MIGRAINE AS PREDICTOR FOR PAIN INTENSITY FOR TMD PATIENTS UNDERGOING TREATMENT

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Dedication

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Abstract

Introduction: Temporomandibular disorders (TMD) occur in about 10% of the adult general population, which makes it a considerable public health problem. Some factors affect treatment outcome of TMD patients seeking care, and among the factors influencing the prognosis of TMD pain, are comorbid pain conditions. Headaches, particularly migraine, have long been reported to be more frequently associated in TMD patients. However, evidence is lacking whether migraine is a prognostic factor for TMD pain at follow-up for patients undergoing TMD treatment.

Objective: To determine in TMD pain patients who undergo common non-surgical treatments whether the presence of migraine at time of diagnosis is associated with worse TMD pain intensity at follow-up over a time period of 18 months.

Materials and Methods: In this prospective cohort study, a consecutive sample of 99 patients with a diagnosis of TMD pain consisting of MFP, arthralgia, and/or TMJ osteoarthritis according to RDC/TMD seeking care at the TMD and Orofacial Pain Clinic, University of Minnesota - School of Dentistry and undergoing common non-surgical treatments for TMD were recruited. Participants received a diagnosis of migraine according to International Classification of Headache Disorders 2nd edition (ICHD-II, 2004), the study exposure, at baseline. Characteristic pain intensity, the study outcome, was measured at 1, 6, 12 and 18 month follow-up and CPI differences at follow-up between patients with and without migraine were analyzed with several generalized equation estimation models and model selection was performed with QIC

(Quasilikelihood under the Independence model Criterion). Baseline CPI status and sociodemographic variables were added to improve the model.

Results: At time of diagnosis (baseline), patients with migraine had a CPI level of 53.9 (95% CI: 43.2-64.6) and patients without migraine had a CPI level of 55.8 (95% CI: 51-60.5). At follow-up, CPI had decreased in both groups but patients with migraine had more pain. The statistically best fitting model predicted CPI values of 45.8, 38.4, 34.8 and 29.2 at 1, 6, 12, and 18 months, respectively for patients without migraine. Patients with migraine showed model-predicted differences, additional CPI compared to patients without migraine, of 10.6 (95% CI: -1.6 -22.9), 8.7 (95% CI: -8.0-25.4), 5.4 (95% CI: -7.3-18.2) and 16.5 (95% CI: 5.2-27.8) at 1, 6, 12, and 18 months, respectively. According to guidelines to interpret effect sizes, the effect was "small."

A simple, more interpretable and still statistically well fitting model predicted that CPI decreases 0.96 per month during follow-up and patients with migraine have 11.6 (95% CI: 2.7-20.4) more CPI over the time period of 1.5 years than patients without migraine.

Conclusion: For TMD patients who undergo common non-surgical treatments, migraine is a potential prognostic factor for TMD pain intensity at follow-up. Patients with migraine at the time of diagnosis have statistically significant more TMD pain intensity over a time period of 1.5 years than patients without. While the migraine effect is small, it suggests that treatment for migraine could possibly be incorporated in the overall treatment plan to improve patient outcomes.

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1. Introduction

Temporomandibular disorders (TMD) is typically a painful condition of the masticatory muscles, the temporomandibular joints, or both. The prevalence of this group of conditions is about 10% in the adult general population, which makes it a considerable public health problem and affects substantially individuals' quality of life (1-3) and it impacts substantially individuals' quality of life (4, 5). Some individuals have chronic pain and while treatment outcome is favorable when care is sought, some patients receive insufficient relief from conservative or even invasive therapeutic approaches. Among the factors influencing the prognosis of TMD pain, comorbid pain conditions are considered very important. Conditions such as widespread pain and fibromyalgia are often associated with TMD pain and they impact the treatment outcome (6, 7).

Other pains in close proximity to TMD pain are naturally potent candidates to influence TMD prognosis. Headaches, particularly migraine, have long been reported to be more frequently associated in TMD patients (8). One study reported that headaches occurred significantly more in subjects with symptoms of TMD pain rather than in those without TMD pain (27.4% versus 15.2%). Another study observed that the overall prevalence of headache in TMD pain patients was 72.7% higher than a control group (without TMD pain) with 31.9% (9). A particular type of headache, migraine, may be particularly important because worldwide, it is the third most common disease and has an estimated prevalence of 14.7% (10). The relevance of migraine for TMD pain could be due to shared mechanisms, and although the origin and mechanisms for these conditions have not been completely established, there is consensus that the trigeminal nerve is

associated with both conditions. Once pain is established, referral anywhere in the trigeminal and cervical complex can occur through central sensitization, and can be amplified by peripheral inputs (11-14).

Studies investigating the relationship between TMD and migraine have looked at the similarities between signs and symptoms of both disorders (15-17). Some studies have established that both migraine and TMD are more prevalent in younger adults and decline in frequency with age and in women during postmenopausal years (2). Hormonal factors also play a role in TMD with pain levels varying across the menstrual cycle (18). There are also studies that found that women with migraines are more likely to have TMD pain when compared to women without migraines (19). Nevertheless, they have not investigated whether the presence of migraine is a predictive factor for the prognosis of TMD pain for patients undergoing common conservative treatment.

