Are Post-traumatic Stress Disorder Symptoms and Temporomandibular Pain Associated? Findings from a Community-Based Twin Registry

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Portions of this research were presented at the First Annual National Institutes of Health Pain Consortium Symposium, Bethesda, Maryland, April 2006.

Aims: *To determine whether symptoms of post-traumatic stress disorder (PTSD) are related to the pain of temporomandibular disorders (TMD) in a community-based sample of female twin pairs, and if so, to ascertain whether the association is due to the presence of chronic widespread pain (CWP) and familial/genetic factors.* ***Methods:*** *Data were obtained from 630 monozygotic and 239 dizygotic female twin pairs participating in the University of Washington Twin Registry. PTSD symptoms were assessed with the Impact of Events Scale (IES), with scores partitioned into terciles. TMD pain was assessed with a question about persistent or recurrent pain in the face, jaw, temple; in front of the ear; or in the ear during the past 3 months. CWP was defined as pain located in 3 body regions during the past 3 months. Random-effects regression models, adjusted for demographic features, depression, CWP, and familial/genetic factors, were used to examine the relationship between the IES and TMD pain.* ***Results:*** *IES scores were significantly associated with TMD pain (*$P < .01$*). Twins in the highest IES tercile were almost 3 times more likely than those in the lowest tercile to report TMD pain, even after controlling for demographic factors, depression, and CWP. After adjustment for familial and genetic factors, the association of IES scores with TMD pain remained significant in dizygotic twins (*$P_{trend} = .03$*) but was not significant in monozygotic twins (*$P_{trend} = .30$*).* ***Conclusion:*** *PTSD symptoms are strongly linked to TMD pain. This association could be partially explained by genetic vulnerability to both conditions but is not related to the presence of CWP. Future research is needed to understand the temporal association of PTSD and TMD pain and the genetic and physiological underpinnings of this relationship.* J OROFAC PAIN 2008;22:41–49

Key words: chronic widespread pain, genetic factors, post-traumatic stress disorder, temporomandibular disorder, twins

Temporomandibular disorders (TMD) are a group of conditions characterized by signs and symptoms of the muscles of mastication, temporomandibular joint, and related structures. Chronic pain is the most common symptom of TMD and the primary reason for seeking treatment. TMD are the most frequent diagnoses among patients with chronic orofacial pain problems.[1] The estimated prevalence of painful TMD is 10% to 12%, and the conditions affect predominantly young women.[2–4] TMD also share characteristics with other types of chronic pain, including behavioral and psychosocial dysfunction.[5] Further, the chronic regional pain associated with TMD may become general-

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ized and extend beyond the facial region.[6–8] In these cases, patients may experience chronic widespread pain (CWP) and fibromyalgia, a common form of nonarticular rheumatism characterized by diffuse musculoskeletal pain and tender points on examination.[9] Several studies have documented the high comorbidity of TMD pain and CWP or fibromyalgia.[10–15]

Although the etiology and pathophysiology of TMD pain are likely multifactorial, there is a substantial body of literature on the relationship between TMD symptoms, specifically TMD pain, and psychosocial factors.[16,17] Several studies have focused on the prevalence of stressful life events in TMD patients.[18–24] For example, in a recent study of 1,221 patients with chronic TMD pain conditions, close to 50% reported having experienced at least 1 traumatic stressor.[20] Several studies also have reported that patients with TMD pain conditions exhibit the symptoms of post-traumatic stress disorder (PTSD), a psychiatric condition that requires exposure to a traumatic event.[18,21,23,24] For example, PTSD appears to be the second most common psychiatric diagnosis among chronic orofacial pain patients after depression.[18] Likewise, the association between PTSD, CWP, and fibromyalgia is well-documented in clinical as well as community samples.[25–30]

Taken together, these previous studies suggest substantial comorbidity between TMD pain and traumatic stressors or PTSD in clinic-based or tertiary care patient samples, which may be biased by issues of clinical ascertainment from a treatment-seeking population. Additionally, no studies to date have addressed whether the association of PTSD with TMD could be partially explained by the coexistence of TMD with CWP and fibromyalgia. The aim of the present study was to determine whether symptoms of PTSD were related to TMD pain in a community-based sample of female twin pairs and, if so, to ascertain whether the association was due to the presence of CWP and familial/genetic factors.

