.97, P= 0.05) when pain was defined by dysfunction. These results were obtained when insomnia were not included in the model.

Table 1. Studies showing association between factors and persistence of pain-related temporomandibular disorders

Authors	Study design	Sample size	Persistence (%)	TMD assessment tool	Factors studied	Factors assessment tool	Results 0R/RR/β (95%CI)
Marlund et al. (20)	Nested case-control study	Cases: 33 Controls: 247	12% (NS)	RDC/TMD	Self-reported bruxism	Self-reported questionnaire	OR_C=2.30 (1.10—4.90)
					Deep bite	Clinical exam	ORc=2.90 (1.20—7.80)
					Mandibular Instability	Clinical exam	OR_c= 4.70 (2.00—11.10)
					Unilateral contact	Clinical exam	OR_c= 3.10 (1.20—7.80)
Velly *et al*. (17)	Cohort study	485 TMD participants	30%	CMI/RDC	Fibromialgia	ACR criteria	OR_{adj}= 2.48 (1.16—5.29)
					Widespread pain	Self-report questionnaire	OR_{adj}=1.73—2.29
					Depression	BDI-II (≥20)	OR_{adj}= 2.48—5.30
John *et al*. (19)	Cohort study	397 TMD participants	20%—40%	-	Widespread pain	Self-reported questionnaire	OR_{adj}= 1.90 (1.20—2.80)
					Average pain intensity	NRS	OR_{adj}= 1.20 (1.10—1.50)

					Dysfunctional pain	GCPS	OR_{adj}= 11.60 (3.70—37.00)
Macfarlane *et al*. (21)	Cohort study	424 orofacial pain participants	54%	Self-reported questionnaire	Age	Self-reported questionnaire (≥54)	RR_{adj}= 1.67 (1.15—2.42)
					Gender (female)	Self-reported questionnaire	RR_{adj}= 1.36 (1.01—1.83)
					Present pain	Self-reported questionnaire	RR_{adj}= 1.33 (1.01—1.76)
					Pain duration	Self-reported questionnaire	RR_{adj}= 1.43 (1.06—1.92)
					Pain disability	Self-reported questionnaire	RR_{adj}= 1.72 (1.22—2.43)
					Widespread body pain	ACR criteria	RR_{adj}= 1.99 (1.41—2.81)
					Psychological factors	GHQ (4—12)	RR_{adj}= 1.87 (1.33—2.64)
Meloto *et al*. (18)	Nested case-control study	72 cases and 75 controls	-	RDC/TMD	CPI score	GCPS 2.0	OR_{adj}= 1.50 (1.00—2.20)
					Pain frequency	RDC/TMD Axis I	OR_{adj}= 1.80 (1.30—2.60)

					Pain duration	RDC/TMD Axis I	OR_{adj}= 1.90 (1.30—2.80)
					Headache	RDC/TMD Axis I	OR_{adj}= 1.50 (1.10—2.20)
					Muscle pain	RDC/TMD Axis I	OR_{adj}= 1.50—2.50
					Joint pain	RDC/TMD Axis I	OR_{adj}= 1.40—2.00
					TMD with joint sounds	RDC/TMD Axis I	OR_{adj}= 1.80—2.10
					Somatization		OR_{adj}= 1.80 (1.20—2.90)
Rammelsberg *et al.* (8)	Cohort study	235 TMD participants	30%	RDC/TMD	Pain frequency	RDC/TMD Axis I	OR_{adj}= 1.79 (1.12—2.87)
					No. Of body pain sites	RDC/TMD Axis I	OR_{adj}= 1.81 (1.00—3.28)
Velly *et al.* (13)	Cohort study	109 acute TMD participants		RDC/TMD	CPI score	GCPS	OR_{adj}= 1.03 (1.01—1.06)
					Average pain intensity	GCPS	OR_{adj}= 5.17 (1.59—16.84)
					Dysfunction	GCPS	OR_{adj}= 1.23—1.27

					Continuous nature of pain	Self-reported questionnaire	OR_{adj}= 2.48 (1.04—5.26)
Garofalo *et al.* (14)	Cohort study	157 acute TMD participants	~ 50%	RDC/TMD	CPI score (≥ 15) Muscle -elated TMD	GCPS RDC/TMD *Axis I*	β= 0.03 β= 1.42
Epker *et al.* (15)	Cohort study	204 acute TMD participants	70%	RDC/TMD	CPI score (≥ 15) Muscle -elated TMD	GCPS RDC/TMD *Axis I*	β= -0.06 β= 0.78
Elsaraj *et al.* (12)	Cohort study	376 TMD participants	69%	DC & RDC/TMD	Fatigue Pain duration Pain dysfunction	FSS (>35) GCPS 2.0 (> 3 months) GCPS 2.0 (IIb—1V)	RR_{adj}= 1.62 (1.13—2.33) RR_{adj}= 1.45 (1.18—1.77) RR_{adj}= 4.03 (2.02—8.02)
Elsaraj *et al.* (11)	Cohort study	378 TMD participants	69%	DC & RDC/TMD	OSA Pain duration Pain dysfunction Gender (female)	ESS (>5) GCPS 2.0(>3 months) GCPS 2.0 (IIb—1V) Self-repot	RR_{adj}= 1.40 (1.00—1.97) RR_{adj}= 1.47 (1.20—1.79) RR_{adj}= 4.21 (2.11—8.36) RRadj= 1.23 (1.01—1.50)
Velly *et al.* (16)	Cohort study	480 TMD participants	32%	CMI/RDC	Catastrophizing	CSQ	OR_{adj}= 1.71—2.16,

	Depression	BDI	β= 0.38– 3.79
	Worst pain intensity	GCPS	β= 0.17 (0.03—0.31)
	Widespread pain	Self-reported questionnaire	OR_{adj}= 1.35 (1.04—1.78)
	Pain intensity	GCPS	OR_{adj}= 1.78 (1.01—3.14)
	Disability	GCPS	β= 0.48 (0.32—0.65)

Note: OR: Odds Ratio, RR: Relative Risk, CI: Confidence Interval, RDC/TMD: Research Diagnostic Criteria/ Temporomandibular Disorders, SCL: Symptom Checklist, ACR= American College of Rheumatology, CMI: Craniomandibular Index, Beck's Depression Index, NRS: Numeric Rating Scale, GCPS: Graded Chronic Pain Scale, GHQ: General Health Questionnaire, CPI: Characteristic Pain Intensity, PHQ: Patient Health Questionnaire, FSS: Fatigue Severity Scale, OSA: Obstructive Sleep Apnea, ESS: Epworth Sleepiness Scale, CSQ: Coping Strategies Questionniare, NS: Non significant.

2.4.3.10 Insomnia as factor for persistence of pain-related temporomandibular disorders

Insomnia is a sleep-wake disorder characterized by self-reported dissatisfaction with sleep quantity and/or quality. Patients suffering from insomnia frequently experience symptoms such as difficulty falling asleep, staying asleep, or heightened arousal, which can manifest either individually or in combination. Importantly, these sleep disturbances persist despite favorable sleeping conditions. Consequently, individuals with insomnia often experience daytime functional impairments, which may include physical symptoms like fatigue and cognitive effects such as negative mood and reduced alertness (73-75).

2.4.3.10.1 Classification of insomnia

Previous classification systems for sleep disorders dichotomized insomnia into primary and secondary types based on pathophysiology. However, this binary categorization faced challenges due to uncertainty regarding the 'nature of associations and direction of causality' in secondary insomnias. In contrast, the most recent International Classification of Sleep Disorders, Third Edition (**ICSD-3**) (76), offers a more comprehensive classification of insomnia. It categorizes insomnia into three main types: 1. Chronic Insomnia Disorder: this term is used when insomnia symptoms persist for at least three months, occurring at a frequency of three times a week, 2. Short-Term Insomnia Disorder: this category applies when symptoms last for less than three months and, 3. Unspecified Insomnia Disorder: insomnia disorders that do not neatly fit into either the chronic or short-term categories are classified as 'unspecified'.

2.4.3.10.2 Epidemiology of insomnia

Insomnia stands out as a significant global public health concern, transcending cultural variations among populations. While the primary manifestation is often difficulty maintaining sleep, mixed challenges in both sleep onset and maintenance prevail more frequently than singular complaints (77-79). The prevalence of insomnia varies widely, ranging from 5% to 50%, depending on the specific definitions applied (80). Notably, when utilizing stringent diagnostic criteria such as those outlined in the Diagnostic and Statistical Manual of Mental Disorders (**DSM**) or ICSD, prevalence rates tend to converge within the range of 6% to 10% (77-79, 81, 82). Incidence rates exhibit substantial diversity across populations, spanning from 2.8% to 30.7% (82-85). These variations can also be attributed to the diverse case definitions employed and the inherent fluctuation in insomnia symptoms. Over a one-year period, the persistence of insomnia symptoms can be as high as 74%. Interestingly, the risk factors and contributors to the persistence of insomnia largely overlap (86). Gender differences play a role, as evidenced by a meta-analysis revealing a 50% increased risk (RR= 1.41, 95%CI: 1.28—1.55) for women compared to men (87). Aging is associated with an increased risk of insomnia, although this correlation may be linked more to age-related health issues than age itself (88). First-degree family members of individuals with insomnia face a higher risk than the general population (83, 89). Insomnia demonstrates strong associations, with OR ranging from 4.00— 6.00, with poor mental and physical health, psychological distress, anxiety, depressive symptoms, somatic complaints, and suboptimal self-rated physical health (78, 81, 85). Additionally, biological vulnerability marked by hyperarousability and heightened hypothalamic–pituitary–adrenal axis

activity have been linked to a higher risk of insomnia (90). Lower socioeconomic status and living alone are further linked to an elevated risk of insomnia.