To study whether migraine is a prognostic factor for TMD pain at follow-up for patients undergoing TMD treatment has relevance. Beyond advancing our knowledge about mechanisms of pain conditions, treatment of migraines could potentially improve TMD pain follow-up, i.e., it could decrease the suffering for a substantial number of TMD patients because migraine is not rare. An observational study in typical TMD patients with a widely applicable diagnosis using RDC/TMD and a standardized migraine assessment could be the first step for establishing the *migraine-TMD pain at follow-up* relationship that could be followed by other more confirmatory studies that also determine the magnitude of a treatment effect when patients suffer from TMD pain and migraine.

2. Aim and Hypothesis

Aim

We aimed to determine in TMD pain patients who undergo common non-surgical treatments whether the presence of migraine at time of diagnosis is associated with worse TMD pain intensity at follow-up over a time period of 18 months.

Hypothesis

Our research hypothesis was that TMD pain patients with migraine have higher, i.e., worse TMD pain intensity over the course of 18 months compared to patients without migraine.

The statistical null hypothesis is that, when taking into account patient's baseline measures, there is no difference in pain intensity over a time period of 18 months between TMD pain patients with and without migraine that are undergoing non-surgical TMD treatments.

3. Material and Methods

3.1. Subjects and setting

In this prospective cohort study, a consecutive sample of patients seeking care at the TMD and Orofacial Pain Clinic, University of Minnesota - School of Dentistry were enrolled in 2010 and 2011. Participants were included when masticatory muscle and TMJ-related pain was their primary concern, if they were at least 18 years of age, and if they fulfilled the criteria for TMD pain diagnosis according to Research Diagnostic Criteria for Temporomandibular Disorders Version 2 (20). Patients were excluded when they were planning to move town or would be out of the country during the follow-ups, if they required an interpreter in the initial consultation or had an insufficient command of the English language, and if they had mental impairments that prevented accurate answers to questions.

At the time of diagnosis (baseline), TMD pain patients were asked to fill out a questionnaire that comprehended questions needed for the diagnosis of TMD pain. It also included questions about the baseline status of the study's outcome characteristic pain intensity (CPI) and other pain-related questions. Filling in the questionnaire took about 10 min of the patient's time.

The study protocol (IRB number 0911M74077) was reviewed and approved by the Institutional Review Board of the School of Dentistry, University of Minnesota. After patients signed the informed consent, the 99 patients started regular standard non-surgical treatments for TMD pain.

Study exposure: Presence of migraine

Subjects were classified according to their diagnosis of migraine, based on the International Classification of Headache Disorders 2nd edition (21). The attending resident and faculty established the migraine diagnoses after detailed evaluation of patient's history and comprehensive clinical exam of each participant. Regarding the migraine diagnosis, the frequency of attacks was not taken into consideration; therefore, episodic migraine and chronic migraine were considered as migraine only.

3.2. Study outcome: Assessment of pain intensity

Characteristic pain intensity is an average of three aspects of pain intensity: pain at the moment, worst pain and average pain in the past 6 months. Responses are given on a 0 to 10 scale, with 0 being no pain and 10 being as bad as it could be. CPI score ranges from 0 to 100 points (higher scores indicate greater pain). The three pain intensities were recorded with the Graded Chronic Pain Status (22) which is a 7-item instrument that is frequently used to measure chronic pain severity in epidemiological studies. It is multidimensional measure that assesses 2 dimensions of overall chronic pain severity: pain intensity and pain-related disability.

The CPI was recorded at 1, 6, 12 and 18 months after initial diagnosis. Patients were mailed a questionnaire with the Graded Chronic Pain instrument, and other pain-related questions that required about 5 min of the patient's time to fill in the information.

3.3 Data analyses

CPI differences for patients with and without migraine were calculated for all follow-ups individually. Confidence intervals for the differences were also computed and their statistical significance was evaluated.

Then, all CPI scores at 1, 6, 12, and 18 months were analyzed together in generalized estimating equation (GEE) models. The GEE method is an extension of the generalized linear model (GLM) method to correlated data and to obtain valid standard error of the parameter estimates. One key difference compared to regular regression analysis is that GEE method is based on the quasilikelihood theory and no assumption is made about the distribution of response observations.

Our data modeling approach progresses in four steps:

1. We included baseline CPI in the model to provide a desired interpretation for the analysis that CPI differences at follow-up between patients with and without migraines are independent of initial CPI status.
2. We built eight models that we deemed potential competitors for explaining the data and selected the best model.
3. We added more covariates to adjust for potential confounders and adjust for treatment modality influence.
4. Finally, the robustness of the findings was checked with data imputation and model diagnostics.

Model building step 1:

We included baseline CPI as a covariate in the model. This variable was incorporated so that follow-up CPI differences (our outcome) between migraineurs and non-migraineurs for the same initial CPI level can be computed. Without this variable in the model, follow-up CPI differences could just be a continuation of baseline differences between patients with and without migraine. Differences at follow-up could have been observed, but these differences could already be present at baseline. With baseline CPI in the model, CPI differences at follow-up were computed for patients with the same level of initial CPI and, therefore, the influence of baseline CPI is adjusted for.

