Title

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

Authors

Gasperi, Marianna
Krieger, John N
Forsberg, Christopher
et al.

Publication Date

2017-11-01

DOI

10.1016/j.jpsychores.2017.09.005

Peer reviewed

HHS Public Access

Author manuscript

J Psychosom Res. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

J Psychosom Res. 2017 November ; 102: 29–33. doi:10.1016/j.jpsychores.2017.09.005.

Chronic Prostatitis and Comorbid Non-Urological Overlapping Pain Conditions: A Co-Twin Control Study

Marianna Gasperi, PhD[1,2], **John N. Krieger, MD**[3], **Christopher Forsberg, MA**[4], **Jack Goldberg, PhD**[3,4], **Dedra Buchwald, MD**[5], and **Niloofar Afari, PhD**[1,2]

[1]Department of Psychiatry, University of California, San Diego, San Diego, CA, USA

[2]VA Center of Excellence for Stress and Mental Health, San Diego, CA, USA

[3]University of Washington, Seattle, WA, USA

[4]Vietnam Era Twin Registry, Seattle, WA, USA

[5]Elson S Floyd College of Medicine, Washington State University, Spokane, WA, USA

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-urological 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.

Corresponding Author: Dr. Niloofar Afari, 9500 Gilman Drive, 0737, La Jolla, CA 92093. Phone: 858-642-3387; nafari@ucsd.edu.

COMPETING INTERESTS

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare that that none of the authors have any competing interests to report.

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.

Keywords

chronic prostatitis; chronic pelvic pain syndrome; lower urinary tract symptoms; discordant twins; comorbidity; twin research; chronic fatigue syndrome; temporomandibular joint disorder; fibromyalgia; irritable bowel syndrome; migraine headaches

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-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.

Materials & Methods

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 1965–1975 (19, 20). In the 1980's U.S. Department of Veterans Affairs established the VET Registry to evaluate the health-related consequences of Vietnam service. With approximately 7,500 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).

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.

Measures

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 more than 95% accurate compared to DNA-based zygosity (22).

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.

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 ≥ 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).

Results

Of 10,539 twins who were alive, locatable, and eligible, 7,079 (67%) returned completed questionnaires. The analytic dataset included 6,824 individuals with known zygosity (4,025 MZ; 2,799 DZ) and 6,133 had CP data; 4,680 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 predominantly middle-aged (mean = 61.1 years, SD = 3.1, range 53–73), White (92.9%), and non-Hispanic (97%). Most were either married or widowed (79.8%) and had at least some college education (70%).

Table 2 presents the lifetime physician-diagnosed prevalence rates for the complete sample and according to CP status. A total of 94 individuals (1.5%) reported a lifetime diagnosis of CP. The lifetime prevalence for COPCs ranged from 1.6% for FM to 9.4% for tension headaches. Approximately one quarter reported chronic back and joint pain. Individuals with CP reported higher rates for each of the COPCs than individuals without CP.

Overall, 59 twin pairs were discordant for CP, meaning that one member reported a lifetime CP diagnosis while the other member did not. Table 3 presents the ORs and CIs for the overall individual- level and within- discordant pair association of CP with COPCs. Individual-level analyses produced highly significant associations of CP with all 6 COPCs. Compared with non-CP individuals, twins with CP were 18–121 times more likely to report COPCs. The largest associations were seen for FM (OR: 121.21, 95% CI: 72.49 – 202.65) and CFS (OR: 106.72, 95% CI: 31.72 – 359.08); smaller, but still large association, was observed for tension headaches (OR: 18.12, 95% CI: 9.81 – 33.47). These results were replicated in a subsample of all 4,680 complete twin pairs (not presented). Within-pair analyses revealed ORs that remained significant but were substantially attenuated. Compared to their non-CP co-twins, CP co-twins were 6-to >30 times more likely to report COPCs. CFS analyses could not be carried out due to empty cells. Familial confounding RRs indicated substantial confounding for FM and TMD and modest confounding for IBS. In contrast to the COPCs, the individual- level and within-pair associations of CP with chronic back and chronic joint pain were not significant, though still evidenced modest familial confounding.