2.4.3.10.3 The association between insomnia and pain-related temporomandibular disorders

Insomnia is one of the most common sleep-wake disorders presented by patients with PTMD. Several studies have shown the association between insomnia and TMDs, and this section summaries the results from the respective studies which have been also enlisted in Table 2.

Boggero *et al*. (32), conducted a cross-sectional study involving 40 TMD patients and 22 healthy controls to examine the relationship between self-reported and actigraphy sleep disturbance measures, and experimental pain outcomes in TMD patients. Sleep measures were recorded using various self-reported formats, including the Insomnia Severity Index (**ISI**), Pittsburgh Sleep Quality Index (**PSQI**), sleep diaries, PROMIS Sleep-related Impairment (**SRI**), and Sleep Disruption (**SD**). Pain measures were assessed using the Situational Pain Catastrophizing and Experimental Pain Intensity testing, with measurements recorded using the Numeric Rating Scale (**NRS**). The findings from multivariable linear regression indicated that a unit increase in sleep disturbance was associated with an expected increase in pain intensity (β= 0.28 – 0.36, $P<0.05$) and situational pain catastrophizing (β= 0.28 – 0.36, $P<0.05$) among TMD patients.

In a cross-sectional study, Lobbezoo *et al*. (41), sought to examine the relationship between health status, sleep disorders, particularly insomnia, and pain in the trigemino-cervical region. The study involved 36 participants without pain, 12 with craniomandibular pain (**CMP**) –

synonymously used for PTMD, 6 with cervical spine pain (**CSP**), and 49 experiencing both CMP and CSP pain. Insomnia was evaluated using the Sleep Disorder Questionnaire (**SDQ**), while painful trigermino-cervical regions were identified through physical examination, and pain intensity was measured using the Visual Analogue Scale (**VAS**). Simple contrast tests showed that a unit increase in insomnia would show an associated increase in pain intensity by about five units (β= 5.40, P= 0.02) in patients with both CMP and CSP when compared with a unit increase in insomnia among participants without pain. Additional findings were that insomnia increased the pain intensity 13 times (β= 12.89, P=0.01) in CSP patients when compared with CMP patients.

A survey involving 437 media personals was conducted by Ahlberg *et al*. (42), to assess the impact of bruxism and insomnia symptoms on perceived orofacial pain. A standardized questionnaire adapted from the GCPS and, a combination of the DSM-IV and ICSD were used to record the orofacial pain intensity and insomnia symptoms, respectively. The findings of this study indicated that insomnia symptoms were notably prevalent among participants categorized under GCPS Grade II. Furthermore, the application of multivariable logistic regression revealed a significant association. Disrupted sleep was found to increase the probable odds of experiencing severe orofacial pain by a factor of two (OR_{adj}= 2.00, β= 0.67, 95% CI: 1.30—2.90, P < 0.001), whereas other insomnia symptoms did not exhibit a significant impact on orofacial pain status.

Smith *et al*. (31), in a cross-sectional study involving 53 myofascial TMD patients assessed the spectrum of sleep disorders that could be prevalent in TMD patients and estimated if sleep disorders could impact the pain thresholds in TMD patients. The RDC/TMD

was used in recruiting patients for the study. A combination of medical history, structured interviews and polysomnographic (**PSG**) data were used to diagnose insomnia. Laboratory pain thresholds were assessed for pressure pain threshold (**PPTh**) on the masseter and brachioradialis muscle, and heat pain threshold (**HPTh**) on the left ventral forearm. The study revealed that 36% of TMD patients had an insomnia diagnosis. Furthermore, TMD patients with primary insomnia (based on DSM-IV criteria) also exhibited a decrease in pain thresholds. Specifically, in the multivariable regression model analysis a unit increase in insomnia, showed an associated decrease in HPTh ($\beta_{\text{standardized (std.)}}$ = -0.37, P= 0.01) and PPTh ($\beta_{\text{std.}}$= -0.42, P= 0.002 in the masseter, and $\beta_{\text{std.}}$= -0.26, P= 0.03 in the dorsal forearm).

A cross-sectional study by Barjandi *et al*. (43), showed that in a sample of 242 pain patients with TMD, 25-56% of the sample reported with insomnia which was measured using the ISI. It was also observed from the multinomial logistic regression that presence of insomnia decreased the likelihood of myalgia compared to myofascial pain (OR_{adj}= 0.47, 95% CI: 0.23—0.96, P ≤ 0.05).

A cross-lagged panel analysis was carried out by Quartana *et al*. (33), to examine if naturalistic one-month changes in self-reported insomnia symptom severity was associated with the succeeding one-month pain intensity changes in the same sample population mentioned in Smith *et al*. study (31). The sample population was followed for 12 weeks, and the ISI and NRS were used to measure insomnia severity and pain intensity, respectively at a regular two-week interval. The mixed regression analysis was controlled for autocorrelation and synchronous correlation to account for extraneous variance which could be a possible explanation for the association. The findings showed that a unit standard deviation (**SDN**) increase in initial month

insomnia change would show an associated increase in the next month pain intensity change by 0.28 units (β= 0.28, P= 0.01) and additionally, initial month insomnia change contributed to almost 10% (R^2= 0.09) of the next month pain intensity changes. Conversely, the analysis aimed at determining whether initial month changes in pain contributed to the subsequent month's changes in insomnia did not yield statistically significant results (β= 0.14, P= 0.19).

A case-control study, involving 124 myofascial TMD patients and 46 matched healthy controls was conducted by Dubrovsky *et al*. (91), to investigate if PSG sleep measures differed in TMD patients when compared to non-TMD patients. RDC/TMD criteria was used to identify the cases and CPI was used to assess the present, worst and average pain. Variables that were noted from the PSG data included sleep efficiency, number of awakenings, respiratory effort related arousal and sleep onset latency. While the study did not directly establish an association between TMD and insomnia, it did reveal a noteworthy connection. Specifically, it was found that the average pain levels recorded during PSG were associated with a likely decrease in sleep efficiency ($\beta_{std.}$= -0.41, P= 0.01) and an increase in the number of awakenings during the night ($\beta_{std.}$= 0.30, P= 0.04).

A cross-sectional study involving 214 TMD patients was designed by Buenaver *et al*. (39) to assess if catastrophizing indirectly impacted pain severity in TMD patients mediated by sleep disturbances. Most of the symptoms related to insomnia were assessed using the PSQI while pain severity and catastrophizing were measured using Brief Pain Inventory (**BPI**) and Pain Catastrophizing Scale (PCS), respectively. Path analysis was conducted and the results revealed that a unit increase in both PCS (path coefficient= 0.05) and global sleep disturbance (path coefficient= 0.12) was associated with an increase in pain severity. Furthermore, there was an

indirect path association between pain catastrophizing and pain severity in TMD patients and sleep disturbance mediated this path (path coefficient= 0.02, 95%CI: 0.01—0.03).

Similar to Buenaver *et al*. (39), Lerman *et al*. (34), analysed the baseline data obtained from a randomized clinical trial and designed a cross-sectional study to estimate if catastrophizing and insomnia mediated the association between ethnicity and pain severity in TMD patients. The study involved 156 female *TMD* patients and pain severity was assessed using the BPI and ISI was used to measure insomnia. Observations from the path analysis found that the pain severity was likely impacted by insomnia (path coefficient= 0.12 – 0.17) ,catastrophizing (path coefficient= -0.18 – 0.13) as well as ethnicity (path coefficient= -0.92 – -0.64), independently. Results from this study also showed that catastrophizing and insomnia mediated the contribution of ethnicity on TMD pain severity in a sequential manner (path coefficient= -0.04, 95% CI: -0.14 – -0.01).

A cross-sectional study was designed by Lerman *et al.* (35), using the baseline data of a randomized clinical trial involving 128 female TMD patients. A multivariable linear regression analysis was carried out to examine if insomnia with objective short sleep duration (**ISSD**) had an impact on clinical and laboratory pain measures, and interleukin-6 (**IL-6**) levels in TMD patients. Qualitative Sensory Testing, self-reported questionnaire and ELISA were performed to measure the pain outcomes, and PSG, actigraphy and ISI were used to access the insomnia. The analysis revealed that there was an associated increase in general pain sensitivity (β= 0.23, 95%CI: 0.00—0.46, P=0.049), central sensitisation index (β= 0.24, 95%CI: 0.01—0.48, P= 0.045) and baseline IL-6 levels (β= 0.27, 95%CI: 0.06—0.47, P= 0.011) for every unit increase in ISSD. Additionally, it was also estimated that ISSD was associated with an increase in the pain severity

(β= 1.14, 95%CI: 0.48—1.80, P= 0.001) and functional limitation of the jaw (β= 24.29, 95%CI: 11.59—36.99, P<0.001) among TMD patients.

Mun *et al*. (36), conducted a cohort study involving 144 female TMD patients who completed the Interactive Voice Response Assessment (**IVR**) and were part of a clinical trial. Path analysis was executed to assess if pain expectancy, positive and negative affect mediated the underlying link between previous night sleep disturbances and next day pain severity. Insomnia symptoms were assessed using actigraphy and the findings showed that pain expectancy (path coefficient= -0.0001, 95%CI: -0.0004—-0.00003) and positive affect (path coefficient= -0.002, 95%CI: -0.0005—-0.000001) mediated the negative impact of previous night total sleep time in insomnia with next day pain severity. These results were obtained when estimating the link between previous day wake after sleep onset and next day pain severity.