Model building step 2:

In our strategy to analyze the CPI differences at follow-up between patients with and without migraine, i.e., the exposure variable of interest, we incorporated in the analyses the time when the follow-up was performed. We did this in several ways:

1. We added follow-up time as a categorical main effect to the analysis and also created an interaction effect with the other, already present main effect, our exposure variable migraine presence (Panel A, Figure 1). This model allowed the CPI follow-up differences between patients with and without migraine to vary freely over follow-up time. In this model, the four CPI differences at follow-up can have all different values.
2. We added follow-up time as a linear main effect and also created an interaction effect with the migraine main effect (Panel B, Figure 1). This

model was more restrictive than model 1. It allowed the CPI follow-up differences between patients with and without migraine to vary, but they varied systematically with follow-up time. Two scenarios could potentially exist. The CPI differences between patients with and without migraine became increasingly larger (as depicted in Panel B, Figure 1) or they could become increasingly smaller. For both scenarios, the four CPI differences at follow-up could have all different values, but the difference was function of time, i.e., they increased (e.g., Panel B, Figure 1) or decreased with a constant factor over follow-up time.

3. We added follow-up time as a categorical main effect to the analysis, but did not add an interaction with the study exposure (Panel C, Figure 1). This model was a simpler version of model 1. The CPI differences between patients with and without migraine could not vary freely in their magnitude over follow-up time anymore. The difference was now constant and consequently instead of four CPI differences at follow-up, only one difference was derived in the analysis. However, the constant CPI difference was added to freely varying CPI levels of the no migraine group (the base group in the analysis).
4. We added follow-up time as a linear main effect, but did not add an interaction with the study exposure (Panel D, Figure 1). This model was a simpler version of model 2. However, it also shared some similarities with model 3 because, like this model, it only contained main effects. This was the simplest model of the four. The CPI differences were constant over time. Only

one difference is derived in the analysis. In both patients with and without migraine, CPI decreased as a function of follow-up time.

We already noted that follow-up CPI scores were correlated and the GEE model took this into account in the analysis. However, the pattern of the correlation or the correlation structure was informative and also needed to be incorporated in the analyses. The GEE model can take this correlation structure into account. Two options for modeling this correlation were explored: an unstructured correlation structure and the more restrictive, but parsimonious, exchangeable working correlation matrix. Whereas the unstructured correlation did not make any assumption about the magnitude of the correlation, the exchangeable correlation matrix assumed that all follow-up measures for an individual are equally correlated. For example, if the matrix would contain a correlation of 0.5, then CPI scores at 1 month correlated with rho=0.50 with the CPI scores at 6 months. Also, the 6 month scores correlated with rho=0.50 with the 12-month scores etc.

Our four models could all be used with the unstructured or the exchangeable correlation structure. Therefore, eight possible models were investigated as possible candidates to explain the data. The selection of the best among the eight available models was performed using QIC (Quasilikelihood under the Independence model Criterion), a method of evaluating model fit for the GEE approach (23). The QIC method allows us to compare models with different parameterizations (different variables in the models, e.g., model 1 through 4) as well as alternative correlation structures (for example, unstructured

or exchangeable correlations) on the same data. In short, a model with the lowest QIC was considered the "best" model in terms of statistical fit.

Model building step 3:

We also added gender, age, education and treatment modality to the analyses. The sociodemographic variables would be considered confounders of the *migraine-TMD with CPI relationship*. Education was grouped as some high school education and at least some college education. Ethnicity was defined as White (Not Hispanic or Latino) and Non-white (Hispanic or Latino). Treatment variables were added to compare CPI for migraineurs and non-migraineurs with similar clinical treatment and therefore to adjust for a possible treatment influence. We divided patients into three categories: treatment A (Patient education/TMD self-care only - SC), treatment B (SC with one additional treatment, either physical therapy or splint) and treatment C (SC with both physical therapy and splint). Physical therapy incorporated any of the following: therapeutic and home exercises, manual therapy and/or modalities. Splint was defined as a stabilization appliance with a flat plane design or a mandibular repositioning appliance.

Model building step 4:

Finally, we were concerned about the influence of missing CPI follow-up information. The number of participants that completed follow-ups was 54.4% at 1-month follow-up, 35.6% for 6 and 12 months, and 55.4% for 1.5 years follow-up. Missing data were imputed. We performed multiple imputations. We generated 10 data

sets and generated the final statistical model in each of the 10, now complete data sets. Then, the GEE model results for each complete set were averaged across the 10 datasets. Before we performed the imputation, we analyzed whether baseline sociodemographic and clinical characteristics influence missing data. When performing the imputation, we took follow-up time, exposures status, and baseline CPI level as influencing factors for imputation of the missing data into account. We intended to counteract any influence from these factors on the missing data. If these variables would have an influence whether data were missing or not, e.g., data was systematically missing according to the patient's initial CPI level, we would expect to see differences between the data analyses with and without imputation. As the last step, we performed model diagnostics to check the robustness of our analytic approach. We calculated "dfbetas", a measure of how much an observation has effected the regression model estimation (there is one DFBETA for each observation in the dataset). Values larger than 2/sqrt(n) in absolute value were considered highly influential. For interpretation of the magnitude of the migraine and other factors' effects in the model, we calculated "omega-squared" for models with unstructured correlation matrix and compared effect size values with guidelines (24).

All analyses were performed using the statistical software package STATA/IC, Release 14 (StataCorp LP, College Station, TX, USA), with probability of a type I error set at 0.05.

4. Results

4.1. Sociodemographic and clinical characteristics as well as baseline CPI of TMD pain patients with and without migraine.