Discussion

In this sample of nearly 7,000 middle-aged male twins, we found that twins with self-reported lifetime physician-diagnosed CP were more likely to report each of the examined COPCs than twins without CP. These substantial associations of CP with COPCs are consistent with previous research suggesting a high degree of comorbidity for unexplained somatic syndromes in women (15). Availability of the VET Registry data, allowed us to extend this body of research to include comorbidity of COPCs and CP in men, especially with regards to comorbidity with conditions like TMD that have not been previously examined in men. Our results also are unique because our co-twin control design allowed us to control for shared familial factors in these associations. We found evidence that familial factors, either genetic or shared environmental risk factors, may play a large role in the relationship of CP and COPCs.

Our findings on the robust link between CP and COPCs in middle-aged men are consistent with community and clinic-based studies that suggest substantial comorbidity between CP/CPPS and COPCs, especially IBS (15). Recent studies from the MAPP Research Network also indicate that patients with comorbid urological chronic pelvic pain (including CP/CPPS and interstitial cystitis/painful bladder syndrome) and COPCs have worse urological symptoms than those with urological chronic pelvic pain alone (28). Although COPCs are typically more common in women (28), our results combined with the literature on the potentially increased morbidity of comorbid CP and COPCs highlight the need to

comprehensively evaluate multiple conditions in men with urological chronic pelvic pain who present for clinical care.

We found a consistent pattern of attenuated associations for within-pair estimates compared to the individual- level estimates in all examined COPCs, suggesting that either genetic or shared environmental risk influences may partially explain the relationship of CP and COPCs. It should be noted that while some of the ORs were very large, and should be interpreted with some caution, the 95% CIs capture a wide range of possible population values due to the low prevalence of CP and COPCs in our sample. Despite this, a conservative comparison of the lower values of the CIs across individual- level and within-pair results maintain a similar pattern of attenuation. This pattern of attenuated within-pair findings is consistent with the interpretation that familial factors play a significant role in the relationship between CP and FM, IBS, TMD, tension headaches, and migraine headaches. Although there are no heritability studies of CP/CPPS, heritability of chronic pelvic pain has been estimated at 46% (29). Genetic influences also have been reported for most COPCs examined in this study, with heritability estimates ranging from 25% for IBS to 27% for TMD, and 49% for migraine headaches (30, 31). Our results on the attenuation of within-pair effects are consistent with recent twin studies examining the association of COPCs and urological chronic pain conditions in women (29, 32). We found the highest confounding RRs for FM and TMD, providing evidence that the associations of CP with FM and TMD were substantially confounded by familial factors. The lowest confounding RR was for IBS, where despite some attenuation of effects indicating partial familial confounding, the within-pair estimate of the association between CP and IBS remained. Within-twin pair associations that persist suggest that a causal effect of exposure on the outcome is possible given other conditions of causation are met (33). These findings suggest that future research is needed to better understand genetic and environmental mechanisms underlying the comorbidity of CP/CPPS and other urological chronic pelvic pain conditions with COPCs, and to determine potentially causal relationships.

One potential explanation for the familial liability between CP and COPCs is central sensitization, or hyper-responsiveness of the central nervous system to a variety of inputs such as pressure, temperature, light, and medication. Central sensitization may involve several ‘top-down’ and ‘bottom-up’ mechanisms, and is increasingly viewed as the basis of much chronic pain (34). Unlike acute pain, which is a response to potential or actual tissue damage, chronic pain is often characterized by altered central nervous system function that amplifies pain perception in the absence of tissue injury (35, 36). Evidence of central sensitization has been observed in FM, CFS, TMD, and migraine headache (37, 38). Some studies suggest that neurogenic inflammation and central sensitization, rather than ongoing prostate disease, may be important in the pathophysiology of CP/CPPS (38). Our findings fit with these potential pathogenic mechanisms. Future research is needed to estimate the heritability of central sensitization, CP and COPCs. Clinical studies also are needed to determine if therapies to treat COPCs and central sensitization improve outcomes for selected patients with urological chronic pelvic pain syndromes.

