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The Effect of Fibromyalgia and Widespread Pain on the Clinically Significant Temporomandibular Muscle and Joint Pain Disorders - A Prospective 18-Month Cohort Study

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Abstract

Although most cases of Temporomandibular Muscle and Joint Disorders (TMJD) are mild and self-limiting, about 10% of TMJD patients develop severe disorders associated with chronic pain and disability. It has been suggested that fibromyalgia and widespread pain play a significant role in the Temporomandibular Muscle and Joint Disorders (TMJD) chronicity. This paper assessed the effects of fibromyalgia and widespread pain on clinically significant TMJD pain (GCPS II-IV). Four hundred eighty-five participants recruited from the Minneapolis/St. Paul area through media advertisements and local dentists received examinations and completed the Graded Chronic Pain Scale (GCPS) at baseline and at 18th months. Baseline widespread pain (OR: 2.53, $P=0.04$) and depression (OR: 5.30, $P=0.005$) were associated with onset of clinically significant pain (GCPS II-IV) within 18 months after baseline. The risk associated with baseline fibromyalgia was moderate, but not significant (OR: 2.74, $P=0.09$). Persistence of clinically significant pain was related to fibromyalgia (OR: 2.48, $P=0.02$) and with depression (OR: 2.48, $P=0.02$). These results indicate that these centrally generated pain conditions play a role in the onset and persistence of clinically significant TMJD.

Keywords

Temporomandibular disorders; widespread pain; fibromyalgia; risk factors; chronic pain

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Perspective: Fibromyalgia and widespread pain should receive important consideration when evaluating and developing a treatment plan for patients with TMJD.

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Introduction

Temporomandibular Muscle and Joint Disorders (TMJD) pain are common, occurring in about 10% of the general population.¹⁶ Most TMJD symptoms are mild in nature, fluctuate over time, and do not constitute a disability to the patient.²⁸⁻³⁰ However, some subjects with TMJD pain will progress to chronic TMJD pain with a significant disability and impact on their life.²⁷

TMJD patients often report co-morbid pain conditions at sites other than the masticatory system.^{3, 9, 25} TMJD pain has been frequently reported or diagnosed among fibromyalgia subjects.^{14, 21, 22, 26} The coexistence of multiple pain conditions may explain why 50% of persons seeking care for TMJD pain still report pain 5 years later and 20% experience long-term disability.^{5,16}

The relationship between fibromyalgia or widespread pain and TMJD pain is not clear. Two prospective cohort studies of both adults³² and adolescents¹⁷ found that the presence of multiple pain conditions elsewhere in the body could predict the onset of TMJD pain within the next 3 years. It has been reported that widespread pain predicts the onset of dysfunctional TMJD pain among women but not its maintenance among either women or men.¹² Rammelsberg *et al.*,²⁴ however, observed that other body pains contributed to the persistence of masticatory myofascial pain.

The purpose of this cohort study was to determine the effect of baseline fibromyalgia and widespread pain without fibromyalgia on the onset and persistence of clinically significant pain (GCPS Grades II-IV) as classified by the Graded Chronic Pain Scale (GCPS).³¹

Methods

Study Design and Study Outcomes

In order to address the objectives of this study, we followed four steps:

First, this cohort study assessed the effect of fibromyalgia and widespread pain without fibromyalgia on: (i) the onset of clinically significant pain defined as moving from GCPS Grade I at baseline to grades II, III, or IV within 18 months after baseline; and (ii) the persistence of clinically significant pain defined as moving from Grade II at baseline to III or IV, or from Grade III to IV, or yet the persistence of the subjects in GCPS II, III or IV, over 18 months after baseline. Second, clinically significant pain was defined according to the GCPS Grades II-IV because these grades classify persons with intense pain commonly accompanied by clinically significant dysfunction.³¹ The GCPS is a measure of global pain severity and disability. Third, in order to assess the relative effect of these two types of risk exposure (i.e. fibromyalgia and widespread pain without fibromyalgia), subjects were recruited from a single cohort; as needed, matching the subjects according to the study methodology. Fourth, we evaluated if the risks related to fibromyalgia or widespread pain without fibromyalgia were modified by gender or depression. Determining the risk factors that predispose a person to developing more severe or disabling TMJD pain is important in providing counsel to patients and in implementing preventive interventions.

Study Population

With Institutional Review Board approval from the Human Subjects Research Protection Program of the University of Minnesota and informed written consent, 591 TMJD subjects were recruited from the Etiology study. This study was a prospective cohort study granted by the NIH/NIDCR DE09737-09) designed to determine which central and peripheral factors are

involved in the etiology of chronic dysfunctional TMD. The recruitment began on September 1, 1997 and ended on June 30, 2002.

