



## A twin study of posttraumatic stress disorder symptoms and chronic widespread pain

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### Abstract

Previous studies of the association between posttraumatic stress disorder (PTSD) and chronic widespread pain (CWP) or fibromyalgia have not examined the role of familial or genetic factors. The goals of this study were to determine if symptoms of PTSD are related to CWP in a genetically informative community-based sample of twin pairs, and if so, to ascertain if the association is due to familial or genetic factors. Data were obtained from the University of Washington Twin Registry, which contains 1042 monozygotic and 828 dizygotic twin pairs. To assess the symptoms of PTSD, we used questions from the Impact of Events Scale (IES). IES scores were partitioned into terciles. CWP was defined as pain located in 3 body regions lasting at least 1 week during the past 3 months. Random-effects regression models, adjusted for demographic features and depression, examined the relationship between IES and CWP. IES scores were strongly associated with CWP ( $P < 0.0001$ ). Compared to those in the lowest IES tercile, twins in the highest tercile were 3.5 times more likely to report CWP. Although IES scores were associated with CWP more strongly among dizygotic than among monozygotic twins, this difference was not significant. Our findings suggest that PTSD symptoms, as measured by IES, are strongly linked to CWP, but this association is not explained by a common familial or genetic vulnerability to both conditions. Future research is needed to understand the temporal association of PTSD and CWP, as well as the physiological underpinnings of this relationship.

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### 1. Introduction

Chronic widespread pain (CWP) is a common problem in the general population, with an estimated prevalence ranging from 7% to 13% across different countries (Neumann and Buskila, 2003). The American College of

Rheumatology defines CWP as pain present in at least 2 contra-lateral body quadrants and the axial skeleton that has persisted for at least 3 months (Wolfe et al., 1990). Many experts believe that both CWP and fibromyalgia (FM), a severe subtype of CWP, represent one end of the spectrum of musculoskeletal pain disorders (Croft et al., 1996; Wolfe, 1997; Croft, 2000). CWP has a modest female predominance and its prevalence increases with age (Hunt et al., 1999; Buskila et al., 2000; Bergman et al., 2002). People with CWP also

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experience poor subjective health, fatigue, sleep disruption, and physical impairments (Prescott and Jacobsen, 1993; Aaron et al., 2002). Despite a growing body of literature, the etiology and pathophysiology of CWP remain poorly understood. Recently, several studies have documented that CWP and FM are strongly associated both with the symptoms of posttraumatic stress disorder (PTSD) (Walter et al., 1998; Wolfe and Skevington, 2000; White et al., 2002) and with the clinically diagnosed disorder itself (Benedikt and Kolb, 1986; Benjamin et al., 2000; Cohen et al., 2002; Roy-Byrne et al., 2004). Conversely, high rates of CWP and FM also have been observed among persons with PTSD (Amir et al., 1997; Dobie et al., 2004; Raphael et al., 2004).

Clinic-based studies have shown that PTSD and CWP, persistent pain, or FM were strongly associated, but the link was potentially attributable to the biases inherent in using clinical samples (Crook et al., 1989; Aaron et al., 1996; Macfarlane et al., 1999). Results from population-based studies, however, have substantiated both the existence and the strength of the association (Benjamin et al., 2000; Buchwald et al., 2005). Additionally, both PTSD and FM are thought to be partially heritable. Family studies have shown that FM aggregates strongly in families (Pellegrino et al., 1989; Buskila et al., 1996; Buskila and Neumann, 1997; Arnold et al., 2004), but linkage studies have found either a weak linkage or none at all (Yunus et al., 1999; Gursoy, 2002). Investigations into the heritability of PTSD have shown that PTSD is related to family history of psychiatric illness (Davidson et al., 1989; Koenen et al., 2002; Koenen et al., 2003).

No previous investigation has controlled for genetic or environmental influences on the relationship between PTSD and CWP. This study addresses some of these limitations by examining the association of PTSD and CWP in a sample of twins enrolled in a community-based registry in Washington State. In these analyses, we address the following questions: (1) Are the symptoms of PTSD and CWP associated? If so, (2) Do familial/genetic factors account for the association of PTSD symptoms and CWP?