Reid *et al*. (37), conducted a cohort study based on the data obtained from a clinical trial. The study included 111 TMD female participants with insomnia to evaluate if nocturnal delta power was associated with nocturnal and daytime pain intensity reports and pain catastrophizing. PSG was used to estimate the sleep delta power values while data collected from pain diary were used to record pain measures. Findings from multivariable linear regression showed that a unit increase in relative delta power throughout the night was associated with a decreased nocturnal pain by 20 units (β = -20.28, 95%CI: -37.94—2.61 P = .03). Specifically, relative delta power during the first part of the night had a greater association with nocturnal pain (β = -17.81, 95%CI: -32.60—-3.01, P = 0.02), next-day pain (β = -13.88, 95%CI: -27.07—-0.68, P = .04,), and next-morning pain (β = -15.75, 95%CI: -29.18—-2,32, P = .02). Relative delta power during the final third of the night was linked to an associated decrease in nocturnal

pain (β = -17.60, 95%CI: -33.34—1.87, P = .03) and next-morning pain (β = -14.94, 95%CI: -29.37—0.51, P =0.04). Delta power did not exhibit a significant association with either nocturnal or daytime pain catastrophizing among TMD patients.

Sanders *et al*. (44), conducted a case-control study on 182 chronic TMD cases and 1534 healthy controls who were embedded within the OPPERA baseline. The Pittsburgh Sleep Quality Index (**PSQI**) was used to assess obstructive sleep apnea (**OSA**) and estimate its association with chronic TMD. It was found from the multivariable logistic regression that the chronic TMD patients had more than double the odds of presenting with OSA (OR_{adj}= 2.98, 95%CI: 1.77—5.00) and bad sleep quality (OR_{adj}= 4.46, 95%CI: 2.75—7.24). Crude Cox regression analysis from the OPPERA prospective cohort involving 2604 participants revealed that fairly bad and very bad sleep quality could double the probability of developing first-onset TMD (HR= 2.11, 95%CI: 1.49 – 3.00).

Mercante *et al*. (38), conducted a cross-sectional study involving 131 TMD patients to analyse if insomnia impacted central sensitization. To measure the symptoms of central sensitization, Central Sensitization Inventory (**CSI**), conditioned pain modulation (**CPM**) and PPTh was tested whereas the DSM criteria and ISI were used to assess insomnia. The results from Spearman test revealed that total sleep time (ρ= -0.27, P= 0.04) and sleep efficiency (ρ= -0.41, P<0.001) which are usually reduced in insomnia had a negative relationship with the CSI score. Additionally, sleep latency (ρ= 0.25, P= 0.05) was positively correlated with CSI scores.

A three-month prospective cohort study was conducted by Elsaraj *et al*. (11), to assess the contribution of insomnia in the transition and persistence of PTMD. The RDC/TMD and

DC/TMD criteria were used to identify 456 PTMD participants and the GCPS scale were used to measure the pain-related measures. Insomnia was recorded using the ISI and the three-month follow-up period was completed by 378 participants. Crude logistic regression showed that presence of insomnia increased the likely risk of transition and persistence of PTMD by at least 43% (RR_{crude}= 1.43, 95%CI: 1.02—2.03, P=0.04) but when other covariates like OSA, age, pain intensity, pain status and psychological factors were controlled in the analysis, the magnitude of risk diminished (RR_{adj}= 1.00, 95%CI: 0.70—1.43, P=0.99).

Table 2. Studies enlisting the association between insomnia and pain-related temporomandibular disorders

Authors	Study Design	Sample Size	Insomnia variable assessed	TMD variable assessed	Results: β/RR/ ρ /HR(95%CI/P value)
Boggero *et al.*(32)	Cross-sectional study	62 (40 TMD patients + 20 controls)	Sleep measures	Pain intensity, Situational Pain Catastrophizing	(β= 0.28 – 0.36, P<0.05) (β= 0.28 – 0.36, P<0.05)
Lobbezoo *et al.* (41)	Cross-sectional study	103 pain patients	Insomnia (SDQ)	Pain intensity	β= 5.40 (0.02) (CMP + CSP) β= 12.89 (0.01) (CSP compared with CSP)
Ahlberg *et al*. (42)	Cross-sectional study	437	Disrupted sleep symptom of insomnia (DSM-IV)	Orofacial pain severity (GCPS)	OR_{adj}= 2.00 (1.30—2.90)
Smith *et al. (*31)	Cross-sectional study	53 myofascial TMD patients	Primary insomnia	Pain sensitivity (QST) HPTh PPTh	β_{std}= -0.37 (0.01) β_{std}= -0.26—-0.42 (≤ 0.03)
Quartana *et al.* (33)	Cohort study	53 TMD patients	Change in insomnia severity (ISI)	Change in pain intensity (NRS)	β = 0.28 (0.01)
Dubrovsky *et al.* (40)	Case-control study	124 female, myofacial TMD cases and 46 controls	Sleep efficiency (PSG) No. of awakenings (PSG) Sleep onset latency	Average pain levels (CPI) during PSG Current pain (pre-PSG)	β_{std}= -0.41(0.01) β_{std}= 0.30 (0.04) β_{std}= -0.29 (0.04)

Buenaver *et al.* (39)	Baseline data from pooled studies (cross-sectional)	214 TMD patients	Sleep disturbance (PSQI)	Pain severity	Path coefficient = 0.12
Lerman *et al.* (34)	Data from clinical trial (cross-sectional study)	156 female TMD patients	Insomnia (ISI)	Clinical pain severity	Path coefficient = 0.12–0.17 (0.07—0.23)
Lerman *et al.* (35)	Data from clinical trial (cross-sectional study)	128 female TMD patients with insomnia (ISI ≥ 8)	Insomnia with objective short sleep duration	Pain sensitivity (QST) Central sensitization index (QST) Base IL-6 (ELISA) Pain severity (NRS) Functional jaw limitation (Self-report)	β= 0.23 (0.00—0.46) β= 0.24 (0.01—0.48) β= 0.27 (0.06—0.47) β= 1.14 (0.48—1.80) β= 24.29 (11.59—36.99)
Mun *et al.* (36)	Data from clinical trial (cohort study)	144 female TMD patients with insomnia (ISI ≥ 8)	Total sleep time (Actigraphy)	Pain severity (NSR + IVR)	Path coefficient (total sleep time, pain expectancy and pain severity) = -0.0001 (-0.0004— -0.00003) Path coefficient (total sleep time, positive affect and pain severity) = -0.002 (-0.0005— -0.000001)
Reid *et al.* (37)	Data from clinical trial (cohort study)	111 female TMD patients with insomnia (ISI ≥ 8)	Delta power of sleep (PSG)	Nocturnal pain (NRS) Next day pain (NRS)	β= -20.28 (-37.94-- -2.61) β= -13.88 (-27.07—-0,68) β= -15.75—- 14.94

				Next morning pain (NRS)	
Mercante *et al.* (38)	Cross-sectional study	131 TMD patients	Total sleep time (PSG)	Central sensitization (QST)	ρ= -0.27 (0.04)
			Sleep efficiency		ρ= -0.41 (<0.001)
			Sleep latency		ρ= 0.25 (0.05)
Elsaraj *et al.* (11)	Cohort study	378 TMD participants	Insomnia severity (ISI ≥ 15)	Transition and persistence of pain	RRc= 1.43 (1.02—2.03)
Barjandi *et al.* (43)	Cross-sectional	242 TMD participants with	Sleep disturbances (ISI ≥ 15)	Type of pain: Myalgia	OR_{adj}=0.47 (0.23—0.96)
Sanders et al. (44)	Case-control study	182 chronic TMD cases and 1534 controls	Subjective sleep quality	Chronic TMD	OR_{adj}= 4.46 (2.75—7.24)
	Cohort study	2,604		First-onset TMD	HR= 2.11 (1.49 – 3.00)

Note: RR: Relative Risk, HR: Hazard Ratio ISI: Insomnia Severity Index, PSQI: Pittsburgh Sleep Quality Index, SRI: Sleep Related Impairment, SD: Sleep Disruption, SDQ: Sleep Disturbance Questionnaire, DSM: Diagnostic and Statistical Manual of Sleep Disorders, GCPS: Graded Chronic Pain Scale, QST: Qualitative Sensory Testing, ELISA: Enzyme Linked Immunosorbent Assay, IL: Interleukin, NRS: Numerical Rating Scale, IVR: Interactive Voice Response, PSG: Polysomnography.

Chapter 3. Study objectives and hypotheses

Building on insights derived from the preceding literature review, multiple studies have highlighted a significant association between symptoms of insomnia and specific pain characteristics of TMD. Notably, Elsaraj *et al*. (11), conducted the sole investigation into the role of insomnia in the persistence of PTMD over a three-month follow-up period. The current prospective cohort study is a part of the Acute to Chronic Transition (**ACTION**) program (92) which aims to extend the existing body of literature on factors associated with the persistence of PTMD. This study, with a particular emphasis on repeated measurements of pain intensity at different time points, seeks to evaluate the contribution of insomnia in the persistence of clinically significant PTMD.

3.1 Primary aims and hypotheses

Aim 1

To estimate the contribution of insomnia in the likelihood of persistent clinically significant PTMD within six-month follow-up period.

Null Hypothesis

Insomnia did not contribute to the likelihood of persistent clinically significant PTMD within the six-month follow-up period.

Aim 2

To determine if insomnia impacted the persistence of clinically significant PTMD in a dose-response manner.

Null hypothesis

Insomnia did not impact the persistence of clinically significant PTMD in dose-response manner.

Chapter 4. Methodology

4.1 Study design

To fulfill the objectives of this study, a multicentre clinic-based prospective design, tracking a cohort of PTMD participants enrolled in the ACTION (92) project over a six-month period was implemented. Data were systematically collected during three distinct visits: the baseline visit, the 3-month follow-up, and the six-month follow-up. Repeated measurements of presence of clinically significant PTMD were assessed at baseline, three and six-month follow-up periods to account for the time-dependent variations in the outcome within the six-month period. The decision to gather data at these specific intervals align with the current and past definitions of chronic pain given by the IASP (61, 93).

The ethical clearance for the ACTION project was secured from the McGill Institutional Review Board in Montreal, Canada (approval number: A12-M113-14A), as well as the Dental Specialists Group in Ottawa, Ontario (approval number: 240-400).