In this consecutive group of TMD pain patients, about every fifth individual suffered from migraine (Table 1). However, patients with and without migraine did not differ much by age and ethnicity and only slightly differed by gender, education and treatment modalities. Most importantly, regardless of the presence of migraine, patients were comparable in their baseline TMD-CPI, i.e., they suffered from similar, moderately intense pain before treatment started. Both groups of patients only differed a trivial two points on the 0 to 100 CPI scale. Overall, patients with and without migraine seemed to be similar at baseline and also received similar treatments.

In addition, all participants were stratified by number of follow-ups to evaluate if there was a significant difference due to missingness of one or more follow-ups (Table 2). Patients with and without migraine at baseline did not differ to a substantial degree in their characteristics and none of the differences was statistically significant. The baseline CPI levels were comparable between these two groups, with a slightly difference of 3 points. Findings suggest that it is unlikely that patients with migraine and with high follow-up CPI levels are missing. Therefore, the CPI differences at follow-up would not be affected by missing data. The difference is also not statistically significant if the presence of migraine is taken into account.

4.2. CPI differences between patients with and without migraine: individual analysis at each follow-up

CPI declined over time in patients with and without migraine. At the end of the study observation time, only about half of the initial pain intensity was still present. Pain after 1.5 years was on average mild in intensity. At two of the four follow-ups, patients without migraine had lower CPI. On two occasions no difference was observed. Confidence intervals for the differences were wide, indicating a substantial uncertainty and always included a zero difference, i.e., they were statistically not significant.

4.3. CPI differences between patients with and without migraine: Combined analysis for all follow-ups and model building

In the GEE analysis, when the CPIs of the four follow-ups were analyzed together and baseline CPI was included to compare patients with and without migraine with similar initial pain intensity (model building step 1), the situation changed. Overall, patients with and without migraine differed more in their CPI at follow-up. Patients with migraine had higher CPI, i.e., they did not decline in their pain intensity as much as patients without migraine.

When we compared the eight statistical models according to the QIC (model building step 2, Table 3), the best model of follow-up CPI measures was model 1 with month as categorical variable and an interaction of this variable with migraine, estimated using an exchangeable correlation structure. This model generated four CPI differences, one for each follow-up. The difference represented the added CPI at follow-up for patients who have migraines at time of diagnosis compared to the CPI for patients

without migraines. The model-derived CPI differences are presented in Figure 2. Confidence intervals for the differences are presented in Table 4.

In our further model building steps, results did not change much. Adding covariates changed the CPI difference only slightly by 3 points or less (Table 4). Finally, model results were deemed to be robust because imputation did not provide substantially different results. The best fit model was evaluated for outliers and influential observations by calculating the dfbeta statistic for each observation. The dfbetas ranged from -0.8 to 2.0. There were 2 observations where dfbeta was greater than 1.0 and 43 observations where dfbeta was greater than 0.1 (using the criteria of 2/squareroot(n) as a criteria for influence.) The model was rerun after deleting these potential outliers and estimates for the effect of migraine before and after deletion of these observations were not substantially different.

4.4. Alternative model to provide a better interpretation of the findings

For simplicity and ease of interpretation, it may be beneficial to consider a simpler model with only migraine exposure and time as a linear variable in its original metric months with no interactions of the two variables.

The model fit for this model was comparable to the model fit of the "best" model (QIC= 56085.82 vs. QIC=55343.11) and the interpretation of the model may be more easily understood and estimated. The model assumed that follow-up CPI level was a function of time, i.e., TMD pain intensity decreased per month by a certain number of

CPI points. In our situation, CPI decreased by 0.96 (95% confidence interval: 0.66 to 1.25) per month. This model-generated decrease was identical in patients with and without migraines; however, these two groups differed by 11.6 (95% confidence interval: 2.7 to 20.4) – a difference that was constant over the time of 18 months. For example, at month 1 patients with migraine had a CPI of 56.7 whereas patients without migraine had a value of 45.1. Because of our model structure, the difference of 11.6 between the two values was still the same at month 18, but now the CPI levels were 40.5 and 28.9 for both groups, respectively. Therefore, patients with migraine improved in their pain intensity by the same rate over time, but their TMD pain magnitude was always worse at a certain follow-up compared to patients without migraine. This model assumed a constant effect of migraine across all time points and, as before for the more complicated, best fitting model, identical correlations between outcome (CPI) measures within an individuals' repeated observations.

Effect sizes (omega-squared) were calculated for the alternative plus covariates model. The migraine and time effects were small (omega-squared 0.03 and 0.12, respectively). The effect size was large for baseline CPI (0.30).

5. Discussion

In this prospective cohort study, we found that patients perceived a steady decline in their pain intensity over the time of 1.5 years and, at the end of this time period, pain dropped to 28.9 CPI points on the non-migraineur group. In comparison, patients with migraine had additional 11.6 CPI points at this point. Therefore, in TMD patients we found an association between baseline migraine, and TMD pain intensity at follow-up. The effect was small, but statistically significant.

Several peer-reviewed articles have reported different thresholds for what should be considered clinically meaningful pain difference (25-30). The rational for those attempts are to judge the relevance of the pain experience, and its difference between groups of conditions. The existence of different thresholds, for what should be considered clinically meaningful pain difference, point to two relevant aspects: First, there is a lively debate in various areas of the study of pain, and, second, that the "clinical difference" is not yet completely established. In essence, there is a large variability in the reported pain ratings across individuals, despite seemingly similar stimuli or interventions (29). Moreover, researchers, clinicians and patients, depending on which criteria was chosen, very often interpret values obtained from pain measurement scales differently (27).