## 2. Methods

### 2.1. 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. Unique to Washington State, drivers' license numbers are derived from a person's last name, first and middle initials, and date of birth. In the past, this led to the issuance of duplicate drivers' license numbers. Hence the Department of Licensing began asking every new applicant if he or she is a member of a twin pair to avoid issuing duplicate license numbers to

twins. Because Washington State agencies 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 one month, a second invitation and survey are mailed. The co-twin is mailed a survey using contact information provided by the index twin. To date, the University of Washington Twin Registry has enrolled 1042 monozygotic (MZ) pairs, 828 dizygotic (DZ) pairs, and 121 pairs of undetermined zygosity. 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.

### 2.2. Survey

The survey contains items on socio demographics, symptoms, physician-diagnosed health conditions including PTSD and depression, habits, health care use, and abridged psychiatric measures, such as the Impact of Events Scale (IES) (Horowitz et al., 1979) and a modified version of the London Fibromyalgia Epidemiology Study Screening Questionnaire (White et al., 1999).

#### 2.2.1. Zygosity assignment

As part of the mailed questionnaire all twins were asked questions about childhood similarity to assess zygosity. Studies have shown that questions about childhood similarity in twin pairs can be used to correctly classify zygosity with an accuracy of 95–98%, in comparison with zygosity determined by biological indicators (Torgersen, 1979; Eisen et al., 1989). The following questions were asked: “As children were you and your twin as alike as 2 peas in a pod or of ordinary family resemblance?” and “When you were children how often did [parents, other relatives, teachers, strangers] have difficulty in telling you apart?” The responses to these similarity questions were then used in a multi-step process to assign zygosity.

#### 2.2.2. Sociodemographic factors and clinical conditions

Sociodemographic factors collected in the survey included age, race, gender, education, and marital status. Age was calculated from the year of birth. The twins were asked if they were White, Black, Asian/Pacific Islander, Native American, Hispanic/Latino, or other. We dichotomized responses to White or other. Marital status was assessed by asking the twin whether he or she was currently single, never married, living with a partner, married, separated, divorced, or widowed. This variable was dichotomized to married or other. For education, we asked about the highest level of education completed (kindergarten to graduate school). One question inquired about a physician diagnosis of depression and another about a physician diagnosis of PTSD. Because studies have shown body mass index and depression to be strongly associated with CWP and FM (McBeth et al., 2001; Yunus et al., 2002) as well as with PTSD (Solter et al., 2002; Karlovic et al., 2004), these variables were included as covariates in the regression models to adjust for their potentially confounding effects.

### 2.2.3. Posttraumatic stress disorder symptoms

PTSD is a disorder in which an overwhelming traumatic event results in intense fear, helplessness, horror, and avoidance of stimuli associated with the trauma (American Psychiatric Association, 1994). PTSD symptoms were identified by using the IES, which assesses current subjective distress resulting from a stressful life event. Because individuals with PTSD are often reluctant to seek evaluation and treatment (Amaya-Jackson et al., 1999), we did not use the self-report of a physician diagnosis of PTSD. The IES captures qualities of conscious experience that encompass stressful life events, such as bereavement or personal injuries from accidents, violence, illness, or surgery (Horowitz et al., 1979). Although the IES is a measure only of the DSM-IV intrusion and avoidance symptom criteria for PTSD (American Psychiatric Association, 1994), previous studies have shown the IES to be strongly correlated with a diagnosis of PTSD. For example, a Dutch study of pain and stress in burn victims found that IES scores  $>26$  were indicative of serious PTSD (Taal and Faber, 1997). 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 (Wohlfarth et al., 2003). More recently, it has been suggested that additional items on hyper-arousal could be added to the IES (Weiss and Marmar, 1997).

We used 11 of the 15 original IES items, deleting 4 of the original items based on the cluster analysis that was conducted by the developers of the IES. These items had the poorest correlation with the IES intrusion and avoidance subscales (Horowitz et al., 1979). Internal reliability of the IES was assessed by 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 strong trend between the IES and a physician diagnosis of PTSD ( $\chi^2_{\text{trend}} = 59.3, P < 0.0001$ ).