Materials and Methods

Sample

The University of Washington Twin Registry is a community-based sample of twins derived from the drivers' license applications of the Washington State Department of Licensing. In Washington, drivers' license numbers are derived from a person's name and date of birth; thus, the Department of Licensing asks every new applicant if he or she is a twin to avoid issuing duplicate license and identification numbers to twins. Because state agencies in Washington are permitted by law to share data, the Department of Licensing has provided a list of all new drivers' license applicants who are twins to the University of Washington since 1998. Upon receiving the names from the Department of Licensing, the University of Washington Twin Registry staff sends each twin an invitation to join, a brief survey to complete, and an incentive. If the twin does not respond within 1 month, a second invitation and survey are mailed. The co-twin is mailed a survey using contact information provided by the index twin. Full details of the construction and characteristics of the University of Washington Twin Registry are described elsewhere.[31] The University of Washington Human Subjects Review Committee approved the procedures for establishing the twin registry and all data collection involved in this study. Informed consent was obtained from all participants. Because TMD and CWP disproportionately affect women, the present analyses were limited to female twins.

Survey

The brief survey contains items on demographics; symptoms; physician-diagnosed health conditions such as depression, PTSD, and TMD; habits; health-care use; and various abridged, standardized measures of physical and mental health.

Zygosity Assignment. As part of the mailed questionnaire, all twins were asked questions about childhood similarity to assess zygosity. Studies in both US and Scandinavian twin registries have repeatedly demonstrated that questions about childhood similarity in twin pairs can be used to correctly classify zygosity with an accuracy of 95% to 98% compared with zygosity determined by biologic indicators.[32–35] Responses to these similarity questions were used in a multi-step process to assign zygosity, which identified 738 monozygotic (MZ) and 296 dizygotic (DZ) female twin pairs eligible for the current study.

Sociodemographic Factors and Clinical Conditions. Sociodemographic factors collected in the survey included age, gender, race, education, and marital status. One question inquired about diagnosis of depression. Questions about CWP were adapted from the self-report form of the London Fibromyalgia Epidemiology Study Screening Questionnaire.[36] The CWP questions were similar to those administered by mail and telephone in several European population-based

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studies conducted to ascertain the prevalence of chronic pain.[37–41] Twins were asked about body pain in 3 regions: *(1)* shoulders, arms, or hands; *(2)* legs or feet; and *(3)* neck, chest, or back. For each region, information was obtained on whether the pain lasted at least 1 week during the past 3 months. CWP was defined as pain experienced in all 3 regions.

PTSD. PTSD occurs when an overwhelming traumatic event results in intense fear, helplessness, horror, intrusive thoughts, and avoidance of stimuli associated with the trauma.[42] PTSD symptoms were identified using the Impact of Events Scale (IES), which assesses current distress resulting from a stressful life event.[43] The IES captures qualities of conscious experiences that encompass stressful life events, such as bereavement or personal injuries from accidents, violence, illness, or surgery.[43] In previous studies, the IES was strongly correlated with a diagnosis of PTSD,[44] even though the IES measures only the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) intrusion and avoidance symptom criteria for PTSD.[42] As a screening measure for PTSD, the sensitivity of the IES ranges from 0.94 to 1.00, and the specificity ranges from 0.78 to 0.84.[45]

Eleven of the 15 IES items were used; the 4 items that correlated most poorly with the IES intrusion and avoidance subscales in the cluster analysis conducted by the developers of the IES were deleted.[43] Internal reliability of the IES was assessed using Cronbach's alpha, and validity was evaluated by its concordance with a self-report of PTSD diagnosed by a physician. For the 11 IES items used in this analysis, the Cronbach's alpha was 0.90, indicating a high degree of internal consistency. Likewise, the validity of the IES was demonstrated by a significant trend based on a simple logistic regression between the terciles of the IES score and a doctor diagnosis of PTSD ($\beta = 0.06$, $P < .001$).