On an attempt to provide some guidelines for this interpretation, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommends that the percentage of patients obtaining reductions in pain intensity from baseline of at least 30% should be reported (28, 31). This was the guideline used in this

study, and this is relevant because patients considered a 30% reduction in pain intensity as moderate improvement in previous peer-reviewed studies (28, 30, 32). In our study, patients did not perceive a constant percent pain difference over the study period. After 1.5 years, patients with migraine experienced 40% more pain at the end of the study compared to patients without migraine. This is a difference we believe would matter to these patients. The same guideline also recommends researchers to report cases of pain reductions greater then a 2-point difference in pain reduction. A 2-point pain reduction would be equivalent to 20 points on the CPI scale. While pain intensity in both migraine and non-migraine groups reduced over 1.5 years, for patients without migraine it was substantially larger. In the non-migraine group, the drop was 26.9 CPI points and in the migraine group the decrease was 13.4 points. According to the guideline, in the non-migraine group the pain reduction is relevant according to the 2-point criterion. In the migraine group it is not. In relative terms, pain intensity dropped 48% in the non-migraine group and 25% in the migraine group. According to the guideline, in the non-migraine group the pain reduction is relevant according to the 30% criterion. In the migraine group it is not. It should also be noted that the difference between the two groups of 11.6, i.e., equivalent to 1.16 on a 0-10 numerical rating scale, did not reach the 2-point criterion and would not be considered clinical relevant.

Summarizing these points, a clinical significant effect was observed according to most criteria of clinical relevance but not for all, leaving some uncertainly about the magnitude of the effect.

The discussion of clinical relevance also benefits from another perspective. An important aspect that should be considered is that the baseline CPI levels for the participants in this study ranged from 53.9 to 55.8. According to a consensus statement from IMMPACT (28), the magnitude of pain reduction that a participant with severe pain would consider minimally important could be greater than the magnitude of reduction that an individual with mild or moderate pain would consider. Therefore, not all patients have experienced a meaningful change. Also, although the use of percentage change can have the potential to correct patients' assessments of differences, the role of baseline pain should be evaluated in each specific situation. Thus, we cautiously followed these recommendations.

In our study, after rigorous and meaningful statistical consideration and analyses, we observed a statistical difference over the 18-month follow-up time. Considering the evidence reported on table 4, the best model (model 2) and the best model plus covariates (model 3) show that the migraineur group had 15 (model 2) and 16.5 (model 3) more CPI points then the non-migraineur group, when taking baseline levels into consideration. If we consider a more robust and parsimonious model (alternative model plus covariates) the migraineur group demonstrated additional 11.6 CPI points. This is a conservative perspective for interpretation of treatment effects.

More insight comes from other studies. A randomized controlled trial by Truelove et al (33) found findings with similar magnitude in terms of CPI reduction levels at a shorter follow-up period (12 months) and with the participants having moderate baseline CPI levels similar to our population group. Therefore, baseline levels of pain intensity are

indeed very influential like in our study, providing supporting information about pain reduction in other TMD patient populations.

While our statistical modeling revealed a complex pattern of varying pain intensity at the different follow-ups in terms of the values for the base group of non-migraineurs as well as the difference of migraineurs compared to the previous group, we were also able to detect a well-fitting parsimonious and clinically very plausible model. In this model, pain decreased in a linear fashion from baseline intensity and we can characterize the migraine effect as constant worsening of pain intensity over the entire time. In addition, the follow-up CPI scores were correlated to the same degree in our study where the time distances between follow-ups were pretty similar. The characteristics of a linear pain decrease, a constant migraine effect and identical correlations between outcomes are certainly a simplification of a complex process; however, in our situation they provided a reasonable and simple explanation, i.e., model, of the data. We also believe that this model sheds some light into how treatments and prognostic factor affect patient outcomes in general.

Comparison with previous findings

Our findings are in line with studies showing an influence of comorbid pain conditions on prognosis of patients with TMD pain. Comorbid pain is frequent in TMD pain patients. Studies that evaluated the effect of different comorbidities in TMD pain showed that 60% of subjects with TMD pain reported concurrent bodily pain conditions

in addition to pain in the facial region (34). Treatment outcomes at follow-ups are further impacted by the presence of concomitant diagnoses (6, 7, 35). More specifically in the field of orofacial pain, observational studies evaluating the effect of migraine on TMD pain showed a migraine diagnosis being not only associated with TMD, but also positively associated with increased TMD pain intensity (9, 36-38). However, these studies generally used either questionnaire for classification of migraine and TMD pain, and/or cross-section study design. We mitigated these limitations by performing a comprehensive clinical and physical exam, which is considered the gold standard for classification. We also performed a prospective, longitudinal study, allowing the determination of a cause-and-effect-relationship. Since the origin of migraine and TMD pain has not yet been established, possible mechanisms for a poor prognosis and treatment outcome can only be speculated. However, the phenomenon of central sensitization in the trigeminal distribution may offer an explanation. The combination of inputs from neurons in the nucleus caudalis (integrates nociceptive input from both intracranial and extracranial tissues) is projected to the thalamus and onto the cortex (39). Thus, nociceptive inputs from the TMJ and/or masticatory muscles could lead to trigeminal activation (14). In addition, the presence of proinflammatory factors (prostaglandin E2, cytokines and tumor necrosis factor), Calcitonin gene-related peptide, nociceptive substance P and serotonin at the TMJ could be another form of sensitization (40-42). Therefore, TMD symptoms could cause an excitatory impact on migraine. Equally, it is possible that migraine leads to activation of the trigeminal system increasing the susceptibility for TMD pain, also via similar mechanism of central sensitization (12,

14). In summary, TMD pain may be a source of headache and perhaps worsen preexisting headache. The opposite may also be true.