4.2 Study population

Participants were enlisted for the ACTION (92) project within the period spanning from August 2015 to December 2022, drawn from four distinct clinical sites in Montreal and Ottawa**:** the Jewish General Hospital General Dental Clinic, the Faculty of Dental Medicine and Oral Health Sciences Oral Diagnosis and Pain Clinic, Montreal General Hospital Orofacial Pain Clinic, and the Ottawa Docs Dental Group TMD-specialized clinic.

To meet the inclusion criteria, subjects were required to fall within the age range of 16 to 85 years and be diagnosed with PTMD (muscle and/or joint) in accordance with the DC/TMD

(54) or RDC/TMD (51) criteria administered by trained dentists. However, individuals with PTMD were excluded from the study if they presented with additional orofacial pain conditions such as dental pain or cancer pain as these conditions could mimic PTMD and lead to misclassification. Patients were also excluded if they lacked access to a telephone. Informed consent was obtained from all PTMD patients willing to participate in the study.

4.3 Pain-related temporomandibular disorder diagnosis

The diagnosis of PTMDs was established through clinical examination, adhering to the *Axis I* criteria of the DC/TMD or RDC/TMD (51, 54). These diagnostic tools, documented to demonstrate excellent validity (sensitivity and specificity > 0.80) and inter-examiner reliability (Kappa ≥ 85) employ a combination of medical histories and clinical examinations (51, 54). Clinical diagnoses were affirmed by trained dentists, each specific to one of the four clinical sites and majority of participants completed their baseline data collection at these specified clinical sites. Repeated measures of clinically significant PTMD were gathered at three-month and six-month follow-up visits through telephone communication.

4.4 Clinically significant pain-related temporomandibular disorders

Clinically significant PTMD in the participants assessed at baseline and within the six-month follow-up period was defined based on the CPI. Obtained from the GCPS (94) , the CPI takes into account Likert (NRS 1—10) questions pertaining to the current pain intensity, worst pain intensity and average pain intensity over the prior 30-day reference period. CPI is calculated by estimating the mean of pain intensity scores (NRS: 0 –10, 0= no pain, 10= severe pain) and multiplying it by 10. The CPI boasts excellent internal consistency (Cronbach's alpha=

0.87) and relative validity (95). Clinically significant PTMD was defined by the presence of moderate to severe pain intensity below which disability is very unlikely and was denoted by CPI score ≥ 50 (96). The reliability of the CPI to dichotomise PTMD based on clinical significance was about 80% (96).

4.5 Assessment of insomnia

Insomnia at baseline was assessed using the ISI, a self-report questionnaire consisting of seven items. This instrument gauges the nature, severity, and impact of insomnia by evaluating sleep onset, sleep maintenance, early morning awakenings, dissatisfaction with sleep, interference of sleep difficulties with daytime functions, noticeable impairments due to sleep problems, and the level of distress attributed to sleep disturbance. Each question was rated on a five-point Likert scale (0 = no problem, 4 = very severe problem), resulting in a score range between 0 and 28, where the scoring pattern is as follows: 1. 0—7: no clinically significant insomnia, 2. 8—14: subthreshold insomnia, 3. 15—21: moderate clinical insomnia, and 4. 22—28: severe clinical insomnia (97). To categorize insomnia, a dichotomous approach was applied based on the ISI cut-off value of 10, which demonstrated good validity (sensitivity and specificity > 85%) in identifying insomnia cases. Insomnia was thus categorized as either absent (< 10) or present (≥ 10) (98).

4.6 Assessment of potential confounders and effect modifiers

A distortion of the true relationship between the exposure and outcome of the study by the mixed effects of other factors is referred to as confounding. The confounder should be independently associated with the exposure as well the study outcome and should be

controlled (99). Effect modification determines whether the association between the exposure and outcome varies according to the level of a third variable (63). The potential confounders and effect modifiers that were considered for this study were age, sex, acute (≤ 3 months) and chronic (> 3 months) pain status and psychological factors (anxiety and/or depression) at baseline.

Self-reported assessment of age, sex and pain status were recorded and the current IASP definition of chronic pain was employed to distinguish between acute and chronic pain (61). Psychological factors, which included depression and anxiety was evaluated using a brief self-report Patient Health Questionnaire-4 (**PHQ-4**). The PHQ-4 is a screening tool with scores ranging from 0–12 and combines the General Anxiety Disorder Screen (**GAD-2**) and Patient Health Questionnaire-2 (**PHQ-2**) (100). This instrument had good internal consistency (Cronbach's α= 0.80), and the validity (sensitivity and specificity ≥ 82) was maximum for screening either anxiety or depression at a cut-off score of 3 (< 3 no anxiety/ depression, ≥ presence of anxiety/ depression) (101).

4.7 Study outcome

The primary study outcome is the persistence of clinically significant PTMD defined by the presence of moderate to severe pain intensity (CPI ≥ 50) within the six-month follow-up period.

4.8 Assessment of persistent clinically significant pain-related temporomandibular disorders

In this study, persistent clinically significant PTMD was characterized by the presence of clinically significant PTMD among the participants over the six-month period. Repeated

measures of clinically significant PTMD were gathered at three-month and six-month follow-up visits through telephone communication. This was done to consider the time-dependent variations in PTMD as well as accounting for the definitions of chronic pain (61, 95).

4.9 Statistical Analyses

Chi-squared and student t-tests were utilized to evaluate the statistical disparities between participants exhibiting persistent clinically significant PTMD and those with non clinically significant PTMD relative to their age, sex, psychological factors, acute and chronic pain status, and insomnia.

Given the absence of previous literature examining the frequencies of expected outcomes among individuals with and without insomnia, we postulated that 20% of those not afflicted by insomnia would display persistent clinically significant PTMD. Sample size determination was conducted using G*Power software, with the assumption that the presence of insomnia would double the odds of the expected outcome. Considering these parameters and accounting for an anticipated dropout rate of 20%, the initial sample size was estimated to be 417 participants to effectively reject the null hypothesis. The type I error and power associated with this estimation were set at 0.05 and 0.80, respectively. A variety of unadjusted and adjusted analytical approaches were employed to explore the impact of baseline insomnia on the persistence of clinically significant PTMD among participants over the six-month follow-up period. These analyses were conducted using SAS software (version 9.4).

Primary Analyses

To estimate the cumulative impact of baseline insomnia on achieving persistence of clinically significant PTMD (CPI ≥ 50) among participants and to evaluate dose-response association within six months of follow-up period, the OR as well as the 95% confidence intervals (**95%CI**) were estimated using univariate and multivariate logistic regression models. The Generalised Estimating Equation (**GEE**) model was incorporated into the regression analyses to account for the repeated clinically significant PTMD measures over the six-month period including the baseline (102). The multivariable logistic regression model included all the potential confounders and effect modifiers, and the likelihood ratio test was used to assess the significance of OR obtained for each model. In addition, the visit at which clinically significant PTMD are assessed were also included in the multivariable model. The change-of-estimate criterion was also employed to determine the statistical significance of potential confounding, and a change exceeding 10% between the adjusted and unadjusted effects were considered significant (16).

4.9.1 Secondary analyses

The multivariable model used to estimate the contribution of insomnia in the persistence of clinically significant PTMD with six-month period were stratified relative to other significant baseline co-variates to assess for effect modification. Additionally, interaction between insomnia and other co-variates were also performed to assess effect modification without compromising on power of the study. The secondary analyses also aimed at estimating the correlations (r) between persistence of clinically significant PTMD and individual symptoms of insomnia which were assessed using the ISI. Furthermore, analysis was done to explore

which measure of CPI, i.e., current pain intensity, average pain intensity or worst pain intensity used to define persistent clinically significant PTMD had associations with insomnia.

Chapter 5. Manuscript

The impact of insomnia in the persistence of pain-related temporomandibular disorders: a six-month cohort study

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5.1 Abstract

Though most pain-related temporomandibular disorders (**PTMD**s) are mild and self-limiting, approximately one-third of patients experience persistent pain, presenting a significant challenge in terms of management and often resulting in substantial disability. Individuals with PTMD commonly exhibit sleep-related comorbidities, with insomnia being a prevalent concern. This article assesses the contribution of insomnia in the persistence of clinically significant PTMD defined by moderate to severe pain intensity within six-month follow-up period. Participants diagnosed with PTMD were recruited from four different clinical sites. Persistence of clinically significant PTMD was defined by pain intensity measured using Characteristic Pain Intensity (**CPI**) scores within six-month follow-up period and insomnia was assessed using Insomnia Severity Index (**ISI**). Out of the 456 PTMD participants, 447 answered the baseline questionnaires, 377 (84.3%) and 370 (82.8%) completed the three-month and six-month follow-up periods, respectively. Insomnia increased the likelihood of persistent clinically significant PTMD (CPI ≥ 50) in both the crude (OR_c= 1.63, 95%CI: 1.24—2.15, P= 0.0005) and multivariable (OR_{adj}= 1.60, 95%CI: 1.10 - 2.31, P= 0.01) analyses, within six-month follow-up among the participants. Additional analysis showed that mild insomnia (OR_{adj}= 1.42, 95%CI: 0.94—2.12, P= 0.09), moderate insomnia (OR_{adj}= 1.95, 95%CI: 1.23—3.08, P= 0.004) and severe insomnia (OR_{adj}= 2.43, 95%CI: 1.37—4.31, P= 0.002) contributed to the persistence of clinically significant PTMD in a dose-response manner. These results indicate that insomnia is related to the persistence of PTMD within six months of follow-up period, and therefore should be considered as an important factor when evaluating and developing treatment plans for patients with PTMD.

Keywords: pain-related temporomandibular disorders, clinically significant pain-related temporomandibular disorders, insomnia, persistence, factors.