The TMJD study population was recruited from the Minneapolis/St. Paul area through media advertisements and notices distributed to local dentists. The inclusion criteria for participation in this study required a diagnosis of any TMJD pain (muscle and/or joint pain) with pain frequency of at least once per week, and duration of at least 3 months. Subjects were excluded if they: 1) presented with systemic rheumatic disease other than fibromyalgia; 2) presented with dental, sinus, or other infection which could cause swelling or tenderness over the jaw area; 3) were taking prescribed steroids or narcotics for a chronic condition; 4) were taking antidepressants but had not been on a stable dose for at least the last 2 months; 5) presented with primary psychiatric disease; 6) reported prior temporomandibular joint (TMJ) surgery; 7) were unable to provide informed consent; 8) were over 65 years of age or under 18 years of age; 9) presented with scheduling problems that would interfere with follow-up (such as leaving town or a work schedule conflict); 10) reported consuming more than 3 alcoholic drinks per day; or 11) were pregnant. In addition, 19 (3%) out of 591 TMJD subjects, 7 (37%) with GCPS I and 12 (63%) with GCPS II-IV, had baseline missing data on fibromyalgia and could not be included in this study. Most of these 19 subjects were female ($n = 18$, 95%) and 3 (16%) presented moderate to severe levels of depression assessed by BDI.

Temporomandibular Disorders Pain Diagnosis at Baseline

The diagnosis of TMJD pain was determined by clinical examination using a modified Craniomandibular Index (CMI) wherein the CMI exam items were redesigned to conform precisely to those specified for the Research Diagnostic Criteria (RDC).⁶ The CMI/RDC examination, referred to by some as the Temporomandibular Index (TI), has been documented to have excellent intra- and interexaminer reliability and clinical validity.²⁰ The CMI/RDC examinations were performed by 1 of 2 calibrated examiners at the University of Minnesota Oral Health Research Center. Each subject's 18 month follow-up examination was performed by the same examiner who had performed the baseline exam.

Definition of Onset and Persistence of Clinically Significant Pain cohorts

To assess the effect of fibromyalgia and widespread pain without fibromyalgia on the onset and persistence of clinically significant pain (GCPS II-IV), TMJD pain subjects were grouped in two cohorts: (i) Onset cohort, that included TMJD pain subjects with clinically non-significant pain at baseline (low TMJD pain intensity GCPS I); and (ii) Persistence cohort, that included subjects with high TMJD pain intensity (GCPS II) or GCPS Grade III-IV disability at baseline.

The Graded Chronic Pain Scale (GCPS) instrument distinguishes pain levels as follows: low disability and low intensity pain (GCPS Grade I); low disability and high pain intensity (GCPS Grade II); or higher disability (GCPS Grades III-IV). It is scored based on the subject's responses to several items: 1) current; 2) worst; and 3) average pain intensity (0–10 numeric scales); 4) pain-related disability days (0–180), and pain-related interference with: 5) daily activities; 6) work; and 7) social or family activities (0–10 numeric).³¹ GCPS instrument was completed at baseline and at 18th months follow-up. Tables 1 and 2 describe scoring for the GCPS.

Assessment of Baseline Fibromyalgia and Widespread pain without Fibromyalgia as the Risk Factors for Onset and Persistence of TMJD Pain

For the diagnosis of fibromyalgia, subjects received a tender-point examination performed by a calibrated examiner at the University of Minnesota Oral Health Research Center. This procedure followed the criteria of the American College of Rheumatology.³⁴ A positive

diagnosis was based on findings of widespread pain in combination with tenderness at 11 or more of the 18 specific tender-point sites. Widespread pain was defined by a self-report of pain. This measure was assessed by one question of the Rheumatic Problems Questionnaire (Table 3): *Do you experience widespread bodily pain (on both your right and left sides as well as above and below the waist)?*

Assessment of Effect Modifiers relative to the Effects of Fibromyalgia and Widespread pain without Fibromyalgia

Potential effect modifiers of risk of onset or persistence of clinically significant pain were specified as gender and depression at baseline. Depression was assessed by the Beck Depression Inventory (BDI-II) ¹ at baseline. The scoring cutoffs for the Beck questionnaire are: 0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; and 29–63: severe depression. Higher total scores indicate more severe depressive symptoms.

Statistical Analysis

Chi-square, Fisher's exact test, ANOVA and Student's t-test were used to test statistical differences between categories of the TMJD subjects relative to their GCPS grades (GCPS I–IV), age, gender, fibromyalgia status, widespread pain, pain intensity, and depression.