Each IES item has 4 response categories, and values are summed to create an overall score (range, 0 to 55). The scores were grouped into terciles representing increasing levels of current distress: 0 to 10 (lowest distress), 11 to 27 (moderate distress), and 28 or more (highest distress). Only twins who answered at least 6 of the 11 IES items were included. Missing values were imputed using the respondent's average score across completed items and published methods.[46]

Temporomandibular Pain. The survey included a question derived from the Life Pain Questionnaire, which was developed by researchers to screen for common chronic pain conditions such as TMD and headaches.[2] Twins were asked about TMD pain as follows: "In the past 3 months, have you had persistent or recurrent pain in the face, jaw, temple, in front of the ear, or in the ear?" This question has been validated and successfully used by other investigators to screen for TMD. The calculated sensitivity for a diagnosis of TMD ranges from 89% to 100%; specificity ranges from 37% to 69%.[47,48] In the twin sample, there was a modest association between the TMD pain question and a self-reported doctor diagnosis of TMD (kappa = 0.22).

Statistical Analysis

Descriptive analyses examined the distribution of sociodemographic factors, depression, CWP, and IES scores according to TMD pain status. The difference across TMD pain status of these variables was statistically examined with a chi-square test for proportions or a *t* test for means. To investigate the association of the IES with TMD pain, a random-effects model was fitted to the twin data, which accounts for the lack of independence of twins within a twin pair.[49]

The association between IES and TMD pain was initially modeled to estimate the overall effect in all female twin pairs; the effect in MZ and DZ pairs was then modeled separately.[50] In the analysis, indicator variables were created for each tercile of the IES, with the lowest tercile serving as the reference level, to obtain odds ratios (ORs) and 95% confidence intervals (CIs). To statistically test for trend, an analysis was conducted using the ordinal IES scores. Follow-up analyses included age, marital status, education, race, depression, and CWP as covariates in the regression models to adjust for their potentially confounding effects. This first set of analyses did not control for familial or genetic contribution.

Next, a second set of regression analyses was conducted. Within-pair effects were specified separately for MZ and DZ pairs. The DZ within-pair ORs were adjusted for familial and some genetic influences; DZ twins share a similar family environment but, on average, only 50% of their genes. Because MZ twins share identical genes, the within-pair effect is an estimate adjusted for both familial and genetic factors. If adjusting for factors twins share, such as familial environment and genetics, eliminates the within-pair association between IES and TMD pain (in contrast with the first set of analyses, which did not adjust for familial and genetic factors), it can then be concluded that shared factors contribute to the IES-TMD pain association. Alternately, if the adjusted within-pair

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Table 1 Demographic and Clinical Characteristics for Female Twins by Temporomandibular Pain Status

Characteristics	All Twins (n =1,738)	Temporomandibular pain		P
		No (n = 1,486)	Yes (n = 252)	
Demographic				
Age (mean years ± SD)	33 ± 14	34 ± 15	32 ± 13	.04
Married (%)	34	34	30	.15
White (%)	85	85	81	.07
Education (mean years ± SD)	14 ± 2	14 ± 2	13 ± 2	.01
MZ (%)	73	72	74	.51
Clinical				
Depression (%)	25	23	39	< .01
CWP (%)	8	6	17	< .01
IES (mean score ± SD)	19 ± 14	18 ± 14	26 ±14	< .01

