



## Chronic prostatitis and comorbid non-urolological overlapping pain conditions: A co-twin control study



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### ABSTRACT

**Objectives:** Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is characterized by pain and voiding symptoms in the absence of an obvious infection or other cause. CP/CPPS frequently occurs with non-urolological chronic overlapping pain conditions (COPCs) of unknown etiology. We conducted a co-twin control study in men discordant for chronic prostatitis (CP), an overarching diagnosis of which approximately 90% is CP/CPPS. The primary aim was to investigate the contribution of familial factors, including shared genetic and common environmental factors, to the comorbidity of CP and COPCs.

**Methods:** Data from 6824 male twins in the Vietnam Era Twin Registry were examined to evaluate the association between self-reported lifetime physician diagnosis of CP with COPCs including fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, temporomandibular disorder, tension headaches, and migraine headaches. Random effects logistic regression models were used and within-pair analyses evaluated confounding effects of familial factors on the associations.

**Results:** There were significant associations between CP and all 6 examined COPCs. After adjusting for shared familial influences in within twin pair analyses, the associations for all COPCs diminished but remained significant. Familial confounding was strongest for the association of CP with fibromyalgia and temporomandibular disorder and smallest for irritable bowel syndrome.

**Conclusions:** CP and COPCs are highly comorbid. These associations can be partially explained by familial factors. The mechanisms underlying these relationships are likely diverse and multifactorial. Future longitudinal research can help to further elucidate specific genetic and environmental mechanisms and determine potentially causal relationships between CP and its comorbidities.

### 1. Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is characterized by pain in the pelvis, genitals, perineum, and pubic area, and is frequently associated with various urinary, ejaculatory, or sexual disturbances [1–3]. CP/CPPS symptoms affect 1.8–10.4% of men in different populations worldwide [4–8], representing the leading reason for urological outpatient consultations for men under age 50 [9]. Men with CP/CPPS have a poor quality of life that is similar to men following acute myocardial infarction or suffering from inflammatory

bowel disease [10,11]. CP/CPPS is associated with lower functional status as measured by the Short Form -12 [12], with patients having scores lower than those of patients with severe diabetes or congestive heart failure [10], and similar to those with Crohn's disease, angina, or myocardial infarction [11].

Factors such as infection, inflammation, neurological and immune dysfunction, and prostatic obstruction or edema have been linked to CP/CPPS [13,14], but none of these factors has been established as the etiology of the vast majority of cases. A small number of studies directly linked CP/CPPS with other unexplained urological syndromes and non-

**Abbreviations:** CI, confidence interval; COPCs, chronic overlapping pain conditions; CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; CP, chronic prostatitis; CFS, chronic fatigue syndrome; DZ, dizygotic; FM, fibromyalgia; IBS, irritable bowel syndrome; MZ, monozygotic; OR, odds ratio; RR, risk ratio; TMD, temporomandibular disorder; VET, Vietnam Era Twin Registry

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urological chronic overlapping pain conditions (COPCs), finding high levels of comorbidity [15]. Recent research suggests that COPCs, particularly fibromyalgia (FM), chronic fatigue syndrome (CFS), and irritable bowel syndrome (IBS), share many demographic, clinical, and psychosocial features, as well as pain-related subjective and objective features, possibly reflecting common underlying mechanisms and/or pathophysiology [15,16].

Studies that explicate mechanisms underlying the association of CP/CPPS and COPCs represent one approach to better understand CP/CPPS [17]. While the source of the association between CP/CPPS and COPCs is not fully understood, one hypothesis is that there is a common underlying familial liability to CP/CPPS and many of the COPCs. Because twin pairs discordant for a condition are matched on a large number of potential confounders (i.e., 100% shared common family environment in both monozygotic (MZ) and dizygotic (DZ); 100% shared genes in MZ, and an average of 50% shared genes in DZ), co-twin control studies provide a powerful method for investigating the potential role of familial (shared genetic and common environmental) factors in the association between the condition and its comorbidities. We conducted a co-twin control study in male twins discordant for chronic prostatitis (CP), an overarching diagnosis of which approximately 90% is CP/CPPS [18]. The aims of this study were to: 1) examine the association of CP with COPCs in middle-aged male twins; and 2) examine the influence of familial factors on the CP-COPCs associations through a within-pair co-twin control analysis. Associations of CP with chronic back and joint pain were conducted to contextualize the findings. We hypothesized that the comorbidity between CP and COPCs would be at least partially explained by familial factors.