An ordinal logistic regression model was used (PROC GENMOD, SAS) with multinomial outcome data to assess the predictors for the onset and persistence of clinically significant TMJD pain over an 18 month period. Two dependent variables were created to assess the two outcomes: onset variable with five levels: 0, I, II, III or IV according to the GCPS; persistence variable with three levels: (i) no clinically significant pain (e.g. GCPS 0 or I); (ii) persistence of clinically significant pain (e.g. GCPS II at baseline persisted at 18th month); and (iii) progression of clinically significant pain (e.g., GCPS II at baseline changed to GCPS III). Odds ratios (ORs) and their 95% confidence intervals (CI) were estimated in all analyses. For each study risk factor (i.e. fibromyalgia and widespread pain), interactions were created with gender and depression to determine whether these covariates modified the odds ratios associated with fibromyalgia and widespread pain. Interaction terms were retained in the model only if the significance level of their regression coefficient was equal to or lower than 0.10. Multivariable models were adjusted by depression, gender, age, worst pain intensity or GCPS at baseline when assessing the risk factors for the onset or persistence of clinically significant pain. Since the BDI scores for our subjects were not normally distributed, we assessed the odds ratio of the onset or progression of clinically significant TMJD pain based on the established scoring cutoffs for the Beck questionnaire-II.¹ The first crude logistic regression analyses showed that BDI scores of 14–19 (mild depression) were not associated with the onset (OR: 0.57, $P = 0.39$) or persistence of clinically significant TMJD pain (OR: 1.30, $P = 0.42$). Those with scores ranging from 20–28 (moderate depression) and from 29–63 (severe depression) were related to: (i) the onset (OR: 5.29, $P = 0.01$, OR: 12.37, $P = 0.02$, respectively) and (ii) persistence of clinically significant TMJD pain (OR: 3.08, $P = 0.02$, OR: 7.72, $P = 0.0004$, respectively). Based on these results, we collapsed the first two BDI categories (0–13 and 14–19) together since BDI scores of 14–19 were not shown to be related to TMJD pain. We also collapsed the remaining two BDI categories (20–28 and 29–63) together to include those subjects whose BDI scores were shown to be associated with TMJD pain. Pain intensity at baseline was assessed using the worst pain intensity (0–10NRS) scale, which is one of the components of the GCPS. The statistical importance of the putative confounders (i.e. depression, gender and age, worst pain intensity or GCPS at baseline) for all multivariable analyses was evaluated based on the change-of-estimate criterion that compares the difference between the adjusted and crude effects for a given factor, with the cutoff for an important change set at 10%. All analyses were performed using the statistical software package SAS (version 9.1, Cary, North Carolina, USA), with the probability of a type I error set at the 0.05 level.

Results

Description of Baseline Onset and Persistence Pain Cohorts

Table 4 shows the onset and persistence cohorts at baseline and their change in GCPS over the ensuing 18 months. At baseline, from 572 study subjects, 262 TMJD (46%) were included in the onset cohort (GCPS I, clinically non-significant pain) and 310 (54%) in the persistence cohort (GCPS II-IV, clinically significant pain).

Sixty (11%) of these 572 participants were positive for a coexisting fibromyalgia diagnosis based on the American College of Rheumatology criteria,³⁴ and 115 (20%) reported widespread pain without a diagnosis of fibromyalgia. Differences between subjects who presented with fibromyalgia, widespread pain without fibromyalgia, or none of these co-morbid conditions are shown in Tables 5 and 6. Females, older subjects, and those with moderate to severe levels of depression, were more likely to test positive for fibromyalgia or widespread pain than subjects without these co-morbid conditions.

Comparing the distribution of risk factors and covariates between the onset (Table 5) and the persistence cohorts (Table 6), subjects with baseline fibromyalgia ($P = 0.02$), widespread pain without fibromyalgia ($P = 0.04$), with moderate to severe depression ($P = 0.008$), severe worst pain (0-10 NRS) intensity ($P = 0.0001$), or who were female ($P = 0.02$) were more likely to be in the persistence cohort (GCPS II-IV) than in the onset cohort (GCPS I). These differences remained, even if weaker, when comparing these pain cohorts for subjects that completed the 18 month follow-up (Tables 7 and 8): fibromyalgia ($P = 0.06$), widespread pain without fibromyalgia ($P = 0.10$), moderate to severe depression ($P = 0.02$), worst pain (0-10 NRS) intensity ($P = 0.0001$) and females ($P = 0.06$). No statistically significant differences were found on the mean age between the two cohorts including 572 subjects ($P = 0.49$) or only those that completed the 18 month follow-up ($P = 0.34$).

Predictors of Onset of Clinically Significant TMJD Pain

There was an 11% incidence of clinically significant pain (GCPS Grades II-IV) among the 262 subjects. This included 26 (10%) and 3 (1%) subjects who moved to Grade II and to Grade III, respectively. The mean age of the 262 subjects in the onset pain cohort at baseline (Grade I) was 36.29 ± 12.51 years (SD), and their worst pain (0-10 NRS) intensity reported at baseline averaged 5.09 ± 1.79 . Most of the subjects in this cohort were female (84%); 7% received the diagnosis of fibromyalgia, 16% reported widespread pain with no diagnosis of fibromyalgia, and their prevalence of moderate to severe depression was 7% (Table 5).