This study has important limitations. Our findings are limited by the use of self-reported physician diagnoses of CP and COPCs which may have underestimated prevalence of the

conditions. Future studies should validate our findings with more rigorously-defined patient populations. Twins in this sample were 61 years old on average and may not have passed through the risk period for CP/CPPS, which is known to be more prevalent with age (39). Thus, some of the discordant pairs may become concordant with age, and some of the non-CP pairs may become discordant with time. Rates of COPCs may also increase with age. We do not have information on whether diagnosis of COPCs preceded diagnosis of CP or vice-versa. Future studies should examine the association of CP and COPCs over time. Finally, the number of discordant MZ and DZ twins was too small to allow evaluation of the relative contribution of genetic versus shared environmental factors contributing to the comorbidity between CP and COPCs. Discordant twin designs of low prevalence conditions such as CP face an inherent challenge of identifying a sufficient number of informative twin pairs. Combining data across studies is one potential way of addressing this limitation in the future.

In summary, we found a high level of comorbidity and familial confounding for CP and multiple COPCs. These results suggest that the relationship between CP and COPCs may be partially a function of familial liability suggesting that these conditions may have some overlap in the genetic or shared environmental factors that contribute to their comorbidity. Shared environmental influences which contribute to similarities in developmental outcomes among the twins may include *in utero* environment and early life factors such as family environment, diet, and socioeconomic status. The mechanisms underlying these relationships between genetic and environmental influences are likely diverse and multifactorial and could, in theory, contribute to the central sensitization processes discussed earlier. Future longitudinal research is needed to elucidate genetic and environmental mechanisms and to determine potential causal relationships between CP and its comorbidities. Finding a high degree of comorbidity among CP and COPCs in this large population of middle-aged twins underscores the need to comprehensively evaluate and address multiple conditions in patients presenting with chronic pelvic pain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported in part by the National Institute of Diabetes and Digestive and Kidney Diseases, Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network grant U01 DK082325. The Cooperative Studies Program of the Office of Research and Development, Clinical Science Research and Development, of the United States Department of Veterans Affairs provided financial support for Cooperative Study #569 and the development and maintenance of the Vietnam Era Twin (VET) Registry. The authors gratefully acknowledge the continued cooperation and participation of the members of the VET Registry; without their contribution, this research would not have been possible. The views expressed in this paper are those of the authors and do not reflect the official policy or position of NIDDK, Department of Veterans Affairs, the United States Government, or any institution with which the authors are affiliated.

Acronyms used in text

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

References

1. Nickel JC, Tripp DA, Chuai S, Litwin MS, McNaughton-Collins M, Landis JR, et al. Psychosocial variables affect the quality of life of men diagnosed with chronic prostatitis/chronic pelvic pain syndrome. BJU Int. 2007
2. Hu JC, Link CL, McNaughton-Collins M, Barry MJ, McKinlay JB. The association of abuse and symptoms suggestive of chronic prostatitis/chronic pelvic pain syndrome: results from the Boston Area Community Health survey. J Gen Intern Med. 2007; 22(11):1532–7. [PubMed: 17763912]
3. Schaeffer AJ, Landis JR, Knauss JS, Propert KJ, Alexander RB, Litwin MS, et al. Demographic and clinical characteristics of men with chronic prostatitis: the national institutes of health chronic prostatitis cohort study. J Urol. 2002; 168(2):593–8. [PubMed: 12131316]
4. Nickel JC, Teichman JM, Gregoire M, Clark J, Downey J. Prevalence, diagnosis, characterization, and treatment of prostatitis, interstitial cystitis, and epididymitis in outpatient urological practice: the Canadian PIE Study. Urology. 2005; 66(5):935–40. [PubMed: 16286098]
5. Cheah PY, Liong ML, Yuen KH, Teh CL, Khor T, Yang JR, et al. Chronic prostatitis: symptom survey with follow-up clinical evaluation. Urology. 2003; 61(1):60–4. [PubMed: 12559266]
6. Krieger JN, Riley DE, Cheah PY, Liong ML, Yuen KH. Epidemiology of prostatitis: new evidence for a world-wide problem. World J Urol. 2003; 21(2):70–4. [PubMed: 12712363]
7. Suskind AM, Berry SH, Ewing BA, Elliott MN, Suttorp MJ, Clemens JQ. The prevalence and overlap of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome in men: results of the RAND Interstitial Cystitis Epidemiology male study. The Journal of urology. 2013; 189(1):141–5. [PubMed: 23164386]
8. Hu JC, Link CL, McNaughton-Collins M, Barry MJ, McKinlay JB. The association of abuse and symptoms suggestive of chronic prostatitis/chronic pelvic pain syndrome: results from the Boston Area Community Health survey. Journal of general internal medicine. 2007; 22(11):1532–7. [PubMed: 17763912]
9. Walz J, Perrotte P, Hutterer G, Suardi N, Jeldres C, Benard F, et al. Impact of chronic prostatitis- like symptoms on the quality of life in a large group of men. BJU Int. 2007; 100(6):1307–11. [PubMed: 17941922]
10. McNaughton Collins M, Pontari MA, O'Leary MP, Calhoun EA, Santanna J, Landis JR, et al. Quality of life is impaired in men with chronic prostatitis: the Chronic Prostatitis Collaborative Research Network. J Gen Intern Med. 2001; 16(10):656–62. [PubMed: 11679032]