5.2 Introduction

Temporomandibular Disorders (**TMD**s) represent a spectrum of musculoskeletal and neuromuscular conditions (1, 2), with pain emerging as the predominant concern for patients seeking relief (3, 4). With the prevalence of 5% to 12% among the general population, TMDs stand as the leading cause of chronic oro-facial pain, ranking only second to back pain in the realm of chronic musculoskeletal discomfort (5). While most individuals experiencing TMDs may find their symptoms to be mild and self-limiting (2, 6, 7), a significant portion, faces a different reality. For these individuals, the pain associated with TMDs persists (8-21), gradually becoming less responsive to treatments (22). This persistence of pain-related temporomandibular (**PTMD**s) poses a considerable challenge to healthcare (23-25) and, more importantly, casts a shadow over the affected individuals' quality of life (26-29).

Studies have demonstrated that persistence of PTMDs are associated with an array of biopsychosocial factors (8, 9, 11-21). Additionally, it has also been noted that sleep disturbances like obstructive sleep apnea (**OSA**) have also impacted persistence of PTMD (11).

Insomnia is a sleep-wake disorder that exhibits strong associations with a diverse range of physical and psychological health conditions (30). The relationship between PTMD and insomnia, including symptoms of insomnia has been demonstrated by several studies (11, 31-45). While studies suggest that insomnia symptoms may raise the risk of TMD (45) and that insomnia can also impact the pain intensity in TMD patients (33, 35, 37, 40-42), it is still

uncertain whether insomnia increases the likelihood of persistent PTMD, particularly clinical significant PTMD when moderate to severe pain intensity is used as a criterion to measure persistence of PTMD. This is particularly relevant given the prevalence of insomnia symptoms among TMD patients (31). We hypothesized that, insomnia would increase the likelihood of persistent clinically significant PTMD and also, this impact would show a dose-response relationship. The primary aims of this article were to estimate the impact of insomnia on the likelihood of persistent clinically significant PTMD and also estimate dose-response relationship between insomnia and persistent clinically significant PTMD within six-month follow-up period when moderate to severe pain intensity was used as a criterion to define clinically significant pain and repeated measurements of pain were assessed. The secondary aims included (i) identification of co-variates that could modify the effect of insomnia on the persistence of clinically significant PTMD, (ii) explore the correlation between specific insomnia symptoms and persistence of clinically significant PTMD, and (iii) to determine the impact of insomnia on the individual pain intensity components (based on CPI) of persistent PTMD.

5.3 Methods

5.3.1 Study design

To fulfill the objectives of this study, a multicentre clinic-based prospective design, tracking a cohort of PTMD participants enrolled in the Acute to Chronic Transition (**ACTION**) (46) project over a six-month period was implemented. Data were systematically collected during three distinct visits: the baseline visit, the 3-month follow-up, and the six-month follow-up. Repeated measurements of presence of clinically significant PTMD were assessed at baseline, three and six-month follow-up periods to account for the time-dependent variations in the

outcome within the six-month period. The decision to gather data at these specific intervals align with the current and past definitions of chronic pain given by the International Association for the Study of Pain (**IASP**) (47, 48).

The ethical clearance for the ACTION project was secured from the McGill Institutional Review Board in Montreal, Canada (approval number: A12-M113-14A), as well as the Dental Specialists Group in Ottawa, Ontario (approval number: 240-400).

5.3.2 Study population

Participants were enrolled for the ACTION (46) project within the period spanning from August 2015 to December 2022, drawn from four distinct clinical sites in Montreal and Ottawa: the Jewish General Hospital General Dental Clinic, the Faculty of Dental Medicine and Oral Health Sciences Oral Diagnosis and Pain Clinic, Montreal General Hospital Orofacial Pain Clinic, and the Ottawa Docs Dental Group TMD-specialized clinic.

To meet the inclusion criteria, subjects were required to fall within the age range of 16 to 85 years and be diagnosed with PTMD (muscle and/or joint) in accordance with the Diagnostic Criteria (**DC/TMD**) (49) or Research Diagnostic Criteria for Temporomandibular Disorders (**RDC/TMD**) (50). However, individuals with PTMD were excluded from the study if they presented with additional orofacial pain conditions such as dental pain or cancer pain as these conditions could mimic PTMD and lead to misclassification. Patients were also excluded if they lacked access to a telephone. Informed consent was obtained from all PTMD patients willing to participate in the study.

5.3.3 Pain-related temporomandibular diagnosis

The diagnosis of PTMDs was established through clinical examination, adhering to the *Axis I* criteria of the DC/TMD or RDC/TMD (49, 50). These diagnostic tools, documented to demonstrate excellent validity (sensitivity and specificity > 0.80) and inter-examiner reliability (Kappa ≥ 85) employ a combination of medical histories and clinical examinations (49, 50). Clinical diagnoses were affirmed by trained dentists, each specific to one of the four clinical sites and majority of participants completed their baseline data collection at these specified clinical sites. Repeated measures of clinically significant PTMD were gathered at three-month and six-month follow-up visits through telephone communication.

5.3.4 Clinically significant pain-related temporomandibular disorders

Clinically significant PTMD in the participants assessed at baseline and within the six-month follow-up period was defined based on the Characteristic Pain Intensity (**CPI**). Obtained from the Graded Chronic Pain Scale (**GCPS**) (51), the CPI takes into account Likert (Numerical Rating Scale (**NRS**) 1—10) questions pertaining to the current pain intensity, worst pain intensity and average pain intensity over the prior 30 days reference period. CPI is calculated by estimating the mean of pain intensity scores (NRS: 0–10, 0= no pain, 10= severe pain) and multiplying it by 10. The CPI boasts excellent internal consistency (Cronbach's alpha= 0.87) and relative validity (52) in determining pain. Clinically significant PTMD was defined by the presence of moderate to severe pain intensity below which disability is very unlikely and was denoted by CPI score ≥ 50 (53). The reliability of the CPI to dichotomise PTMD based on clinical significance was about 80% (51).

5.3.5 Assessment of insomnia

Insomnia at baseline was assessed using the Insomnia Severity Index (**ISI**), a self-report questionnaire consisting of seven items. This instrument gauges the nature, severity, and impact of insomnia by evaluating sleep onset, sleep maintenance, early morning awakenings, dissatisfaction with sleep, interference of sleep difficulties with daytime functions, noticeable impairments due to sleep problems, and the level of distress attributed to sleep disturbance. Each question was rated on a five-point Likert scale (0 = no problem – 4 = very severe problem), resulting in a score range between 0 and 28, where the scoring pattern is as follows: 1. 0—7: no clinically significant insomnia, 2. 8—14: subthreshold insomnia, 3. 15—21: moderate clinical insomnia, and 4. 22—28: severe clinical insomnia (54). To categorize insomnia, a dichotomous approach was applied based on the ISI cut-off value of 10, which demonstrated good validity (sensitivity and specificity > 85%) in identifying insomnia cases. Insomnia was thus categorized as either absent (ISI < 10) or present (ISI ≥ 10) (55).

5.3.6 Assessment of potential confounders and effect modifiers

The potential confounders and effect modifiers that were considered for this study were age, sex, acute (≤ 3 months) and chronic (> 3 months) pain status and psychological factors (anxiety and/or depression) at baseline. Self-reported assessment of age, sex and pain status were recorded and the current IASP definition of chronic pain was used to differentiate acute and chronic pain status (47). Psychological factors, which included depression and/or anxiety was evaluated using a validated (sensitivity and specificity ≥ 82) brief self-report Patient Health Questionnaire-4 (**PHQ-4**) with a cut-off score of 3 (< 3 'no anxiety/ depression', ≥ 3 meant 'presence of anxiety and/or depression') (56, 57).

5.3.7 Study outcome

The primary study outcome is the persistence of clinically significant PTMD defined by the presence of moderate to severe pain intensity (CPI ≥ 50) within the six-month follow-up period.

5.3.8 Assessment of persistent clinically significant pain-related temporomandibular disorder

In this study, persistent clinically significant PTMD was defined by the presence of clinically significant PTMD among the participants within the six-month period. Repeated measures of clinically significant PTMD were gathered at three-month and six-month follow-up visits through telephone communication. This was done to consider the time-dependent variations in PTMD as well as accounting for the definitions of chronic pain (47, 48).

5.3.9 Statistical Analyses

Chi-squared and student t-tests were utilized to evaluate the statistical disparities between participants exhibiting persistent clinically significant PTMD and those with non clinically significant PTMD relative to their age, sex, psychological factors, acute and chronic pain status, and insomnia.

Given the absence of previous literature examining the frequencies of expected outcomes among individuals with and without insomnia, we postulated that 20% of those not afflicted by insomnia would display persistent clinically significant PTMD. Sample size determination was conducted using G*Power software, with the assumption that the presence of insomnia would double the odds of the expected outcome. Considering these parameters and accounting for an anticipated dropout rate of 20%, the initial sample size was estimated to

be 417 participants to effectively reject the null hypothesis. The type I error and power associated with this estimation were set at 0.05 and 0.80, respectively. A variety of unadjusted and adjusted analytical approaches were employed to explore the impact of baseline insomnia on the persistence of clinically significant PTMD among participants over the six-month follow-up period. These analyses were conducted using SAS software (version 9.4).

5.3.9.1 Primary analyses

To estimate the cumulative impact of baseline insomnia on achieving persistence of clinically significant PTMD among participants (CPI ≥ 50) and to evaluate dose-response association within six months of follow-up period, the OR as well as the 95% confidence intervals (**95%CI**) were estimated using univariate and multivariate logistic regression models. The Generalised Estimating Equation (**GEE**) model was incorporated into the regression analyses to account for the repeated clinically significant PTMD measures over the six-month period including the baseline (58). The multivariable logistic regression model included all the potential confounders and effect modifiers, and the likelihood ratio test was used to assess the significance of OR obtained for each model. In addition, the visit at which clinically significant PTMD are assessed were also included in the multivariable model. The change-of-estimate criterion was employed to determine the statistical significance of potential confounding, and a change exceeding 10% between the adjusted and unadjusted effects were considered significant (16).