Table 7 shows the distribution of the risk factors and covariates at baseline among 232 onset cohort subjects (GCPS I clinically non-significant pain) who presented at the 18 month follow-up visit. The mean age of the 232 subjects was 36.53 ± 12.65 years (SD, $P = 0.81$), and their worst pain (0-10 NRS) intensity reported at baseline averaged 5.02 ± 1.79 ($P = 0.63$). Within 18 months after baseline, the 29 subjects who changed to a clinically significant pain (GCPS II-IV) tested positive for fibromyalgia, widespread pain without fibromyalgia and depression more frequently than those who remained without clinically significant pain. No statistically significant differences were found on the distribution of risk factors and covariates between the 262 subjects at baseline (Table 5) and those 232 who were present at the 18 month follow-up: fibromyalgia (8%, $P = 0.70$), widespread pain without fibromyalgia (17%, $P = 0.81$), females (85%, $P = 0.86$), and moderate to severe depression (7%, $P = 0.86$) (Table 7).

Based on the findings for the onset pain cohort, subjects with fibromyalgia presented a high risk for onset of clinically significant pain (GCPS Grades II-IV) within the 18 months following the baseline (crude OR: 3.27, $P = 0.04$). When this crude analysis was adjusted for widespread pain, depression, pain intensity at baseline, age, and gender, the fibromyalgia risk remained

positive, but not significant (OR: 2.74, $P = 0.09$). Widespread pain was associated with the onset of clinically significant pain (GCPS Grades II-IV) within the 18 months following the baseline, in the crude (OR: 3.08, $P = 0.009$) and in the adjusted analysis (OR: 2.53, $P = 0.04$) in the adjusted analysis. All widespread pain, with or without fibromyalgia, was related to the onset of clinically significant pain within 18 months after baseline, in the crude (OR: 3.14, 95% CI: 1.50-6.57, $P = 0.002$) and multivariable analyses (OR: 2.29, 95% CI: 1.03-5.09, $P = 0.04$). Moderate to severe depression was related to the onset of clinically significant pain (OR: 5.30, $P = 0.0005$). No significant associations were found between the onset of clinically significant pain and age, gender, or worst pain intensity at baseline (Table 9). No significant interactions were found between depression and fibromyalgia ($P = 0.26$) or widespread pain ($P = 0.80$).

Predictors of Persistence of Clinically Significant TMJD Pain

Of the persistence baseline cohort ($n = 310$), 9 subjects presented a progression from Grade II to III, 3 subjects progression from II to IV and 1 subject changed from Grade III to IV. The proportion of subjects progressing to Grades III or IV was not common (4%). The majority of the subjects presented a decrease to clinically non-significant pain (GCPS I) or showed no change (Table 4).

Most of the 310 subjects in this cohort were females (95%); their mean age was 35.58 ± 12.48 (SD). The mean worst pain intensity reported at baseline was 8.32 ± 1.28 (0-10 NRS), 13% received a diagnosis of fibromyalgia, 23% reported widespread pain without fibromyalgia, and 13% reported moderate to severe depression (Table 6).

At 18 months follow-up, subjects who persisted with clinically significant pain (GCPS II-IV) classification presented with fibromyalgia, widespread pain without fibromyalgia, and depression more frequently than those who remained without clinically significant pain (Table 8). The characteristics are similar between the 310 baseline subjects (Table 6) and the 253 that completed the 18 month follow-up (Table 8): fibromyalgia (13%, $P = 0.94$); widespread pain without fibromyalgia (23%, $P = 0.98$); females (91%, $P = 0.85$); and those with moderate to severe depression (13%, $P = 0.94$). The mean age of the 253 subjects was 35.47 ± 12.49 years (SD, $P = 0.92$), and their worst pain (0-10 NRS) intensity reported at baseline averaged 8.29 ± 1.29 ($P = 0.81$).

Based on this cohort (GCPS II-IV), fibromyalgia in the Grade II-IV subgroup was associated with persistence of clinically significant pain within 18 months after baseline, in multivariable (OR: 2.48, $P = 0.02$) and crude analyses (OR: 2.49, $P = 0.01$). Table 10 shows that in multivariable analysis, moderate to severe depression (OR: 2.48, $P = 0.02$) but not age (OR: 0.98, $P = 0.12$) or gender (OR: 1.94, $P = 0.15$) was related to the persistence of clinically significant pain. In addition, it was found a borderline significant interaction between fibromyalgia and depression ($P = 0.13$). No significant association with widespread pain was noted in the crude (OR: 1.78, $P = 0.06$) or multivariable analyses (OR: 1.67, $P = 0.11$, Table 10). However, widespread pain with or without fibromyalgia, was related to the persistence of clinically significant pain within 18 months after baseline, in the crude (OR: 1.91, 95% CI: 1.17-3.12, $P = 0.01$) and multivariable analyses (OR: 1.73, 95% CI: 1.02-2.92, $P = 0.04$).