11. Wenninger K, Heiman JR, Rothman I, Berghuis JP, Berger RE. Sickness impact of chronic nonbacterial prostatitis and its correlates. J Urol. 1996; 155(3):965–8. [PubMed: 8583619]
12. McNaughton Collins M. The impact of chronic prostatitis/chronic pelvic pain syndrome on patients. World J Urol. 2003; 21(2):86–9. [PubMed: 12682773]
13. Shoskes DA, Lee CT, Murphy D, Kefer J, Wood HM. Incidence and significance of prostatic stones in men with chronic prostatitis/chronic pelvic pain syndrome. Urology. 2007; 70(2):235–8. [PubMed: 17826477]
14. Nickel JC, Freedland SJ, Castro-Santamaria R, Moreira DM. Chronic Prostate Inflammation Predicts Symptom Progression in Chronic Prostatitis/Chronic Pelvic Pain (CP/CPPS) Patients. The Journal of Urology. 2017:122–8.
15. Rodríguez MÁB, Afari N, Buchwald DS. Evidence for overlap between urological and nonurological unexplained clinical conditions. The Journal of urology. 2009; 182(5):2123–31. [PubMed: 19758633]
16. Aaron LA, Herrell R, Ashton S, Belcourt M, Schmaling K, Goldberg J, et al. Comorbid clinical conditions in chronic fatigue: a co-twin control study. J Gen Intern Med. 2001; 16(1):24–31. [PubMed: 11251747]
17. Kraemer HC. Statistical issues in assessing comorbidity. Statistics in Medicine. 1995; 14(8):721–33. [PubMed: 7644854]
18. Holt JD, Garrett WA, McCurry TK, Teichman JM. Common questions about chronic prostatitis. American family physician. 2016; 93(4):290–6. [PubMed: 26926816]
19. Eisen S, Neuman R, Goldberg J, Rice J, True W. Determining zygosity in the Vietnam Era Twin Registry: an approach using questionnaires. Clin Genet. 1989; 35(6):423–32. [PubMed: 2736790]
20. Goldberg J, Curran B, Vitek ME, Henderson WG, Boyko EJ. The Vietnam Era Twin Registry. Twin Res. 2002; 5(5):476–81. [PubMed: 12537880]
21. Tsai M, Mori AM, Forsberg CW, Waiss N, Sporleder JL, Smith NL, et al. The Vietnam Era Twin Registry: a quarter century of progress. Twin Research and Human Genetics. 2013; 16(01):429–36. [PubMed: 23177374]
22. Forsberg CW, Goldberg J, Sporleder J, Smith NL. Determining zygosity in the Vietnam era twin registry: an update. Twin Research and Human Genetics. 2010; 13(05):461–4. [PubMed: 20874468]
23. Landis JR, Williams DA, Lucia MS, Clauw DJ, Naliboff BD, Robinson NA, et al. The MAPP research network: design, patient characterization and operations. BMC urology. 2014; 14(1):1. [PubMed: 24383457]
24. Burcusa SL, Iacono WG, McGue M. Adolescent twins discordant for major depressive disorder: shared familial liability to externalizing and other internalizing disorders. Journal of Child Psychology and Psychiatry. 2003; 44(7):997–1005. [PubMed: 14531582]
25. Lyons MJ, Bar JL, Kremen WS, Toomey R, Eisen SA, Goldberg J, et al. Nicotine and familial vulnerability to schizophrenia: a discordant twin study. Journal of abnormal psychology. 2002; 111(4):687–93. [PubMed: 12428784]
26. McGue M, Osler M, Christensen K. Causal Inference and Observational Research: The Utility of Twins. Perspect Psychol Sci. 2010; 5(5):546–56. [PubMed: 21593989]
27. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing; Vienna, Austria: 2016.
28. Krieger JN, Stephens AJ, Landis JR, Clemens JQ, Kreder K, Lai HH, et al. Relationship between chronic nonurological associated somatic syndromes and symptom severity in urological chronic pelvic pain syndromes: baseline evaluation of the MAPP study. The Journal of urology. 2015; 193(4):1254–62. [PubMed: 25444992]
29. Vehof J, Zavos HM, Lachance G, Hammond CJ, Williams FM. Shared genetic factors underlie chronic pain syndromes. PAIN?®. 2014; 155(8):1562–8. [PubMed: 24879916]
30. Svedberg P, Johansson S, Wallander M-A, Pedersen NL. No evidence of sex differences in heritability of irritable bowel syndrome in Swedish twins. Twin Research and Human Genetics. 2008; 11(02):197–203. [PubMed: 18361721]