Each IES item has 4 response categories (0, not at all; 1, rarely; 3, sometimes; 5, often). These values are summed to create an overall score (range 0–55). We grouped the scores into terciles representing increasing levels of current subjective distress: 0–6 (lowest distress), 7–24 (moderate distress), and 25+ (highest distress). We included only twins who answered at least 6 of the 11 IES items, and as previously recommended, missing values were imputed by using the respondent's average score across completed items (Ware et al., 1980). For example, if a twin did not answer 2 IES items, we used the mean score across the 9 completed items to impute values for the missing items.

### 2.2.4. Chronic widespread pain

The survey included 3 of 4 questions about CWP adapted from the self-report form of the London Fibromyalgia Epidemiology Study Screening Questionnaire (White et al., 1999). Our questions also were similar to those used in several European population-based studies, conducted by mail and telephone interviews, on the prevalence of chronic pain (Croft et al., 1993; Macfarlane et al., 2001; Smith et al., 2001; Allison et al., 2002; Papageorgiou et al., 2002). Twins were asked about body pain in 3 regions as follows: "In the past 3 months have you had pain in your muscles, bones, or joints lasting at least one week in your: (1) shoulders, arms, or hands? (2) legs

or feet? (3) neck, chest, or, back?". CWP was defined as pain experienced in all 3 regions.

### 2.3. Statistical analysis

Initial descriptive analyses examined the distribution of sociodemographic factors and depression according to IES tercile. The trend across terciles of these variables was statistically tested by using a  $\chi^2$  test for trend for proportions or a one-way ANOVA for means. To investigate the association of the IES with CWP, a random-effects model was fitted to the twin data (Goldstein, 1995). This approach is appropriate because observations within twin pairs cannot be assumed to be statistically independent, an assumption which classical statistical approaches make for estimation and testing. This type of data is considered to be multilevel or clustered, where twins are the cluster. The random-effects model accounts for the lack of independence by using a random-effects term to model the between-pair variance. Additionally, these models can be used with incomplete data, so that half-pairs (in which data on CWP are available from only one member of a pair) can still contribute to portions of the estimation and testing.

We initially modeled the association between the IES and CWP to estimate the overall effect in all twin pairs. In the analysis, we created indicator variables for each tercile of the IES, with the lowest tercile serving as the reference level, to obtain odds ratios and 95% confidence intervals. To statistically test for trend, we conducted an analysis using the continuous IES scores. This overall model specification represents a weighted average of within- and between-pair information (Begg and Parides, 2003). We then obtained separate estimates of the IES-CWP association within and between pairs. In this context, the between-pair effects are an estimate of the IES-CWP association unadjusted for familial environment and genetic influence, whereas the within-pair effects are adjusted for shared familial influences in DZ twins and both shared familial and genetic influences in MZ twins. If adjusting for factors that twins share (i.e., shared familial environment and genetics) eliminates the association between IES and CWP as seen in the within-pair effect, then it is possible to conclude that these shared factors contribute to the IES-CWP association. Alternately, if the adjusted association (within-pair effect) is attenuated but still significant, it suggests that the IES-CWP association in part is explained by shared familial factors in DZ twins and familial and genetics factors in MZ twins. Lastly, if within-pair and between-pair effects are similar, it suggests that familial and genetic factors may not play a significant role in the association between IES and CWP.

In our subsequent modeling, we specified within and between effects separately for MZ and DZ pairs. The DZ within-pair odds ratios are adjusted for familial as well as some genetic influences; DZ twins share a similar family environment, but they share only 50% of their genes on average. Because MZ twins share identical genes, the within-pair effect is an estimate adjusted for both familial and genetic factors. Thus, significantly greater within-pair effects for DZ than MZ twins would suggest shared genetic influence on both CWP and IES. The resulting odds ratios were adjusted for age, sex, race, marital status, education, body mass index, and depression. We used SAS software, Version 8.2 for all statistical analyses (SAS Institute, 2000).