5.3.9.2 Secondary analyses

The multivariable model used to estimate the contribution of insomnia in the persistence of clinically significant PTMD with six-month period were stratified relative to other significant baseline co-variates to assess for effect modification. Additionally, interaction between insomnia and other co-variates were also performed to assess effect modification without compromising on power of the study. The secondary analyses also aimed at estimating the correlations (r) between persistence of clinically significant PTMD and individual symptoms of insomnia which were assessed using the ISI. Furthermore, analysis was done to explore which measure of CPI, i.e., current pain intensity, average pain intensity or worst pain intensity used to define persistent clinically significant PTMD had associations with insomnia.

5.4 Results

5.4.1 Description of the sample

From among 516 individuals informed of the study, 10 refused to participate, and 50 were deemed ineligible due to time constraints and emotional distress. Out of the 456 enrolled PTMD participants, 447 (100%) completed the baseline questionnaire, and 377 (84.3%) and 370 (82.8%) completed the CPI at the three-month and six-month follow-up visits, respectively. Therefore, the drop-out rate of this study was less than 20%.

Table 3, demonstrates the baseline characteristics of the PTMD participants with and without clinically significant PTMD over the six-month follow-up period. The frequency of clinically significant PTMD was higher among participants with insomnia compared to those without insomnia across all three visits within the six-month follow-up period: baseline (201 vs 98, P= 0.0005), three-month visit (67 vs 23, P= 0.01), and six-month visit (67 vs 23, P= 0.01).

Additionally, participants facing psychological issues such as anxiety and/or depression exhibited a higher occurrence of clinically significant PTMD compared to those without psychological problems at all three visits (baseline: 157 vs 141, P= 0.0001; three-month visit: 54 vs 36, P= 0.004). However, this difference was not statistically significant at the six-month mark (48 vs 41, P= 0.10). Although clinically significant PTMD were more prevalent among females than males, and participants with chronic pain demonstrated a higher frequency of clinically significant pain compared to those with acute pain, these differences did not reach statistical significance (P > 0.05).

5.4.2 Persistence of clinically significant pain-related temporomandibular disorders

Clinically significant PTMD as mentioned earlier was defined by a CPI score ≥ 50. The results from the crude and multivariable models analysing the impact of insomnia in the persistence of clinically significant PTMD with six-month period have been enlisted in Table 4. Significant results were obtained from the analyses showing that presence of insomnia at baseline increased the likely odds of persistent clinically significant PTMD by about 60% among PTMD patients within the six-month period both, in the crude (OR_c= 1.62, 95%CI: 1.24—2.15, P= 0.0005) and adjusted (OR_{adj}= 1.59, 95%CI: 1.10—2.31, P= 0.01) models. It could also be inferred that this association was not confounded by other factors since the difference in OR values was less than 10% between the crude and adjusted models. Presence of psychological factors which included anxiety and/or depression was the only other covariate included in the study that significantly increased the odds (OR_c= 1.69, 95%CI: 1.30—2.19, P < 0.0001, OR_{adj}= 1.67, 95%CI: 1.18—2.35, P= 0.004)) of clinically significant PTMD among participants within six-month period. Additionally, mean age showed a borderline association with persistent clinically

significant PTMD in both the crude (OR_c= 1.01, 95%CI: 0.99—1.02, P= 0.06) and multivariable analyses (OR_c= 1.01, 95% CI: 0.99—1.02, P=0.08).

Multivariate logistic regression analysing the contribution of insomnia in the persistence of clinically significant PTMD within six-month period in a dose-response manner has been demonstrated in Table 5. It was observed that increase in insomnia severity also increased the likelihood of persistent clinically significant PTMD within the six-month period. While subthreshold insomnia increased the odds by only about 40% (OR_{adj}= 1.43, 95%CI: 0.95—2.14, P= 0.09), moderate (OR_{adj}= 1.95, 95%CI: 1.23—3.08, P= 0.004) and severe insomnia (OR_{adj}= 2.43, 95% CI: 1.37—4.31, P= 0.002) doubled the odds of persistent clinically significant PTMD showing a dose-response relationship.

5.4.3 Results from secondary analysis

Since psychological factors were the only other covariate statistically associated with the persistence of clinically significant PTMD, the impact of insomnia in the persistence of clinically significant PTMD was stratified to estimate if psychological factors modified this effect. It was observed that there were no differences in the OR_{adj} when the multivariable model for assessing the contribution of insomnia in persistence of clinically significant PTMD was stratified by psychological factors (OR_{adj} for both substrata were 1.48, P= 0.08). Furthermore, no statistically significant interaction was observed between insomnia and psychological factors (P= 0.67) at baseline. Additionally, the interactions between insomnia and the follow-up visits were not significant (P < 0.05), and hence these interaction terms were not included in the statical model.

These results showed that the impact of insomnia in the persistence of clinically significant PTMD was not modified by psychological factors and follow-up visits.

Secondary analysis (Table 6) also showed that all the symptoms of insomnia specified in the ISI showed a positive correlation with persistent clinically significant PTMD though some variations were observed between the symptoms. It was difficulty maintaining sleep (r= 0.12, P < 0.0001) and interference with daily activities (r= 0.12, P < 0.0001) that showed greater correlation with the persistence of clinically significant PTMD.

Additionally, analyses showed that insomnia also impacted all three measures of CPI almost equally, i.e., current pain intensity (OR_{adj}=1.59, 95%CI: 1.10—2.28, P= 0.01), worst pain intensity (OR_{adj}= 1.56, 95%CI: 1.08—2.24, P= 0.02) and average pain intensity (OR_{adj}= 1.52, 955CI: 1.05—2.18, P= 0.03) within six-month of follow-up.

5.5 Discussion

This prospective cohort study demonstrated that insomnia contributed to the likelihood of persistent clinically significant PTMD within the six-month follow-up period and notably, a dose-response association was present between insomnia and persistent clinically significant PTMD. The results were not confounded and modified by the other co-variates included in the study. In addition, no statistically significant (P < 0.05) interaction terms were found between insomnia and the other co-variates which could contribute to the persistence of clinically significant PTMD. The magnitudes of OR indicated that insomnia could be considered as a predictive factor for the continued presence of clinically significant PTMD among patients.

Though literature shows that several studies have found an association between insomnia, including the insomnia symptoms and TMDs (11, 31-45) , most of them were cross-sectional studies. Till date, only one study by Elsaraj *et al*. (11), assessed whether insomnia contributed to the transition and persistence of PTMD. The crude analysis in Elsaraj *et al*. study showed that insomnia was associated with an increased risk (RR_c= 1.43, 95%CI: 1.02—2.03, P= 0.04) of PTMD transition and persistence by 40% when chronic pain was defined by dysfunction. But the association did not exist in the multivariable model (11). Our present study added to the existing literature by showing that insomnia impacted particularly, the persistence of clinically significant PTMD within the six-month period and also showed that insomnia contributed to persistent clinically significant PTMD in a dose-response manner. Our study in addition, used the validated CPI (52) which measures pain intensity to define persistence of pain and also used GEE (58) to account for repeated measurements within the six-month period.

Our study showed quite similar frequency of participants (approximately 24%) who presented with persistent clinically significant PTMD when compared with the previous studies (16, 17, 19). Smith *et al*. (31), Ahlberg *et al*. (42), and Barjandi *et al*. (43), in their respective cross-sectional studies estimated that about 36%, 50% and 25—56% of TMD patients presented with insomnia. Polysomnography (**PSG**) was used by Smith *et al*., while ISI was used in the other study. Findings from our study in Table 3, showed that nearly 61% of PTMD patients presented with insomnia at baseline. This increased frequency in insomnia could be attributed to the reason that while Barjandi *et al*., used an ISI cut-off of 15 to dichotomise insomnia, our study used a lower ISI cut-off value of 10 which included sub-threshold insomnia according to the ISI scoring (54).

This is the first study to show that a dose-response association can exist between insomnia and the persistence of clinically significant PTMD. Though Table 5, shows that statistical significance could not be obtained in estimating the contribution of subthreshold insomnia in the persistence of clinically significant PTMD, it could be inferred from the 95% CI as well as the P value that a greater sample in this substratum could produce statistically significant results. Each specific symptoms of insomnia (Table 6) also show to be correlated with the persistence of clinically significant PTMD within six-month period and this is the first study to show this association. It could be also inferred from the study that insomnia contributed to current pain intensity, average pain intensity and worst pain intensity which defined persistence of clinically significant PTMD. Similar results have been obtained from the study by Dubrovsky *et al*. (40), which showed that average and current pain levels were associated insomnia symptoms measured using PSG.

Psychological factors like anxiety and/or depression were also associated with an increase in the odds of persistent clinically significant PTMD (Table 4), which were in congruence with the findings from other studies (16, 17, 21). It was also observed from the results that the OR obtained from the crude and adjusted analyses differed by 3%. This value implies that the association between insomnia and persistent clinically significant PTMD was not confounded by anxiety and/or depression as well as the other study variables. Furthermore, the stratification analysis and interaction terms revealed that the impact of insomnia on the persistence of PTMD was not modified by the presence or absence of psychological factors assessed in this study.

A limitation of our prospective study relates to the dropout rates of 15.7% and 17.2% at three and six-month follow-up visits, respectively. No significant differences were noted between the dropouts and participants who completed the study. This study does not determine the causality between insomnia and persistence of pain, rather the study is predictive in nature. Though validated self-reported questionnaires were used to assess clinically significant PTMD, insomnia and psychological factors, these instruments are still liable to misclassification and were mostly utilized for screening. The hypothesis of repeated measure analysis is that the OR obtained accounts for the increase in likelihood of persistent TMD at both three and six months. If a difference in the estimates of OR between the two time periods exists, it cannot be estimated. We did not assess variables like other psychological factors, race or medical intervention for pain management that could act as potentials confounders or effect modifiers and hence their impact on the exposure and study outcome could not be analysed. In this study, we did not account for obstructive sleep apnea as a potential confounder because from the previous study by Elsaraj *et al*. (11), we assume that multicollinearity exists between insomnia and OSA.