In the literature, there are very few studies designed to clinically evaluate association between headache and TMD pain over time periods that are clinically relevant (43, 44). One of the previous studies concluded that in female patients with comorbid migraine and TMD pain, treating migraine alone was no different than not treating migraine, and treating only TMD pain was also not effective. The better patient response and treatment outcome was observed when combining treatment to address both disorders simultaneously (45).

Strengths and limitations

The present study has several strengths. Our study design comprehended a meaningful 18-month follow-up period, which is clinically informative. Patients were diagnosed following the gold-standard approach with complete clinical exam following valid international guidelines (20, 21, 46, 47). Although we selected participants from a specialized center at a major university, the sample could be similar to broader population studies, since many patients in our sample had their first treatment while participating in this study. The majority of our sample was female, young adults and educated; which is consistent with the demographics of both migraine and TMD pain studies (2, 19, 48). Their baseline pain severity is also similar to other patient population, and while patient populations may differ, the influence on our findings comparing between TMD pain with and without migraine is likely less pronounced. Our primary outcome was pain intensity

(measured by CPI from the GCP) that is a recommended core outcome measure by IMMPACT (31). In addition, our statistical analysis was comprehensive and based on specific methods for longitudinal studies by using the GEE approach. Results with and without covariate adjustment were similar, indicating that sociodemographic factors and treatment modalities did not have a substantial influence on the findings.

Our study also has some limitations. Although there are different and contradictory recommendations in the pain literature on what should be considered a positive clinical change, we based the interpretation of our findings on an international valid guideline (28, 31, 49). Nevertheless, we recognize that there are other debatable methods to report minimal clinically important difference (MCID), such as anchor-based and distribution-based MICD approaches (50, 51). We also only used pain intensity as the outcome measurement. Several other multidimensional physical and psychosocial measures could be used in addition to pain severity. However, pain intensity is one of the four core domains for chronic pain outcomes (28). We could have assessed migraine presence at each follow-up. This would have led to a different research question than our interest in the prognostic value of migraine presence when the patients is diagnosed and starts treatment. In regards to treatment, we do know which treatments were recommended to the participants; however, we did not evaluate if and when patients stopped their treatments. Most likely, they continued with some TMD self-care. Finally, we had a low response rate resulting in substantial missing data. While we cannot exclude a bias due to non-response, our data imputation adjusted for major methodological threats such as missingness influenced by baseline TMD pain intensity.

Additional non-response analyses did not find evidence for a major bias due to non-response. Our findings seemed robust also against outliers in the data.

6. Conclusion

In summary, the results presented support for the conclusion that migraine could be considered a potential prognostic factor for worse pain intensity at follow-up in TMD pain patients being treated by common non-surgical treatments for TMD. The magnitude and the clinical relevance of this effect are challenging to interpret due to different guidelines available for the absolute and the relative size of the change.

Future longitudinal clinical studies are needed to evaluate if and how much pain severity and disability would improve treating both conditions concurrently. However, given the cumulative evidence suggesting the comorbid nature of TMD pain and migraine and the two conditions bidirectional relationship, our findings point into the direction that combined therapeutically approach, addressing both conditions simultaneously, in patients with TMD and migraine could possibly lead to improved outcomes in these patients.

Table 1: Sociodemographical and clinical characteristics of TMD pain patients with and without migraine as comorbid condition.

		TMD patients without migraine		**TMD patients with migraine**		
	N	mean (SD) or %	N	mean (SD) or %	Difference between means (95% CI)	p-value[a]
Age [years]	81	37.5 (13.3)	18	35.2 (14.0)		0.51
Female	81	72%	18	89%		0.14
≥Some college	81	77%	18	89%		0.26
White	81	96%	18	94%		0.72
Treatment A	81	12%	18	6%		0.42
Treatment B	81	56%	18	50%		0.67
Treatment C	81	32%	18	44%		0.32
CPI baseline	81	55.8 (21.4)	18	53.9 (21.5)	1.9 (-9.2 to 12.9)	
CPI 1 month FU	46	45.4 (18.2)	9	50.7 (24.0)	-5.3 (-19.3 to 8.7)	
CPI 6 months FU	32	35.9 (21.6)	4	35.8 (28.9)	0.1 (-23.9 to 24.1)	
CPI 12 months FU	27	34.1 (20.7)	9	33.3 (28.8)	0.7 (-17.2 to 18.7)	
CPI 18 months FU	45	26.5 (21.1)	11	35.8 (26.4)	-9.2 (-24.2 to 5.7)	

a) p-value derived from logistic regression.

Table 2: Sociodemographical and clinical characteristics of all patients and stratified by number of follow-ups.