Table 1  
Socio demographic and clinical characteristics of all twins and across terciles of the Impact of Events Scale

Variable	Total ( <i>n</i> = 3,740)	Impact of Events Scale scores		
		Tercile 1 <sup>a</sup> ( <i>n</i> = 1,154)	Tercile 2 ( <i>n</i> = 1,186)	Tercile 3 ( <i>n</i> = 1,153)
Monozygotic (%)	56	55	57	57
Age, mean ( <i>SD</i> )	33.0 (14.8)	34.3 (15.7)	32.5 (15.0)	32.1 (13.7)
Females <sup>b</sup> (%)	61	51	61	71
White (%)	87	87	88	86
Married <sup>b</sup> (%)	33	37	32	28
Education				
Less than college (%)	43	43	42	45
College (%)	46	45	47	47
Graduate school <sup>b</sup> (%)	11	13	12	8
Body mass index, mean ( <i>SD</i> )	24.7 (5.0)	24.9 (5.0)	24.5 (5.0)	24.7 (5.2)
CWP <sup>b</sup> (%)	7	4	8	10
PTSD <sup>b</sup> (%)	3.8	1.3	2.3	8.4
Depression <sup>b</sup> (%)	20	9	18	34

<sup>a</sup> Impact of Events Scale score tercile ranges: tercile 1 = 0–6; tercile 2 = 7–24; tercile 3 = 25+.

<sup>b</sup>  $P_{\text{trend}} < 0.01$ .

### 3. Results

Table 1 describes the socio demographic and clinical characteristics of the entire sample and across terciles of IES scores. More than 55% of the sample consisted of MZ twins, the mean age was 33 years, 61% of the twins were female, and 62% had some college education. The prevalence of self-reported depression was 20%. We observed an increasing trend of CWP, self-reported PTSD and depression, and female gender with higher IES scores ( $P_{\text{trend}} < 0.01$ ). Conversely being married and having higher graduate-level education was associated with lower IES scores ( $P_{\text{trend}} < 0.01$ ).

Table 2 presents unadjusted odds ratios and 95% confidence intervals for the association of the IES with CWP in all twins and separately for MZ and DZ pairs. There was a strong and highly significant association between the IES score and CWP in all twins ( $P_{\text{trend}} < 0.0001$ ). Compared to those in the lowest IES tercile, twins in the highest IES tercile were 3.5 times more likely to report CWP. A similar pattern was observed in both MZ and DZ twin pairs.

Table 3 displays the between- and within-pair associations of the IES and CWP separately in MZ and DZ

pairs, adjusted for age, sex, race, marital status, education, body mass index, and depression. The between-pair effects in MZ and DZ twins showed a strong association of IES with CWP ( $P_{\text{trend}} = 0.01$  in MZ pairs;  $P_{\text{trend}} = 0.01$  in DZ pairs), but did not differ according to zygosity ( $P = 0.95$ ). Within-pair trends were significant in both MZ ( $P_{\text{trend}} = 0.04$ ) and DZ pairs ( $P_{\text{trend}} = 0.01$ ). After adjusting for sociodemographic factors, body mass index, depression, and familial and genetic influences, MZ and DZ twins at the highest IES tercile were 2.6–3.0 times more likely to report CWP than twins in the lowest tercile, suggesting that shared familial and genetic factors may not contribute to the relationship between IES scores and CWP. Although the within-pair effect for DZ twins was slightly larger than that found for MZ twins, the difference was not significant ( $P = 0.52$ ).

### 4. Discussion

We found that symptoms of PTSD, as measured by the IES, were strongly related to the presence of CWP. Further, the increased prevalence of CWP across terciles of increasing IES scores was strong and significant even

Table 2  
The association of the Impact of Events Scale and chronic widespread pain in monozygotic and dizygotic twins

Impact of Events Scale	All twins		Monozygotic twins		Dizygotic twins	
	Odds ratio	95% CI <sup>a</sup>	Odds ratio	95% CI	Odds ratio	95% CI
Tercile 1 <sup>b</sup>	1.0	–	1.0	–	1.0	–
Tercile 2	2.4	1.6–3.7	2.3	1.3–4.1	2.6	1.4–4.9
Tercile 3	3.5	2.3–5.3	3.8	2.2–6.6	3.1	1.7–5.9
	$P_{\text{trend}} < 0.0001$		$P_{\text{trend}} < 0.0001$		$P_{\text{trend}} < 0.0001$	

<sup>a</sup> CI = confidence interval.