31. Plesh O, Noonan C, Buchwald DS, Goldberg J, Afari N. Temporomandibular disorder-type pain and migraine headache in women: a preliminary twin study. Journal of orofacial pain. 2012; 26(2): 91–8. [PubMed: 22558608]
32. Altman D, Iliadou AN, Lundholm C, Milsom I, Pedersen NL. Somatic comorbidity in women with overactive bladder syndrome. The Journal of urology. 2016; 196(2):473–7. [PubMed: 26907510]
33. McGue M, Osler M, Christensen K. Causal inference and observational research: The utility of twins. Perspectives on Psychological Science. 2010; 5(5):546–56. [PubMed: 21593989]
34. Nijs J, Meeus M, Van Oosterwijck J, Ickmans K, Moorkens G, Hans G, et al. In the mind or in the brain? Scientific evidence for central sensitisation in chronic fatigue syndrome. European journal of clinical investigation. 2012; 42(2):203–12. [PubMed: 21793823]
35. Phillips K, Clauw DJ. Central pain mechanisms in chronic pain states–maybe it is all in their head. Best Practice & Research Clinical Rheumatology. 2011; 25(2):141–54. [PubMed: 22094191]
36. Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. Progress in neurobiology. 2009; 87(2):81–97. [PubMed: 18952143]
37. Lorduy KM, Liegey-Dougall A, Haggard R, Sanders CN, Gatchel RJ. The prevalence of comorbid symptoms of central sensitization syndrome among three different groups of temporomandibular disorder patients. Pain Practice. 2013; 13(8):604–13. [PubMed: 23336585]
38. Pontari MA, Ruggieri MR. Mechanisms in prostatitis/chronic pelvic pain syndrome. The Journal of urology. 2004; 172(3):839–45. [PubMed: 15310980]
39. Krieger JN, Lee SWH, Jeon J, Cheah PY, Liong ML, Riley DE. Epidemiology of prostatitis. International journal of antimicrobial agents. 2008; 31:85–90. [PubMed: 18054206]

Highlight

- Chronic prostatitis and non-urological chronic overlapping pain conditions are comorbid.
- These associations can be partially explained by familial factors.
- Potential shared genetic influence should be investigated in the future.