Characteristic	All patients		Patients who completed all follow-ups		Patients who missed at least one follow-up		p-value[a]
	N	mean (SD) or proportion of subjects	N	mean (SD) or proportion of subjects	N	mean (SD) or proportion of subjects	
Age [years]	99	37.0 (13.4)	19	35.8 (15.1)	80	37.3 (13.0)	0.65
Female	99	75 %	19	74%	80	75%	0.90
≥Some college	99	78 %	19	84%	80	77%	0.75
White	99	96 %	19	95%	80	96%	0.58
Treatment A	99	80 %	19	79%	80	81%	0.75
Treatment B	99	42 %	19	37%	80	44%	0.58
Migraine	99	18 %	19	16%	80	19%	1.00
CPI baseline [points]	99	55.4 (21.3)	19	52.8 (20.6)	80	56.0 (21.5)	0.55

a) Statistical significance comparing patients with complete and incomplete follow-ups

Table 3: Comparison of eight candidate models to characterize CPI in TMD patients undergoing treatment over a time period of 1.5 years: QIC for model selection under normal distribution.

Correlation Structure	Variables	Parameters	QIC	QIC_u
Unstructured	cpi baseline, dx, month (cat), dx x month (cat)	9	55736.23	55734.97
Exchangeable	**cpi baseline, dx, month (cat), dx x month (cat)**	**9**	**55343.11**	**55734.97**
Unstructured	cpi baseline, dx, month (cat)	6	56601.26	56597.7
Exchangeable	cpi baseline, dx, month (cat)	6	56085.82	56081.5
Unstructured	cpi baseline, dx, month (con)	4	56821.3	56816.14
Exchangeable	cpi baseline, dx, month (con)	4	56688.48	56682.57
Unstructured	cpi baseline, dx, month (con), dx x month (con)	5	56725.57	56720.83
Exchangeable	cpi baseline, dx, month (con), dx x month (con)	5	56587.84	56582.31

QIC: Quasilikelihood under the Independence model Criterion, cpi: characteristic pain intensity, dx: diagnosis, cat: categorical, con: continuous, dx x month (cat): interaction diagnosis and categorical month, dx x month (con): interaction diagnosis and continuous month.

Table 4: Model predicted CPI differences showing best and alternative models.

	Model 2 (best model)		**Model 3 (best model plus covariates)**		**Model 4 (best model plus covariates plus imputation)**		**Alternative model plus covariates**	
	CPI level for patients w/o migraine	Additional CPI for patients w migraine	CPI level for patients w/o migraine	Additional CPI for patients w migraine	CPI level for patients w/o migraine	Additional CPI for patients w migraine	CPI level for patients w/o migraine	Additional CPI for patients w migraine
1 month	45.9	8.9	45.8	10.6	47.3	8.4	45.1	11.6
	(41.4-50.4)	(-3.2-21.0)	(41.4-50.2)	(-1.6-22.9)	(42.0-52.6)	(-3.4-20.2)	(41.0-49.2)	(2.7-20.4)
6 months	38.2	5.7	38.4	8.7	39.8	7.4	40.4	11.6
	(32.7-43.7)	(-10.9-22.3)	(33.0-43.8)	(-8.0-25.4)	(34.5-45.1)	(-5.7-20.6)	(37.0-43.8)	(2.7-20.4)
12 months	35.1	3.1	34.8	5.4	35.7	5.1	34.6	11.6
	(29.7-40.5)	(-9.6-15.7)	(29.5-40.1)	(-7.3-18.2)	(30.7-40.8)	(-6.3-16.5)	(31.3-37.9)	(2.7-20.4)
18 months	29.2	15.0	29.2	16.5	29.6	10.3	28.9	11.6
	(24.8-33.7)	(3.7-26.3)	(24.8-33.5)	(5.2-27.8)	(25.4-33.9)	(-1.1-21.7)	(24.8-33.0)	(2.7-20.4)

Figure 1: Progression of modeling approach.