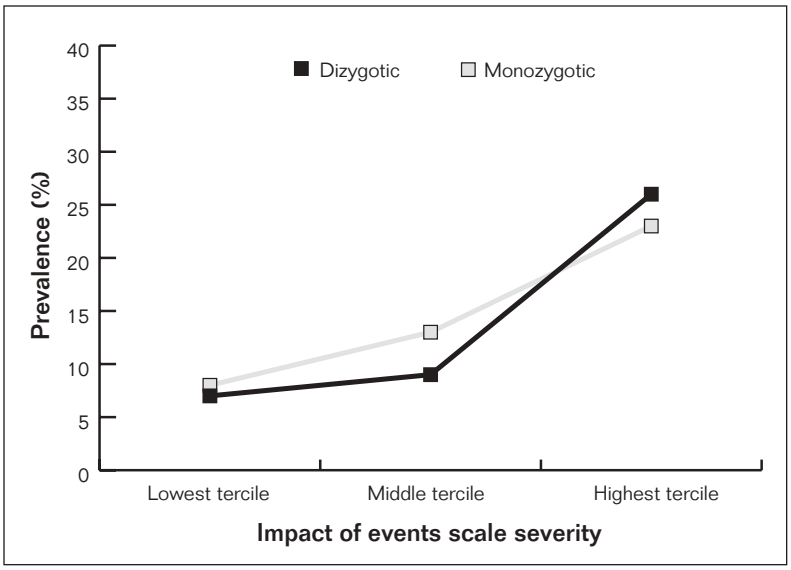

Fig 1 Prevalence of temporomandibular pain by IES score. Lowest tercile, score of 0 to 10; middle tercile, score of 11 to 27; highest tercile, score of 28 to 55.

effects are attenuated but still significant, it suggests the IES-TMD pain association is only partly explained by shared familial factors in DZ twins and familial and genetics factors in MZ twins. Additionally, greater within-pair effects for DZ than MZ twins suggest shared genetic influence on both IES scores and TMD pain. Lastly, if the within-pair association between IES and TMD pain remains robust (ie, similar to the first set of analyses, which did not adjust for familial and genetic factors), then the hypothesis that familial and genetic factors play a role in the association between TMD pain and PTSD symptoms could be rejected. In this set of analyses, the resulting ORs were adjusted for age, marital status, education, race, depression, and CWP. Stata/SE software version 9.0 was used for all statistical analyses.[51]

Results

Of the 738 MZ and 296 DZ female twin pairs enrolled in the registry, 630 MZ and 239 DZ female pairs had complete data on all study variables and were included in the analyses (1,738 individual twins). Table 1 presents the demographic and clinical characteristics of these twins by their TMD pain status. More than 70% of twins were MZ. Among all twins, the mean age was 33 years. Eighty-five percent were white, 34%

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Table 2 The Overall Unadjusted and Adjusted Associations of the IES and Temporomandibular Pain in Female MZ and DZ Twins

	All Twins		MZ Twins		DZ Twins	
IES score*	OR[2]	95% CI	OR	95% CI	OR	95% CI
Unadjusted						
Lowest tercile	1.0	—	1.0	—	1.0	—
Middle tercile	1.7	1.1–2.6	1.8	1.1–2.8	1.5	0.7–3.4
Highest tercile	3.8	2.6–5.6	3.4	2.1–5.3	5.3	2.5–11.3
	$P_{trend} < .01$		$P_{trend} < .01$		$P_{trend} < .01$	
Adjusted†						
Lowest tercile	1.0	—	1.0	—	1.0	—
Middle tercile	1.5	1.0 – 2.2	1.6	1.0 – 2.6	1.2	0.5 – 2.6
Highest tercile	2.8	1.9 – 4.2	2.6	1.6 – 4.1	3.8	1.8 – 7.9
	$P_{trend} < .01$		$P_{trend} < .01$		$P_{trend} < .01$	

*Lowest tercile of IES, score of 0 to 10; middle tercile, score of 11 to 27; highest tercile, score of 28 to 55.
†For sociodemographic characteristics (age, marital status, education, and race), depression, and CWP.