## 2. Materials & methods

### 2.1. Population

The Vietnam Era Twin (VET) Registry is an ongoing study of male twin pairs born between 1939 and 1957 who both served in the U.S. military from 1965 to 1975 [19,20]. In the 1980s U.S. Department of Veterans Affairs established the VET Registry to evaluate the health-related consequences of Vietnam service. With approximately 7500 twin pairs, the Registry is one of the largest twin registries in the U.S. Initial contact occurred in 1987 when demographic information, health assessment, and zygosity evaluation occurred. The VET Registry has been described in detail previously [20,21].

### 2.2. Procedures

Between 2010 and 2012, living VET Registry twins were contacted for participation in VA Cooperative Study #569, “The course and consequences of post-traumatic stress disorder in Vietnam-era Veteran twins.” This study’s primary purpose was to examine long-term health many decades after discharge from active duty. A wide-range of physical and mental health dimensions were obtained using a mailed questionnaire, including questions on CP and COPCs. An initial contact letter was mailed to eligible twins inviting participation in the study. Because of the size and scope of the study, data collection was done under contract by Abt SRBI, Inc., a survey research organization. The Veterans Administration Central Institutional Review Board approved the protocol and participants provided informed consent. The Research and Development Committee at VA San Diego Healthcare System approved the current analyses.

### 2.3. Measures

#### 2.3.1. Demographics and zygosity

Age, race (White versus non-White), and Hispanic ethnicity were available from the Registry database. Current marital status, and years of education were obtained as part of the mailed questionnaire.

Zygosity was assigned using an algorithm based on childhood similarity questions that have been shown to be > 95% accurate compared to DNA-based zygosity [22].

#### 2.3.2. Self-reported CP and COPCs

The questionnaire assessed physical health conditions related to functioning and disabilities commonly seen in middle-aged men. Due to concerns regarding questionnaire length that might reduce response rate, we focused on self-reported lifetime physician-diagnosed CP and COPCs as opposed to symptom-based standardized questionnaires. As a result, we were able to assess the more general diagnostic category of CP instead of CP/CPPS. Twins were asked, “Have you ever been told by a doctor or other health professional that you had ...” followed by a list of conditions including CP, FM, CFS, IBS, temporomandibular disorder (TMD), tension headaches, and migraine headaches. COPCs were based on those of interest to the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network [23]. Additional health conditions were assessed by asking, “Have you ever had any of the following health problems ...,” followed by a list of conditions including chronic back and joint pain.

#### 2.3.3. Data analyses

Means and standard deviations (SD) were calculated for continuous variables and percentages for categorical variables. Since MZ and DZ twins did not differ in their prevalence rates of CP or any of the COPCs or chronic pain conditions, all study analyses were conducted with MZ and DZ pairs combined. Combining MZ and DZ twins in the absence of zygosity differences is common in discordant twin studies [24,25]. We followed a multiple step analytic procedure to examine the association of CP and COPCs and determine if evidence of familial confounding exists [26]. First, we evaluated the association between CP and COPCs treating twins as individuals. A series of random effects logistic regression models were used to account for the lack of independence of twin pair members. This “individual-level” analysis produced measures of association equivalent to that seen in unrelated singletons. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated after adjusting for the potential confounding influence of age. Next, using twin pairs discordant for CP we conducted within-pair analyses of the association of CP and each of the COPCs, estimating matched-pair ORs and 95% CIs for each association of CP with COPCs.

Importantly, the within-pair ORs are free from confounding due to familial factors (genetic and common environmental factors shared by co-twins) while individual-level ORs are unadjusted for these influences. Examining the within-pair and individual-level estimates can reveal the influence of familial factors on the comorbidity between CP and COPCs. If individual-level and within-pair results are of a similar magnitude, then little to no familial confounding is inferred. A pattern of smaller within-pair effects in comparison to individual-level effects would be consistent with the interpretation that familial factors play a confounding role in the relationship between CP and COPCs.

The confounding risk ratio (RR), a ratio of the individual-level OR to the within-pair OR, was calculated to provide an indication of the magnitude of confounding by genetic/shared familial factors. A confounding RR  $\geq 0$  reflects the extent that familial confounding factors account for the individual-level association, while a value of 1 suggests that confounding factors have no effect on the individual-level association. All analyses were conducted using R version 3.3.1 [27].

## 3. Results

Of 10,539 twins who were alive, locatable, and eligible, 7079 (67%) returned completed questionnaires. The analytic dataset included 6824 individuals with known zygosity (4025 MZ; 2799 DZ) and 6133 had CP data; 4680 individuals were members of complete pairs. Table 1 presents the demographic characteristics of the analytic sample and by CP status. Consistent with the VET Registry sample, participants were

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