The strengths of this study include firstly the study design – being a prospective cohort study, temporality can be established. The exposure, insomnia always preceded the outcome of pain persistence and hence the direction of prediction can be inferred. Second, this study was multi-centred and was conducted in four clinics across two cities in Canada. The recruitment of participants at different sites not only reduces the chance of selection bias but also improves the external validity. Third, we used highly reliable and validated instruments to diagnose PTMD. Insomnia and psychological factors were also assessed using highly validated

instruments while we used the most updated versions to define pain and differentiate between acute and chronic pain. The same protocol and instruments were utilized at all the four sites and these measures reduced the chance for misclassification and information bias. The study has sufficient sample size to assess the odds ratio which a power of 80%. The study followed a longitudinal study design, and repeated measurements of pain were assessed to define the outcome. This aided in accounting for the time-dependent variations in pain and this type of analysis yielded interesting results. A dose-response relationship could also be assessed from the study which shows a cause-effect relationship.

It is crucial to recognize that TMD constitutes a group of symptoms primarily marked by pain in the temporomandibular joint (**TMJ**) and/or the surrounding muscles and structures. Though evidence suggests that PTMDs can occur in individuals with peripheral damage or due to localised injury, PTMD in some patients have been generated, maintained, suppressed and exacerbated by central nervous system mechanisms and this has been widely accepted by the scientific community (59). An increasing amount of evidence also shows that central sensitization could be one of the pathophysiological mechanism for TMD (60). Central sensitization is defined by phenomena such as allodynia, hyperalgesia, hypersensitivity and increased receptive field, and typically, prolonged pain persisting after the stimulus has been removed (61). Studies also suggest that insomnia symptoms of total sleep time (ρ= -0.27, P= 0.04) and sleep efficiency (ρ= -0.41, P<0.001) measured using PSG had negative effects on central sensitization (38). There is evidence showing that insomnia has an effect on the interleukin 6 levels (**IL-6**) in TMD patients (35) and a spectrum of studies have shown that sleep disturbances and pain have a bidirectional association (62). Several potential mechanism

involving the opioid system, monoaminergic system and hypothalamus-pituitary adrenal axis which mainly involve the central nervous system have been hypothesized to show the underlying relationship between sleep disturbance and chronic pain (63). The result from our study reveals evidence that support previous literature showing that presence of insomnia can have an impact in the likelihood of persistent PTMD. Thus, from our study it can be inferred that it would be necessary to consider the assessment of possible insomnia and, also address management of insomnia while treating PTMD. Further studies are required to assess the pathways by which insomnia could contribute to persistent PTMD.

In conclusion, this prospective cohort study establishes a novel link, revealing that insomnia increases the likelihood of persistent clinically significant PTMD within six-month follow-up period. Notably, the findings also indicate the presence of a dose-response relationship between insomnia and the persistence of PTMD. While these results provide valuable insights, it is important to acknowledge the study's limitations and future research should aim to address these constraints and delve deeper into the mechanisms underpinning the association between insomnia and the persistence of pain. The implications of our study are profound, suggesting that in the treatment protocol for PTMD patients, attention to the assessment and management of insomnia is crucial. This integrative approach could enhance therapeutic outcomes and contribute to a more comprehensive understanding of the interplay between sleep disturbances and persistent pain conditions.

5.6 Conflict of interest

The authors do not have any conflict of interest associated with this manuscript.

Table 3. Baseline characteristics of pain-related temporomandibular patients relative to factors at first visit (baseline), three-month and six-month follow-up periods

Factors/ Covariate	Category	At baseline n (%)		P value	Three-month visit n (%)		P-value	Six-month visit n (%)		P-value
		447 (100)			377 (100)			370 (100)		
		Cli. Pain	Non-cli.		Cli. Pain	Non.cli		Cli. pain	Non.cli	
Insomnia	No (ISI < 10)	98 (21.92)	74 (16.55)	0.0005	23 (6.10)	114 (30.24)	0.01	23 (6.22)	109 (29.46)	0.01
	Yes (ISI ≥ 10)	201 (44.97)	74 (16.55)		67 (17.77)	173 (45.89)		67 (18.11)	171 (46.22)	
Sex	Male	66 (14.77)	39 (8.72)	0.32	14 (3.74)	76 (20.32)	0.02	18 (4.90)	67 (18.26)	0.45
	Female	233 (52.13)	109 (24.38)		76 (20.32)	208 (55.61)		71 (19.35)	211 (57.49)	
Age	Mean (y)	43.69	39.06	0.005	41.54	42.03	0.81	44.08	41.24	0.15
Psychological factors	No (PHQ-4 ≤ 3)	141 (31.61)	98 (21.97)	0.0001	36 (9.65)	162 (43.43)	0.004	41 (11.20)	155 (42.35)	0.10
	Yes (PHQ-4 > 3)	157 (35.20)	50 (11.21)		54 (14.48)	121 (32.44)		48 (13.11)	122 (33.33)	

Pain status	Acute (≤ 3 m)	82 (18.47)	36 (8.11)	0.45	18 (4.85)	82 (22.10)	0.09	18 (4.95)	81 (22.25)	0.13
	Chronic (> 3 m)	214 (48.20)	112 (25.23)		71 (19.14)	200 (53.91)		68 (18.68)	197 (54.12)	

Note: Cli. pain: Clinical significant pain, Non-cli.: Non clinically significant pain, ISI: Insomnia Severity Index, PHQ-4 : Physical Health Questionnaire, m: months, y: years.

Table 4. Crude and multivariable logistic regression analyses assessing the contribution of insomnia on persistence of clinically significant pain-related temporomandibular disorders within six-month follow-up period

Factors/ Covariate at baseline	Category	OR_C (95% CI)	P value	OR_{adj} (95% CI)	P value
Time at which clinically significant PTMD was recorded	Baseline	1.0 (Reference)	< 0.0001	1.0 (Reference)	< 0.0001
	Three (m)	0.16 (0.12—0.20)		0.14 (0.10—0.19)	
	Six (m)	0.16 (0.12—0.20)		0.14 (0.10—0.19)	
Insomnia	No (ISI < 10)	1.0 (Reference)	0.0005	1.0 (Reference)	0.01
	Yes (ISI ≥ 10)	1.62 (1.24—2.15)		1.59 (1.10—2.31)	
Sex	Male	1.0 (Reference)	0.09	1.0 (Reference)	0.24
	Female	1.30 (0.95—1.78)		1.25 (0.86—1.85)	
Age	Mean (y)	1.01 (0.99—1.02)	0.06	1.01 (0.99—1.02)	0.08
Psychological factors	No (PHQ-4 ≤ 3)	1.0 (Reference)	< 0.0001	1.0 (Reference)	0.004
	Yes (PHQ-4 > 3)	1.69 (1.30—2.19)		1.67 (1.18—2.35)	
Pain status	Acute (≤ 3 m)	1.0 (Reference)	0.47	1.0 (Reference)	0.99
	Chronic (> 3 m)	1.11 (0.84—1.47)		1.00 (0.71—1.41)	

Note: OR_C: Crude odds ratio, OR_{adj}: Odds ratio (adjusted), CI: Confidence Intervals, ISI: Insomnia Severity Index, PHQ: Patient Health Questionnaire, m: months, y: years

Table 5. Multivariable logistic regression analysis estimating the dose-response impact of insomnia on the persistence of clinically significant pain-related temporomandibular disorders within six-month follow-up period

Factors/ Covariate at baseline	Category	OR_{adj}	95%CI	P-Value
Time at which clinically significant PTMD was recorded	Baseline	1.0	(Reference)	< 0.0001
	Three (m)	0.14	0.11—0.19	
	Six (m)	0.14	0.10—0.19	
Insomnia	No (ISI 0—7)	1.0	(Reference)	
	Subthreshold insomnia (ISI 8—14)	1.43	0.94—2.14	0.09
	Moderate insomnia (ISI 15—21)	1.95	1.23—3.08	0.004
	Severe insomnia (ISI 22—28)	2.43	1.37—4.31	0.002
Sex	Male	1.0	(Reference)	0.16
	Female	1.32	0.89—1.93	
Psychological factors	No (PHQ-4 ≤ 3)	1.0	(Reference)	0.02
	Yes (PHQ-4 > 3)	1.53	1.08—2.17	
Pain status	Acute (≤ 3 m)	1.0	(Reference)	0.94
	Chronic (> 3 m)	0.99	0.69—1.39	

Note: OR_{adj}: Odds ratio (adjusted), CI: Confidence Intervals, ISI: Insomnia Severity Index, PHQ: Patient Health Questionnaire, m: months, y: years

Table 6. Pearson correlation between insomnia symptoms measured using Insomnia Severity Index and persistence of clinically significant pain-related temporomandibular disorders within six-month period

Symptoms of Insomnia	Persistent clinically significant PTMD; r (P value)
Difficulty falling asleep	0.09 (0.001)
Difficulty maintaining sleep	0.12 (< 0.0001)
Early morning awakening	0.10 (0.0003)
Dissatisfaction with sleep	0.07 (0.02)
Interference with daily activities	0.12 (< 0.0001)
Sleep problems noticeable to others	0.12 (< 0.0001)
Distress due to sleep problem	0.12 (< 0.0001)

Note: PTMD: Pain-related temporomandibular disorders

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Chapter 6. Discussion

6.1 Rationale

A significant portion of TMDs persist (8-21) and some patients with PTMD tend to report with sleep disturbances which included poor sleep quality, longer sleep latency and lower sleep efficiency. Smith *et al*.(31), estimated that TMD patients presented with insomnia as the most frequent sleep disorder and several other studies show the association between TMD and insomnia (11, 31-45, 103). Despite the rich literature, there has been just one study by Elsaraj *et al*. (11), that assessed the contribution of insomnia in the persistence of PTMD. Nevertheless, the relationship between insomnia and persistent clinically significant PTMD still remains unclear. Therefore, additional research is needed to understand this relationship and the rationale of using pain intensity as a characteristic to measure persistent PTMD is based on the existing literature that insomnia and PTMD intensity are associated (33, 35, 37, 40-42).