Table 1

Demographic characteristics for the entire sample and by chronic prostatitis (CP) status.

	Overall Sample N = 6824	CP no n = 6039	CP yes n = 94	P*
Age as of Jan 2011, M ± SD	61.1 ± 3.1	61.0 ± 3.1	62.0 ±3.2	0.007
Education, %				0.01
< High School	5.0	4.8	4.4	
HS Grad	25.0	24.7	19.8	
Some College	31.0	31.1	15.4	
College +	39.0	39.4	60.4	
Race, %				0.17
White	92.9	93.2	96.8	
Non-white	7.1	6.8	3.2	
Ethnicity, %				0.16
Hispanic	3.0	2.9	5.3	
Non-Hispanic	97.0	97.1	94.7	
Marital Status, %				0.92
Married/Widowed	79.8	80.2	80.6	
Not Married	20.2	19.8	19.4	

Note:

* p-values are from 2-sided T-test for means, and $\chi 2$ tests for binary or categorical variables

Table 2

Overall prevalence rates of lifetime self-reported physician-diagnosed conditions for the entire sample and by chronic prostatitis status.

Diagnosis	Prevalence (%)			
	Overall Sample N = 6824*	CP no n = 6039*	CP yes n = 94*	P
Chronic Prostatitis	94/6133 (1.5)	–	–	–
COPCs				
FM	101/6148 (1.6)	53/6012 (0.9)	44/91 (48.4)	<.001
CFS	142/6161 (2.3)	96/6025 (1.6)	43/92 (46.7)	<.001
IBS	268/6163 (4.3)	212/6025 (3.5)	47/92 (51.1)	<.001
TMD	217/6164 (3.5)	162/6024 (2.7)	47/92 (51.1)	<.001
Tension Headaches	580/6172 (9.4)	510/6018 (8.5)	43/92 (46.7)	<.001
Migraine Headaches	474/6174 (7.7)	412/6025 (6.8)	41/92 (44.6)	<.001
Other Pain Conditions				
Chronic Back Pain	1733/6444 (26.9)	1552/5954 (26.1)	33/93 (35.5)	0.04
Chronic Joint Pain	1532/6413 (23.9)	1374/5939 (23.1)	29/92 (31.5)	0.06

Note: CP = chronic prostatitis; FM = fibromyalgia; CFS = chronic fatigue syndrome; IBS = irritable bowel syndrome; TMD = temporomandibular disorder; COPCs= chronic overlapping pain conditions.

*Denominators differ from total N due to missing data.

Table 3

Individual- level and within pair associations of CP with COPCs.

	All Twins N = 6133		Within-Pair Effects N = 59		Confounding Risk Ratio [c]
Diagnosis	**OR [a]**	**95% CI**	**OR [b]**	**95% CI**	
COPCs					
FM	121.21*	72.49 – 202.65	13.50*	3.39 – 117.15	8.98
CFS	106.72*	31.72 – 359.08	--	--	--
IBS	49.76*	23.63 – 104.81	30.00*	4.99 – 1223.93	1.66
TMD	68.82*	31.06 – 152.49	9.0*	2.77 – 46.35	7.65
Tension Headaches	18.12*	9.81 – 33.47	6.25*	2.16 – 24.71	2.90
Migraine Headaches	23.62*	12.27 – 45.49	11.00*	2.7 – 96.5	2.15
Other Pain Conditions					
Chronic Back Pain	1.72	1 – 2.95	1.09	0.44 – 2.73	1.58
Chronic Joint Pain	1.66	0.97 – 2.83	1.30	0.53 – 3.31	1.28

Note: CP = chronic prostatitis; FM = fibromyalgia; CFS = chronic fatigue syndrome; IBS = irritable bowel syndrome; TMD = temporomandibular disorder; CI = confidence interval; COPCs= non-urological associated chronic somatic syndromes.

[a] Mixed-effects logistic regression models accounting for twin pairs and adjusted for age.

[b] McNemar's test used to test the matched pair odds ratios.

[c] Measure of the magnitude of confounding by familial factors. CFS within-pair effects not computed due to lack of cases.

* $p < .001$