Dropout

Four hundred eight five (85%) of the 572 subjects completed the 18 month follow-up visit. The majority of the characteristics of those 87 subjects that dropped out are similar to those that remained in the study. Most of them were females ($n = 77$, 89%, $P = 0.86$), the mean age was 35.40 ± 12.16 (SD, $P = 0.68$), 9% reported moderate to severe depression ($n = 8$, $P = 0.75$), 18% had widespread pain ($n = 16$, $P = 0.57$), and 8% received a diagnosis of

fibromyalgia ($n = 7$, $P = 0.37$). The mean worst pain intensity, however, was significantly different (7.49 ± 2.03 (0-10 NRS, $P = 0.003$). The dropout rate was higher among GCPS IV ($n = 8/23$, 35%) than among GCPS III ($n = 9/48$, 19%), II ($n = 40/239$, 18%) and GCPS I ($n = 30/262$, 12%, Table 4). There is a statistically significant difference on the GCPS distribution ($P = 0.01$) between subjects that remained in the study ($n = 485$) and those that dropped out ($n = 87$): 8 (9%) subjects from GCPS IV dropped out of the study and 15 (3%) GCPS IV remained.

Discussion

This prospective cohort study showed an increased risk for the onset of clinically significant TMJD pain, when subjects were exposed to fibromyalgia or widespread pain. In addition, we found that fibromyalgia, but not widespread pain predicted the persistence of clinically significant pain. The borderline statistically significant interaction between fibromyalgia and depression found in our study suggests that fibromyalgia related risk of persistence of clinically significant pain is modified by depression. Our results partially agree with John *et al.*¹² who found that widespread pain was related to onset of dysfunctional TMJD pain (GCPS II-IV), but only among females. They also found a weak and not statistically significant association between report of widespread pain and persistence of dysfunctional TMJD pain. Furthermore, the findings between fibromyalgia and the increased risk for the onset of clinically significant TMJD pain may be interpreted with caution because of the lack of statistical significance.

A specific mechanism to explain these estimated risks has not been identified. Wessely *et al.*³³ proposed using a centrally generated “functional somatic syndrome model” to explain these overlapping conditions. Stress was hypothesized to predispose persons to amplification of somatic symptoms. In our study, we found that the amplification of pain symptoms from mild to moderate or severe pain and disability (Grades II-IV) within 18 months after baseline, was associated with fibromyalgia, widespread pain, and depression at baseline. We do not have an explanation why only fibromyalgia and not widespread pain contributed to the persistence of severe pain and disability symptoms. Possibly other mechanisms related to a dysregulation of pain modulatory systems involving the central (CNS), peripheral nervous and the immune systems related to fibromyalgia could explain our results.^{2, 4, 11, 13, 18, 23}

In addition, it has been suggested that the mechanistic similarities between co-morbidities such as chronic low-back pain, chronic fatigue syndrome, and post-traumatic stress disorder are associated with brain atrophy.¹⁵ Kuchinad *et al.*¹⁵ noted that subjects with fibromyalgia had higher risk of age-associated decrease in gray matter than healthy controls. The longer the individuals had fibromyalgia the greater was their gray matter loss. In our study, the risks of fibromyalgia or widespread pain were not modified by age, and age did not predict the amplification of the symptoms either. Our results suggest that duration exposed to fibromyalgia or widespread pain did not increase the co-morbidity risk for the onset and persistence of clinically significant TMJD pain.

This study has several clinical implications. This study found that fibromyalgia and widespread pain both constitute factors that will complicate management of TMJD and thus, need to be considered in both evaluation and management of TMJD. Treatment of TMJD can range from simple cases with transient mild pain to complex cases involving widespread pain and interrelating co-morbid conditions including the presence of fibromyalgia and widespread pain. Simple cases with no co-morbid conditions, and minimal behavioral and psychosocial involvement can typically be managed by a single clinician with single treatments. However, the difficulty in management of complex cases of TMJD lies in the critical need to match the level of complexity of the management program with the complexity of the patient. The difficulty in long-term management often lies in the complex task of changing the patient's attitudes, lifestyle, and social and physical environment integrally related to the pain. Failure

to identify and address the entire problem, including all areas of pain, co-morbid conditions including fibromyalgia, and other contributing factors may lead to failure to improve the pain, improve function, and perpetuation of the problem. Evaluation of TMJD patients using a rheumatic conditions questionnaire can help identify these co-morbid risk factors (Table 3). Once identified, complex TMD patients, particularly those who also have co-morbid conditions can best be managed within an interdisciplinary pain clinic setting that uses a team of clinicians to address different aspects of the problem in a concerted fashion.