6.2 Summary of the results

This prospective cohort study demonstrated that insomnia contributed to the likelihood of persistent clinically significant PTMD within the six-month follow-up period and notably, a dose-response association was present between insomnia and persistent clinically significant PTMD. The results were not confounded and modified by the other co-variates included in the study. In addition, no statistically significant ($P < 0.05$) interactions were found between insomnia and the other co-variates which could contribute to the persistence of clinically significant PTMD. The magnitudes of OR indicated that insomnia could be considered a predictive factor for the continued presence of clinically significant PTMD among patients.

6.3 Comparison with similar studies

Though literature shows that several studies have found an association between insomnia, including the insomnia symptoms and TMDs (11, 31-45), most of them were cross-sectional studies. Till date, only one study by Elsaraj *et al*. (11), assessed whether insomnia contributed to the transition and persistence of PTMD. The crude analysis in Elsaraj *et al*. study showed that insomnia was associated with an increased risk (RR_c= 1.43, 95%CI: 1.02—2.03, P= 0.04) of PTMD transition and persistence by 40% when chronic pain was defined by dysfunction. But the association did not exist in the multivariable model (11). Our present study added to the existing literature by showing that insomnia impacted particularly, the persistence of clinically significant PTMD within the six-month period and also showed insomnia contributed to persistent clinically significant PTMD in a dose-response manner. Our study in addition, used the validated CPI (95) which measures pain intensity to define persistence of pain and also used GEE (102) to account for repeated measurements within the six-month period.

Our study showed quite similar frequency (approximately 24%) of participants who presented with persistent clinically significant PTMD when compared with the previous studies (16, 17, 19). Smith *et al*. (31), Ahlberg *et al*. (42), and Barjandi *et al*. (43), in their respective cross-sectional studies estimated that about 36%, 50% and 25—56% of TMD patients presented with insomnia. PSG was used by Smith *et al*., while ISI was used in the other study. Findings from our study in Table 3, showed that nearly 61% of PTMD patients presented with insomnia at baseline. This increased frequency in insomnia could be attributed to the reason that while Barjandi *et al*., used an ISI cut-off of 15 to dichotomise insomnia, our study used a lower ISI cut-off value of 10 which included sub-threshold insomnia according to the ISI scoring (97).

This is the first study to show that a dose-response association can exist between insomnia and the persistence of clinically significant PTMD. Though Table 5, shows that statistical significance could not be obtained in estimating the contribution of subthreshold insomnia in the persistence of clinically significant PTMD, it could be inferred from the 95% CI as well as the P value that a greater sample in this substratum could produce statistically significant results. Each specific symptoms of insomnia (Table 6) also show to be correlated with the persistence of clinically significant PTMD within six-month period and this is the first study to show this association. It could be also inferred from the study that insomnia contributed to current pain intensity, average pain intensity and worst pain intensity which defined persistence of clinically significant PTMD. Similar results have been obtained from the study by Dubrovsky *et al*., which showed that average and current pain levels were associated insomnia symptoms measured using PSG (40).

Psychological factors like anxiety and/or depression were also associated with an increase in the odds of persistent clinically significant PTMD (Table 4), which were in congruence with the findings from other studies (16, 17, 21). It was also observed from the results that the OR obtained from the crude and adjusted analyses differed by 3%. This implies that the association between insomnia and persistent clinically significant PTMD were not confounded by anxiety and/or depression as well as other study variables. Furthermore, the stratification analysis and interaction terms revealed that the impact of insomnia in the persistence of clinically significant PTMD was not modified by psychological factors assessed in our study.

6.4 Methodological considerations

6.4.1 Bias

Systematic errors termed as bias can occur in design or conduct aspect of a study (63). This could lead to incorrect observations regarding the exposure and outcome relationship. To minimise the bias and to improve the internal validity of any study care should be taken to meticulously choose participants, measure the outcome and predictors, and also account for other variants so that study objectives can be answered. The following section addresses the types of bias that could arise in our study and the steps taken to minimise them.

6.4.1.1 Selection bias

A systematic error that occurs in the process of identifying the study participants is referred to as selection bias (63). A major selection bias that occurs in prospective design is loss during follow-up. In our study, the dropout within the six-month period was estimated to be less than 20% and it was also identified that there were no difference in baseline characteristics between people who completed the study and those who dropped out. This shows that bias arising due to dropout is minimal. This study also recruited participants from four different sites, thus minimizing bias that arises as a result of factor being unique to specific site.

6.4.1.2 Information bias

Inaccurate and unvalidated methods of collecting information from participants, and misclassifying the outcome or exposure may lead to incorrect evaluation of the association between the exposure and outcome (63). To overcome these biases, a standardised protocol was followed by all the four clinical sites and use of validated questionnaires improved the internal validity.

6.4.1.3 Accounting for confounding

Confounders are covariates that are associated with the exposure as well as independently act as risk for the outcome (63). Presence of confounders produce mixing of effects and hence it is necessary to account for them. Thus, in our study we accounted for age, sex, pain status and psychological factors as potential confounders. We did not account for other potential confounders.

6.5 Study limitations and strengths

A limitation of our prospective study relates to the dropout rates of 15.7% and 17.2% at three and six-month follow-up visits, respectively. No significant differences were noted between the dropouts and participants who completed the study. This study does not determine the causality between insomnia and persistence of pain, rather the study is predictive in nature. Though validated self-reported questionnaires were used to assess clinically significant PTMD, insomnia and psychological factors, theses instruments are still liable to misclassification and were mostly utilized for screening. The hypothesis of the repeated measure analysis is that the OR obtained accounts for the increase in likelihood of persistent TMD at both three and six months. If a difference in the estimates of OR between the two time periods exists, it cannot be evaluated. We did not assess variables like other psychological factors, race or medical intervention for the pain management that could act as potential confounders or effect modifiers and hence their impact on the study exposure and outcome could not be analysed. In this study, we did not account for OSA as a potential confounder because from the previous study by Elsaraj *et al*. (11), we assume that multicollinearity exists between insomnia and OSA.

The strengths of this study include firstly the study design – being a prospective cohort study, temporality can be established. The exposure, insomnia always preceded the outcome of pain persistence and hence the direction of prediction can be inferred. Second, this study was multi-centred and was conducted in four clinics across two cities in Canada. The recruitment of participants at different sites not only reduces the chance of selection bias but also improves the external validity. Third, we used highly reliable and validated instruments to diagnose PTMD. Insomnia and psychological factors were also assessed using highly validated instruments while we used the most updated versions to define pain and differentiate between acute and chronic pain. The same protocol and instruments were utilized at all the four sites and these measures reduced the chance for misclassification and information bias. The study has sufficient sample size to assess the odds ratio with a power of 80%. The study followed a longitudinal study design, and repeated measurements of pain were assessed to define the outcome. This aided in accounting for the time-dependent variations in pain and this type of analysis yielded interesting results. A dose-response relationship could also be assessed from the study which shows a cause-effect relationship.

6.6 Implication of results

It is crucial to recognize that TMD constitutes a group of symptoms primarily marked by pain in the TMJ and/or the surrounding muscles and structures. Though evidence suggests that PTMDs can occur in individuals with peripheral damage or due to localised injury, PTMD in some patients have been generated, maintained, suppressed and exacerbated by central nervous system mechanisms and this has been widely accepted by the scientific community (104). An increasing amount of evidence also shows that central sensitization could be one of the

pathophysiological mechanism for TMD (105). Central sensitization is defined by phenomena such as allodynia, hyperalgesia, hypersensitivity and increased receptive field, and typically, prolonged pain persisting after the stimulus has been removed (106). Studies also suggest that insomnia symptoms of total sleep time (ρ= -0.27, P= 0.04) and sleep efficiency (ρ= -0.41, P<0.001) measured using PSG had negative effects on central sensitization (38). There is evidence showing that insomnia has an effect on the IL-6 levels in TMD patients (35) and a spectrum of studies have shown that sleep disturbances and pain have bidirectional association (107). Several potential mechanism involving the opioid system, monoaminergic system and hypothalamus-pituitary adrenal axis which mainly involve the central nervous system have been hypothesized to show the underlying relationship between sleep disturbance and chronic pain (108). The results from our study reveals evidence that support previous literature showing that presence of insomnia could have an impact in the persistence of PTMD. Thus, from our study it can be inferred that it would be necessary to consider the assessment of possible insomnia and also address management of insomnia while treating PTMD. Further studies are required to assess the pathways by which insomnia could contribute to persistent PTMD.

Chapter 7. Conclusion

In conclusion, this prospective cohort study establishes a novel link, revealing that insomnia increases the likelihood of persistent clinically significant PTMD within six-month follow-up period. Notably, the findings also indicate the presence of a dose-response relationship between insomnia and the persistence of PTMD. While these results provide valuable insights, it is important to acknowledge the study's limitations and future research should aim to address these constraints and delve deeper into the mechanisms underpinning the association between insomnia and the persistence of pain. The implications of our study are profound, suggesting that in the treatment protocol for PTMD patients, attention to the assessment and management of insomnia is crucial. This integrative approach could enhance therapeutic outcomes and contribute to a more comprehensive understanding of the interplay between sleep disturbances and persistent pain conditions.

Chapter 8. References

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