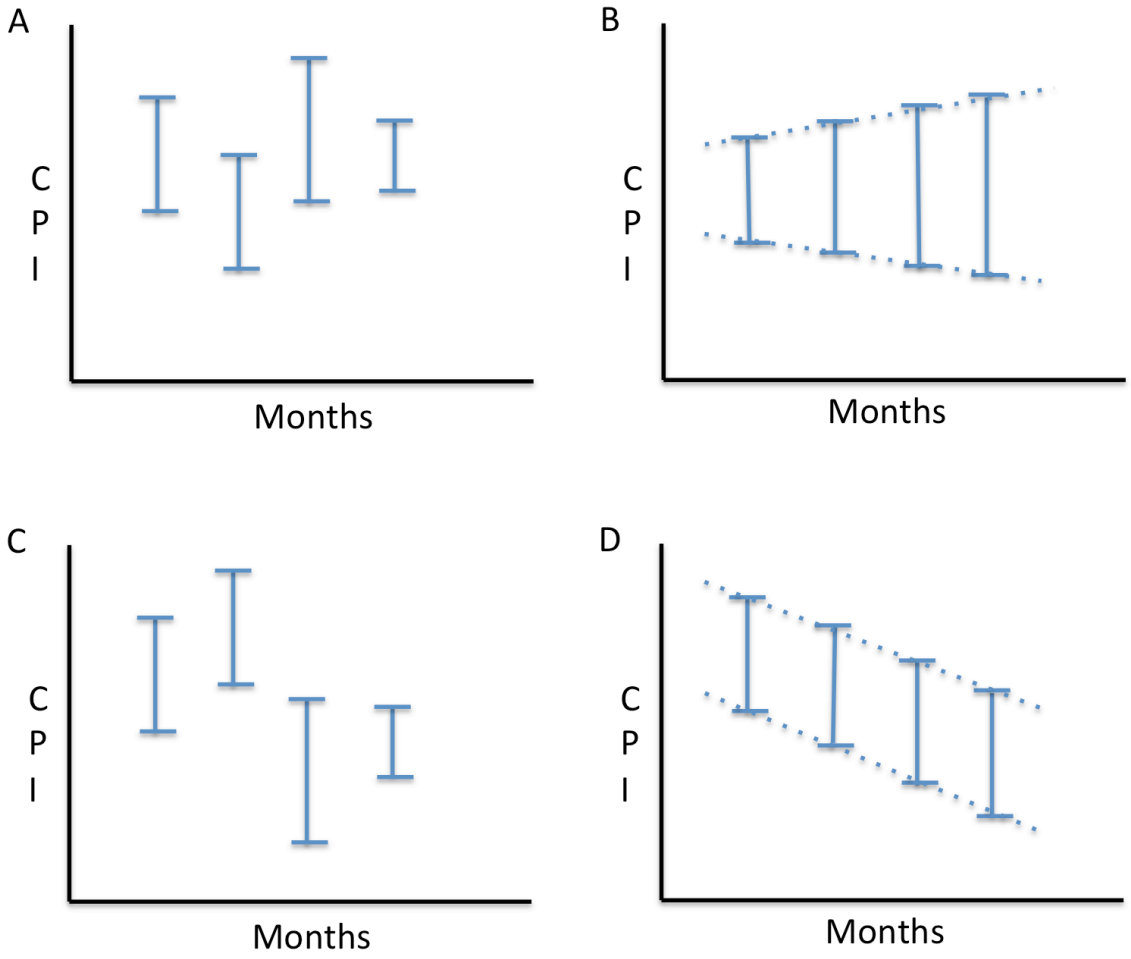
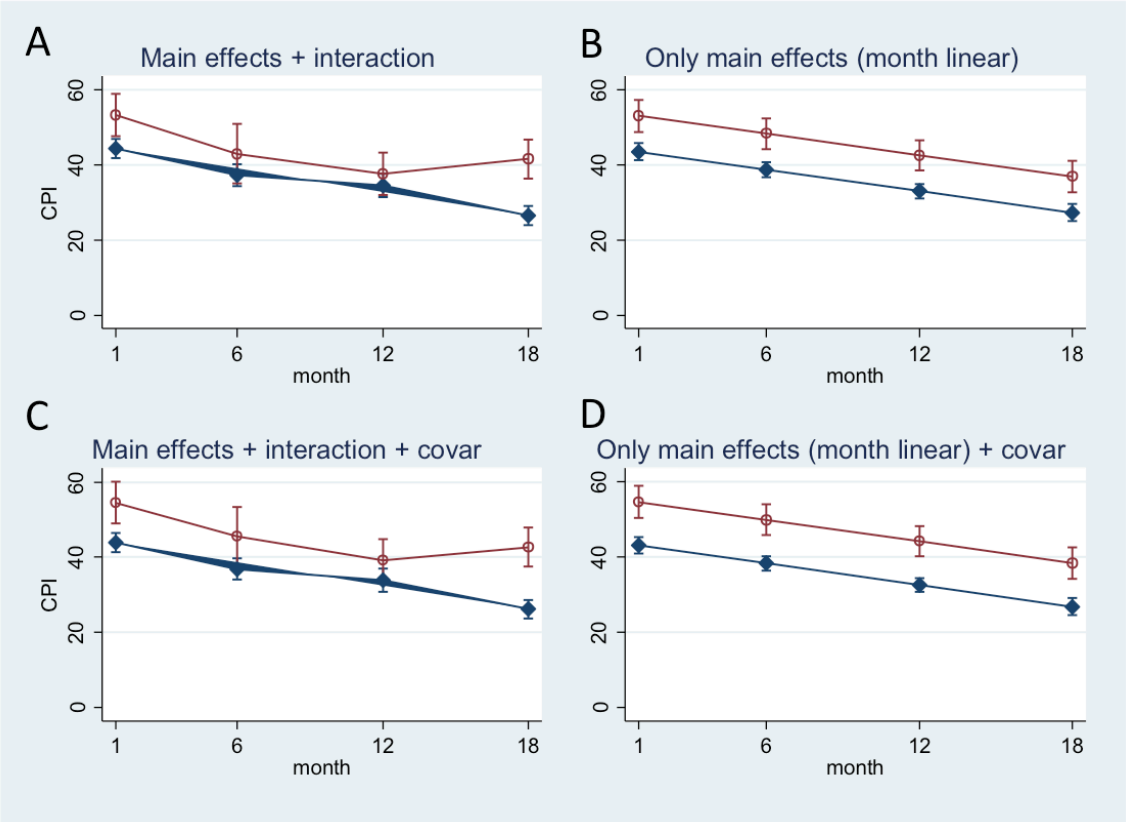


Figure 2: Graphic representation of the model predicted CPI differences showing best and alternative models.



Best model (C) shows a combination of main effects, interactions and covariates. The alternative model (D) shows only main effects with covariates.

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