Our study has a number of limitations. First, widespread pain was assessed by one question on the Rheumatic Problems Questionnaire, "Do you experience widespread bodily pain (on both your right and left sides as well as above and below the waist)?" This question did not include pain specific to the axial skeleton. This omission may increase the chance of non differential fibromyalgia misclassification because the error in the classification of fibromyalgia in this prospective study should be independent of TMJD pain classification. This non differential misclassification assumption is based on the study methodology: (i) Fibromyalgia diagnosis was performed at baseline, 18 months before the TMJD pain classification on the onset or persistence of clinically significant TMJD pain; and (ii) TMJD pain classification was based on the Graded Chronic Pain Scale (GCPS) instrument completed by the patient. Consequently, the calibrated examiners at the University of Minnesota Oral Health Research Center who performed the tender-point examinations were unaware of the TMJD pain classification at baseline. Second, the relationship between fibromyalgia and widespread pain with clinically significant TMJD pain may be biased by unmeasured confounding variables. Third, we could not establish whether either widespread pain or fibromyalgia increased the risk for the onset of TMJD, because all of the subjects had TMJD pain (at least GCPS Grade I) at baseline as specified in the inclusion criteria. Therefore, we could not evaluate the study of Hedenberg-Magnusson *et al.*¹⁰ which suggests that fibromyalgia is one of the causes of TMJD. Fourth, a non differential measurement error on self-report of widespread pain may explain the lack of association between widespread pain and the persistence of clinically significant pain. Fifth, since 85% of the subjects completed the 18 month follow-up visit there is a low possibility for selection bias. Since the participants who completed the study were generally similar, with the exception that responders were less likely to be those with disabilities (GCPS IV), the effects of selection bias are not likely to be substantial. This lower prevalence of GCPS IV subjects who completed the study may lead to underestimation of the risk due to a lower exposure in the responders.

Our study methodology has several strengths. First, we able to estimate the risk for the onset and persistence of TMJD pain when subjects are exposed to either fibromyalgia or to widespread pain without defined fibromyalgia, in the same cohort of patients. This is essential for comparing the relative strength of the risk of these different definitions of chronic pain. Second, we estimated the study risk factors for the onset and persistence of clinically significant TMJD pain prospectively. Using this study design, it is almost certain that risk factors (e.g., fibromyalgia) or GCPS misclassifications are non differential and would attenuate estimates of association. Third, the prevalence of TMJD pain with disability at baseline was similar to that noted by John *et al.* (2003).¹² The frequencies of fibromyalgia and widespread pain in our study were lower than those noted in other studies.^{12, 22, 25, 29} These lower prevalences suggest that the participants were not over reporting widespread pain, which would decrease the chance of a differential bias in the risk estimate. Fourth, we assessed whether the risks associated with fibromyalgia and widespread pain would be modified by depression or gender, the latter especially in view of the gender differences in pain physiology and clinical outcomes.^{7, 8, 19}

In conclusion, the current study demonstrated that fibromyalgia was associated with the onset as well as persistence of clinically significant pain to a more severe condition. Widespread pain

was related to the onset, but not with the persistence of clinically significant TMJD pain. This study supports the hypothesis that states that clinically significant TMJD pain has centrally generated mechanisms related to fibromyalgia and widespread pain. TMJD pain, widespread pain and fibromyalgia may have overlapping peripheral and central mechanisms of pain. Understanding the interrelationships between TMJD, fibromyalgia, and widespread pain will lead to better management of these patients.

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Table 1
Description of Graded Chronic Pain Scale (GCPS)

Graded Chronic Pain	Grade	Pain Intensity (0-100) ^a	Disability level (points) ^b
Normal	Grade 0	None	None
Low intensity pain	Grade I	Low (<50)	Low (< 3 points)
High pain intensity	Grade II	High (≥50)	Low (< 3 points)
Moderate Disability	Grade III	Low or High	Moderately limiting (3-4 points)
High Disability	Grade IV	Low or High	Severely limiting (5-6 points)

^aNote: Pain Intensity (0-10) = mean (pain now, worst pain, average pain) × 10;

^bDisability Level (0-6 points) = disability days (0-3 points) + disability score (0-3 points) (see Table 2)

Table 2
Description for Disability Points Scores

Disability Days (0-180)	Points	Disability Score (0-100)	Points
0-6 days	0 points	0-29	0 points
7-14 days	1 point	30-49	1 point
15-30 days	2 points	50-69	2 points
31+ days	3 points	70+	3 points

Note: Disability Score (0-100) = Mean (daily activities, social activities, work activities) $\times$ 10

Table 3

Rheumatic Problems Questionnaire

1.	Do you experience widespread bodily pain (on both your right and left sides as well as above and below the waist)?	A.	Yes	
		B.	No	
Joint Problems				
2.	Have you experienced any of the following joint problems during the last five years?			
Temporomandibular Joints (right TMJ, left TMJ or both):				
	Pain	A.	Yes	B No
	Swelling	A.	Yes	B No
	Limited Movement	A.	Yes	B No
	Stiffness	A.	Yes	B No
Other Joints:				
	Pain	A.	Yes	B No
	Swelling	A.	Yes	B No
	Limited Movement	A.	Yes	B No
	Stiffness	A.	Yes	B No
Muscle Problems				
3.	Have you experienced the following problems in more than one of your muscles during the last five years?			
	Pain	A.	Yes	B No
	Weakness	A.	Yes	B No
4.	Do you experience morning stiffness or arising which lingers more than 1 hour?			
		A.	Yes	
		B.	No	
5.	Do you feel fatigue more easily than normal?			
	Sun sensitive rash	A.	Yes	B No
	Pain with breathing	A.	Yes	B No
	Seizures	A.	Yes	B No
	Tight skin	A.	Yes	B No
	Dry eyes or mouth	A.	Yes	B No
6.	Have you been diagnosed in the last five years as having any of the following arthritic or rheumatic problems?			
		A.	Yes	B No
	Rheumatoid arthritis	A.	Yes	B No