Table 3 The Unadjusted and Adjusted Within-Pair Associations of the IES and Temporomandibular Pain in Female MZ and DZ Twins

	MZ within-pair		DZ within-pair	
IES score*	OR	95% CI	OR	95% CI
Unadjusted				
Lowest tercile	1.0	—	1.0	—
Middle tercile	1.1	0.6–2.1	1.3	0.4–3.8
Highest tercile	1.7	0.8–3.2	3.8	1.3–11.2
	$P_{trend} = .11$		$P_{trend} < .01$	
	P within (MZ) vs. within (DZ) = .18			
Adjusted†				
Lowest tercile	1.0	—	1.0	—
Middle tercile	1.0	0.5–1.9	0.9	0.3–2.7
Highest tercile	1.4	0.7–2.7	2.7	0.9–7.9
	$P_{trend} = .30$		$P_{trend} = .03$	
	P within (MZ) vs within (DZ) = .13			

*Lowest tercile of IES, score of 0 to 10; middle tercile, score of 11 to 27; highest tercile, score of 28 to 55.
†For sociodemographic characteristics (age, marital status, education, and race), depression, and CWP.

were married, and the average length of schooling was 14 years. Twins with TMD pain were younger ($P = .04$), had fewer years of education ($P = .01$), were more likely to report depression and CWP, and had higher IES scores ($P < .01$) than twins without TMD pain.

Of 1,738 twins, 252 (14.5%) reported experiencing TMD pain in the preceding 3 months. Figure 1 shows the prevalence rates of TMD pain by IES severity. The prevalence of TMD pain increased with increasing IES terciles, from 8% and 7% in the lowest terciles to 23% and 26% in the highest terciles for MZ and DZ, respectively.

Table 2 presents the unadjusted and adjusted ORs and 95% CIs for the association of the IES with TMD pain in all twins and separately for MZ and DZ pairs, without adjustment for familial or genetic contribution. Even after the analysis was adjusted for sociodemographic factors, self-reported depression, and CWP, IES score and TMD pain were associated in all twins ($P_{trend} < .01$). Compared to those in the lowest IES tercile, twins in the highest tercile were 2.8 times more likely to report TMD pain. A similar pattern was observed in both MZ and DZ twin pairs.

Table 3 displays the unadjusted and adjusted within-pair associations of the IES and TMD pain separately in MZ and DZ pairs. After the analysis was adjusted for sociodemographic factors, depression, CWP, *and* familial and genetic influences,

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within-pair trends were not significant in MZ twins (P_{trend} = .30). However, they remained significant in DZ pairs (P_{trend} = .03). ORs at the highest tercile were 1.4 and 2.7 in MZ and DZ pairs, respectively. Although the within-pair effect was much larger in DZ than MZ twins, the difference did not reach statistical significance (P = .13).

Discussion

Symptoms of PTSD, as measured by the IES, were strongly related to the presence of TMD pain. Further, the increased prevalence of TMD pain across terciles of increasing IES scores was strong and significant even after adjusting for sociodemographic factors, depression, and CWP. Because these findings from a community-based sample were consistent with those from clinically ascertained samples,[18,21,24] the relationship between PTSD symptoms and TMD pain does not appear to be an artifact of clinical ascertainment. Additionally, this association was not affected by the co-occurrence of CWP with TMD pain.

This is the first study of PTSD symptoms and TMD pain in a twin population. It examined whether the relationship between PTSD symptoms and TMD pain was due to shared familial/genetic factors. After shared familial and genetic factors had been controlled for, no association was found between PTSD symptoms and TMD pain in MZ twin pairs; furthermore, the association was attenuated in DZ twin pairs. Additionally, the within-pair effect was diminished in MZ pairs compared with DZ pairs, although the difference was not statistically significant. Taken together, these findings suggest that confounding due to genetic influences may partially explain the strong association between PTSD symptoms and TMD.