<sup>b</sup> Impact of Events Scale score tercile ranges: tercile 1 = 0–6; tercile 2 = 7–24; tercile 3 = 25+.

Table 3

Between- and within-pair association of the Impact of Events Scale and chronic widespread pain in monozygotic and dizygotic twins adjusted for sociodemographic factors, body mass index, and depression

Zygosity		Overall		Between pairs <sup>c</sup>		Within pairs <sup>d</sup>	
		Odds ratio <sup>a</sup>	95% CI <sup>b</sup>	Odds ratio <sup>a</sup>	95% CI	Odds ratio <sup>a</sup>	95% CI
Monozygotic	Tercile 1 <sup>e</sup>	1.0	–	1.0	–	1.0	–
	Tercile 2	2.2	1.2–4.1	2.9	1.3–6.7	1.6	0.7–3.9
	Tercile 3	2.7	1.4–4.9	2.8	1.3–6.0	2.6	1.0–6.6
		$P_{\text{trend}} < 0.0001$		$P_{\text{trend}} = 0.01$		$P_{\text{trend}} = 0.04$	
		$P$ between vs. within = 0.55					
Dizygotic	Tercile 1	1.0	–	1.0	–	1.0	–
	Tercile 2	3.1	1.5–6.5	2.9	1.2–7.1	3.5	1.2–9.8
	Tercile 3	3.2	1.5–6.6	3.3	1.4–8.1	3.0	1.0–8.6
		$P_{\text{trend}} < 0.001$		$P_{\text{trend}} = 0.01$		$P_{\text{trend}} = 0.01$	
		$P$ between vs. within = 0.58					

<sup>a</sup> Odds ratios are adjusted for age, sex, race, marital status, education, body mass index, and depression.

<sup>b</sup> CI = confidence interval.

<sup>c</sup> Interaction test comparing monozygotic vs. dizygotic between-pair effects,  $P = 0.95$ .

<sup>d</sup> Interaction test comparing monozygotic vs. dizygotic within-pair effects,  $P = 0.52$ .

<sup>e</sup> Impact of Events Scale score tercile ranges: tercile 1 = 0–6; tercile 2 = 7–24; tercile 3 = 25+.

after adjusting for socio demographic factors, body mass index, and depression. These results are congruent with several other studies. Clinical studies of FM patients have found high rates of PTSD or PTSD symptoms (Benedikt and Kolb, 1986; Sherman et al., 2000; Cohen et al., 2002; Sharp, 2004), and studies conducted in pain clinic patients, female veterans, and a community sample of women have found that individuals diagnosed with FM are at ~3-fold increased risk of experiencing PTSD or PTSD symptoms compared to those without FM (Dobie et al., 2004; Raphael et al., 2004; Roy-Byrne et al., 2004). Taken together, these previous studies have confirmed the association between PTSD and CWP, although none of them adjusted for genetic and shared environmental influences on this relationship.

This is the first study of PTSD symptoms and CWP in a twin population. Several previous studies have demonstrated that both PTSD and CWP in individuals have a familial or genetic component. For example, a family study of Cambodian refugees living in the United States found that parental PTSD was associated with a 5-fold increased risk of PTSD in their offspring (Sack et al., 1995). Findings from a study of male twins from the Vietnam Era Twin Registry suggested that a shared familial vulnerability contributes to the co-occurrence of PTSD and major depression and that genetic factors may mediate this vulnerability (Koenen et al., 2003). Similarly, studies of FM have demonstrated a familial or genetic influence. For example, a high prevalence of FM has been found repeatedly among offspring of mothers with FM, and relatives of people with FM have a lower tender point threshold than the general population (Buskila et al., 1996; Arnold et al., 2004). Another study showed that husbands of women with FM had a

high prevalence of FM (Buskila and Neumann, 1997). This is intriguing, because the prevalence of FM in men is substantially lower than in women (Yunus, 2001, 2002) and, more importantly, because familial or environmental influences would be implicated in this association, rather than genetic ones.