B.	Systemic lupus erythematosus	A.	Yes	B	No
C.	Polymyositis	A.	Yes	B	No
D.	Sjogren's syndrome	A.	Yes	B	No
E.	Scleroderma	A.	Yes	B	No
F.	Arthritis associated with spondylitis	A.	Yes	B	No
G.	Arthritis associated infectious diseases	A.	Yes	B	No
H.	Gouty arthritis (gout)	A.	Yes	B	No
I.	Osteoarthritis (osteoarthritis, degenerative joint disease)	A.	Yes	B	No
J.	Rheumatism associated with disorders such as diabetes, liver or thyroid disease	A.	Yes	B	No
K.	Osteoporosis	A.	Yes	B	No
L.	Fibrositis, fibromyalgia	A.	Yes	B	No
M.	Myofascial pain syndrome	A.	Yes	B	No
Other		A.	Yes	B	No
None		A.	Yes		

7. Are you presently being treated by a physician for any medical problems?

- A. Yes
B. No

8. How many aspirin or other analgesic/anti-inflammatory tablets do you take per day for pain?

Table 4
Distribution of GCPS Grades at Baseline and at 18th Month Follow-up

Cohorts	Distribution of subjects (%)							
	GCPS at baseline	GCPS at 18 months baseline					Total	
		0	I	II	III	IV		
Onset	GCPS I, n (%)	262 (46)	17 (7)	186 (80)	26 (11)	3 (1)	0	232 (48)
Persistence	GCPS II, n (%)	239 (42)	9 (5)	97 (49)	81 (41)	9 (5)	3 (2)	199 (41)
	GCPS III, n (%)	48 (8)	1 (3)	18 (46)	14 (36)	5 (13)	1 (3)	39 (8)
	GCPS IV, n (%)	23 (4)	1 (7)	2 (13)	4 (27)	6 (40)	2 (13)	15 (3)
Total	GCPS I-IV, n (%)	572 (100)	28 (6)	303 (63)	125 (26)	23 (5)	6 (1)	485 (100)

Table 5
Differences between co-morbid and non co-morbid cohorts at baseline among 262 TMJD pain subjects with GCPS I

Onset cohort (GCPS I, clinically non-significant pain)						
n = 262						
Covariates	Non co-morbid	Widespread pain	Fibromyalgia	Total	P-value	
	n (%)	n (%)	n (%)	n (%)	a, b *	a, c **
Moderate-severe depression, n (%) (BDI: 20-63)	7 (4)	7 (16)	3 (16)	17 (7)	0.001	0.01
Female, n (%)	163 (82)	39 (91)	19 (100)	221 (84%)	0.14	0.05
Mean (SD) age, years	35.04 (12.29)	39.42 (12.22)	42.37 (13.06)	36.29 (12.51)	0.04	0.01
Mean (SD) worst pain intensity (0-10 NRS)	5.05 (1.76)	5.05 (1.83)	5.68 (1.70)	5.09 (1.79)	0.99	0.14
Total, n (%)	200 (76)	43 (16)	19 (7)	Not applicable		

* Note: widespread pain compared to non co-morbid

** fibromyalgia compared to non co-morbid

Table 6
Differences between co-morbid and non co-morbid cohorts at baseline among 310 TMJD pain subjects with GCPS II-IV at baseline

Persistence cohort (GCPS II-IV, clinically significant pain)						
n = 310						
Covariates	Non co-morbid	Widespread pain	Fibromyalgia	Total	P-value	
	n (%)	n (%)	n (%)	n (%)	a, b *	a, c **
Moderate-severe depression, n (%) (BDI: 20-63)	14 (7)	18 (25)	9 (22)	41 (13)	<.0001	0.003
Female, n (%)	179 (91)	64 (89)	39 (95)	282 (95)	0.63	0.37
Mean (SD) age, years	33.46 (11.72)	38.17 (13.37)	41.19 (12.07)	35.58 (12.48)	0.005	0.0002
Mean (SD) worst pain intensity (0-10 NRS)	8.32 (1.23)	8.29 (1.34)	8.39 (1.45)	8.32 (1.28)	0.90	0.73
Total, n (%)	197 (64)	72 (23)	41 (13)	Not applicable		

* Note: widespread pain compared to non co-morbid

** fibromyalgia compared to non co-morbid

Table 7
Baseline profile of the onset cohort among 232 GCPS I subjects who completed the 18 month follow-up visit