These results are interesting in light of the literature on the familial/genetic contributions to both PTSD and TMD. There is substantial evidence from twin studies that genetics plays a moderate but significant role in trauma exposure and PTSD.[52–56] However, findings on TMD have been equivocal. For example, in 1 of only a handful of twin studies, MZ twins were not more similar on various TMD signs and symptoms than DZ twins.[57] Heritability of TMD pain was estimated at 24%, but it was not significant. Thus, it was concluded that individualized environmental factors were the major determinants of variance.[57] Further, a family study observed symptoms of myofascial TMD and other musculoskeletal conditions were not greater in first-degree relatives of probands with TMD than controls.[58] Alternately, another twin study of TMD symptoms in a small adolescent twin sample found higher MZ than DZ concordance rates for jaw pain.[59] In the largest twin study of TMD to date, structural equation modeling was used to estimate the variance components of TMD pain due to additive genetic, common environmental, and unique environmental factors.[60] The best-fitting model in female twin pairs included additive genetic and unique environmental factors (25% of variance and 75% of variance, respectively). These findings support other research in which variants of catecholamine-O-methyltransferase (COMT) gene have been associated with pain sensitivity and increased risk of developing TMD.[61–63] Taken together, these findings suggest that genes may play a modest but significant role in increasing vulnerability to TMD and influencing symptom severity.[64] Twin and family studies of other pain conditions also have demonstrated familial/genetic influences, which supports this hypothesis.[65–67]

The mechanisms responsible for the association between chronic pain conditions such as TMD, CWP, and PTSD are unknown.[68] The present findings suggest that the shared-genetic-susceptibility hypothesis may be worthy of further analysis. Models of mutual maintenance and shared vulnerability also have gained some acceptance in recent years.[69,70] Pre-existing abnormalities in hypothalamic-pituitary-adrenal and autonomic function could also predispose an individual to chronic pain conditions, PTSD, or both after a traumatic event.[71] Brain-imaging studies have found that psychological trauma and pain are processed in overlapping areas of the brain.[72,73] Understanding the underlying physiology of this overlap in the brain regions involved in the experience of trauma and pain could shed light on this intriguing association. Regardless of the underlying mechanism, however, the present findings underscore the need to recognize the link between PTSD and TMD, assess patients with either condition for comorbidity, and treat the symptoms of both disorders.

This study had several limitations. First, although the IES is used extensively as a measure of PTSD symptoms, the complete 15-question version was not included. However, the internal consistency and validity of the 11 questions that were retained were high. Second, the IES records PTSD symptoms that are not anchored to a specific traumatic experience, so the impact of a specific event is unclear. Thus, the IES may be measuring a "trait" rather than a "state," that is, a stereotypical way of responding to traumatic events rather than

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a specific response to a single event. Third, the sample predominately comprised MZ twins. Finally, measurement of TMD pain was based on a single question, which had a modest association with self-reported doctor diagnosis of TMD. This study should be replicated using a comprehensive assessment of TMD pain.

In conclusion, in our large, unselected sample of twins, PTSD symptoms and TMD pain were strongly associated and not explained by coexisting CWP. This relationship could be partially explained by shared genetic vulnerability to both conditions. Previous studies of PTSD and TMD typically have involved clinical samples with unknown selection biases and did not control for the presence of generalized pain conditions such as CWP. Future studies need to examine the viability of mutual maintenance and shared genetic and environmental vulnerability models, as well as the central nervous system mechanisms that may play a role in the link between PTSD and pain.

Acknowledgments

This research was supported by National Institutes of Health awards 5 U19 AI38429-08 (Dr Buchwald) and R55AR051524 (Dr Afari). Dr Afari is supported by National Institutes of Health award R01 AR051524 and the VA Center of Excellence for Stress and Mental Health.

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