Twin studies of other pain conditions also have demonstrated familial and genetic influences. One study of low back and neck pain found that these conditions may be highly heritable, with 52–68% of the variance for low back pain and 35–58% of the variance for neck pain attributable to gene factors (MacGregor et al., 2004). Conversely, a twin study of temporomandibular joint disorder found that environmental factors were the major determinants of variance (Michalowicz et al., 2000). In our study, we examined whether the relationship between PTSD symptoms and CWP was due to familial or genetic factors. The MZ and DZ within-pair effects were similar to the between-pair effects, suggesting that familial factors do not play a role in the relationship between CWP and PTSD symptoms. Likewise, the MZ within-pair effect was only slightly attenuated compared to the DZ within-pair effect. These findings suggest that the strong association between PTSD symptoms and CWP cannot be explained by confounding due to genetic influences. Thus, one can conclude that individual differences in trauma may explain the robust association between PTSD symptoms and CWP. There are, however, other possible factors that vary within a pair, for example medical or social support, which could also confound this relationship.

Although some evidence now exists to support the relationship between PTSD and CWP, the mechanisms remain enigmatic. The relationship between PTSD and CWP has been postulated to be mutually maintaining,

where CWP serves as a traumatic stimulus for the development of PTSD, and the hyper-arousal, stress intolerance, and selective attention typical of PTSD worsen the pain (Sharp and Harvey, 2001). Other researchers have proposed a model of shared vulnerability, in which the relationship of PTSD and pain is mediated by a third factor, such as anxiety sensitivity, which increases vulnerability either to PTSD symptoms or to pain (Asmundson et al., 2002). Still others postulate that baseline abnormalities in hypothalamic pituitary adrenal and autonomic function may serve as a diathesis that predisposes to either CWP or PTSD or both after a traumatic event (McLean et al., 2005). Studies using brain imaging methods, such as functional MRI, to investigate how the brain reacts to psychological trauma and pain have found that pain is processed in more regions than previously thought, and that some of these overlap with regions activated with psychological trauma (Shin et al., 1997; Coghill et al., 1999). Understanding the patterns and linkages of the overlapping brain regions involved in the experience of pain and trauma could shed light on this intriguing association. Regardless of the underlying mechanism, however, our findings strongly support the need to assess for PTSD and CWP comorbidity and to provide adequate treatment for the symptoms of both disorders.

This study has several limitations. First, although the IES has been used extensively as a measure of PTSD symptoms, we were unable to use the complete 15-question version. While the 4 questions eliminated were those least correlated with their respective intrusion or avoidance subscale measures, we are unable to examine the impact of these deletions on the true score. However, the internal consistency of the 11 questions that were retained was quite high. Second, the IES is an indicator of PTSD symptoms that is not anchored to a specific traumatic experience, so the severity or impact of the traumatic experience is unclear. When used in this manner, the IES may in part be measuring a “trait” rather than a “state” (i.e., a stereotypical response to many traumatic events rather than a specific response to a single event). Finally, our measure of CWP is not ideal because it was designed to screen for FM during a telephone interview. Although 100% sensitive for FM and 100% specific for the absence of pain, the screener has an estimated specificity of 57% and a false positive rate of 43% among individuals with other forms of chronic pain such as rheumatoid arthritis.

In conclusion, our analysis was based on a large, unselected sample of twins identified from the community of licensed drivers in Washington State. Previous studies of PTSD and CWP typically have involved clinical samples with unknown selection biases. We found a strong association between PTSD symptoms and CWP that was not explained by a shared familial or genetic vulnerability to both conditions. Future studies need

to examine the viability of mutual maintenance and shared vulnerability models, as well as the central nervous system mechanisms that may play a role in the link between PTSD and pain.

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