Risk factors and covariates	Onset cohort				
	GCPS at baseline	GCPS at 18 th month follow-up			
	I	0	I	II	III
Fibromyalgia, n (%)	19 (8)	0 (0)	15 (8)	3 (12)	1 (33)
Widespread pain, n (%)	40 (17)	1 (6)	30 (16)	8 (31)	1 (33)
Moderate-severe depression, n (%) (BDI: 20-63)	16 (7)	0 (0)	10 (5)	3 (12)	3 (100)
Female, n (%)	197 (85)	14 (82)	159 (86)	22 (85)	2 (67)
Mean (SD) age, years	36.53 (12.65)	39.70 (13.38)	35.91 (12.24)	38.84 (14.92)	39.66 (14.01)
Mean worst pain intensity (SD)	5.02 (1.79)	4.88 (2.12)	4.92 (1.79)	5.84 (1.38)	4.86 (2.31)
Total, n (%)	232 (100)	17 (7)	186 (81)	26 (11)	3 (1)

Table 8
Baseline profile of the persistence cohort among 253 GCPS II-IV subjects who completed the 18 month follow-up visit

Risk factors and covariates	Persistence Cohort				
	GCPS at baseline	GCPS at 18 th month follow-up			
	II-IV	0	I	II	III-IV
Fibromyalgia, n (%)	34 (13)	1 (9)	10 (9)	20 (20)	3 (11)
Widespread pain, n (%)	59 (23)	3 (27)	24 (21)	20 (20)	12 (46)
Moderate-severe depression, n (%) (BDI: 20-63)	34 (13)	1 (9)	9 (8)	13 (13)	11 (70)
Female, n (%)	229 (91)	9 (82)	104 (89)	92 (93)	24 (92)
Mean (SD) age, years	35.47 (12.49)	39.0 (11.48)	36.32 (13.36)	33.95 (11.49)	34.10 (10.47)
Mean worst pain intensity (SD)	8.29 (1.29)	8.27 (1.0)	7.92 (1.27)	8.65 (1.22)	8.50 (1.49)
Total, n (%)	253 (100)	11 (4)	117 (46)	99 (39)	26 (10)

Table 9
Crude and multivariable logistic regression analyses assessing the predictors of the onset of clinically significant pain (GCPS II-IV) from the onset cohort (GCPS I, n = 232)

Risk factors and covariates at baseline	Model 1			Model 2		
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Fibromyalgia	No	1 (reference)	1 (reference)		1 (reference)	
	Yes	3.27 (1.08-9.90)	0.04		2.74 (0.86-8.80)	0.09
Widespread pain	No	1 (reference)			1 (reference)	
	Yes	3.08 (1.33-7.12)	0.0009		2.53 (1.05-6.08)	0.04
Depression	No-mild	1 (reference)			1 (reference)	
	Moderate-Severe	6.79 (2.24-20.56)	0.0007		5.30 (1.67-16.81)	0.005
Gender	Male	1 (reference)			1 (reference)	
	Female	0.94 (0.38-2.32)	0.91		0.71 (0.27-1.85)	0.49
Mean age	Years	1.00 (0.98 to 1.03)	0.82		1.00 (0.97-1.03)	0.75
Mean worst pain intensity	0-10 NRS	1.19 (0.99-1.43)	0.06		1.19 (0.98-1.44)	0.07

Note: Model1: Crude analyses for each risk factors and covariates; Model 2: Multivariable analysis including all risk factors and covariates in only one model.

Table 10
Crude and multivariable logistic regression analyses assessing the predictors of the persistence of clinically significant pain GCPS (II-IV) from the persistence pain cohort (GCPS II-IV, n = 253)

Risk factors and covariates at baseline	Model 1			Model 2		
		OR (95% CI)	P-value	OR (95% CI)	P-value	P-value
Fibromyalgia	No	1 (reference)		1 (reference)		
	Yes	2.49 (1.21-5.13)	0.01	2.48 (1.16-5.29)		0.02
Widespread pain	No	1 (reference)		1 (reference)		
	Yes	1.78 (0.98-3.24)	0.06	1.67 (0.89-3.14)		0.11
Depression	No-mild	1 (reference)		1 (reference)		
	Moderate-Severe	4.17 (1.99-8.72)	0.0002	2.48 (1.13-5.47)		0.02
	Male	1 (reference)		1 (reference)		
Gender	Female	1.81 (0.77-4.24)	0.17	1.94 (0.79- 4.74)		0.15
	Years	0.99 (0.97-1.00)	0.27	0.98 (0.96-1.01)		0.12
Mean age	II-III	2.42 (0.79-7.49)	0.12	2.06 (0.64-6.59)		0.22
	II-IV	2.69 (1.0-7.22)	0.05	2.07 (0.73-5.28)		0.17
	III-IV	1.11 (0.57-2.15)	0.77	1.01 (0.50-2.02)		0.12

Note: Model1: Crude analyses for each risk factors and covariates; Model 2: Multivariable analysis including all risk factors and covariates in only one model.