

Chronic prostatitis and related psychological problems. Which came first: The chicken or the egg? A systematic review

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COHORT STUDIES

Chung 2013	Cohort study Taiwan Longitudinal Health Insurance Database 8,088 subjects with CP/CPPS and 24,264 randomly matched subjects.	Cases with Anxiety Disorders (panic disorder, agoraphobia, specific phobias, social phobias, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, and generalized anxiety disorders) based on ICD-9-CM codes	Anxiety Disorders (AD) in 930 (11.5%) cases and 1379 (5.7%) controls (p<0.001). OR for prior AD among cases was 2.10 (95% CI = 1.92~2.29, p<0.001)
Collins 2002	Cohort studies 31,681 United States health professionals	Self-reported history of prostatitis	Prevalence of prostatitis 16% Subjects reporting stress at home or work had 1.5- and 1.2-fold greater odds of moderate or severe lower urinary tract symptoms
Gao 2019	Cohort study from urological clinics in 5 cities in China N=1280 CP/CPPS N=801	Cerbal questionnaire	CP/CPPS Anxiety: [OR: 2.24, CI: 1.57-2.69] Depression: [OR: 2.04, CI: 1.33-2.71] Loss of sleep: [OR: 1.56, CI: 1.03-3.35] Decline in memory: [OR: 1.87, CI: 1.45-2.36]
Mandar 2020	Cohort study 20- to 59-year-old male residents of Estonia (from population register) 82 men with prostatitis-like symptoms (PLS) 711 men without PLS	NIH-CPSI Giessener Prostatitis Symptom Score (GPSS) Oulu University questionnaire	Men with PLS vs without PLS Depression 25.6% vs 11.9% Consumption of antidepressants, sedative, or sleeping pills 30.4% vs 14.4% Calm% 13.4 vs 28.5% Hasty 4.8% vs 6.8% Worrying 37.8% vs 21.3% Pedantic 3.6% vs 4.5% Indifferent 2.4% vs 2.1% Depends on situation 7.3% vs 4.5% "I can manage" type 26.8% vs 25.4%

Mehik 2001	Cohort study all men resident in the two northernmost provinces of Finland (Oulu and Lapland) aged 20±59 years N= 1832 261 (14.2%) current or previous symptoms of prostatitis	Multiple-choice questionnaire (102 questions including 20 on various aspects of the mental stress, fears and sexual disturbances)	Subjects with prostatitis Busy, nervous or meticulous men rather than 'peaceful' and 'calm' men. Fear of having prostate cancer or a sexually transmitted disease and suicidal tendencies
Wallner 2009	Cohort studies A probability sample of African-American men selected from households located in Genesee County 703 African-American men, aged 40-79	Structured interview-administered questionnaire	Forty-seven (6.7%) of the 703 men reported a history of prostatitis Poor emotional and physical health, high perceived stress and low social support associated with an increased risk of prostatitis history

Characteristics of cohort studies (N =6)

Representativeness of the exposed cohort

Chung *et al.* (2013) reported subjects retrieved from a database from medical claims records of the *Taiwan National Health Insurance program*. Collins *et al.* (2002) evaluated subjects from the *Health Professionals Follow-Up Study* which is an ongoing prospective cohort study of health professional in the *United States*. Gao *et al.* (2019) recruited patients from urology clinics in five cities in *China*. Mandar *et al.* (2020) evaluated male residents of *Tartu County (Southern Estonia)* randomly sampled from the *Population Register of Estonia*. Mehik *et al.* (2001) mailed all the men resident in the two northernmost provinces of *Finland (Oulu and Lapland)*. Wallner *et al.* (2009) evaluated African-American men selected from households located in *Genesee County*.

Selection of the non-exposed cohort

All the five studies drawn the non-exposed cohort from the same community as the exposed cohort.

Ascertainment of exposure

Chung *et al.* (2013) assessed exposure (psychological dysfunction) according to diagnosis by certified psychiatrists. Collins *et al.* (2002) did not report about the modality of assessing the amount of stress in daily life at home and at work. Gao *et al.* (2019) assessed psychological burden by a verbal questionnaire. Mandar *et al.* (2020) and Mehik *et al.* (2001) assessed personality type by a self-administered questionnaire. Wallner *et al.* (2009) evaluated stress by a home epidemiologic interview and a validated questionnaire (PSS).

Demonstration that outcome of interest was not present at start of study

Chung *et al.* (2013) selected cases who had received a first-time diagnosis of CP/CPPS at the index date. They were considered as exposed only if they had received a diagnosis of psychological dysfunction (anxiety disorder) within 3 years prior to the index date. Demonstration that outcome of interest was not present before exposure was not provided in other studies (Collins *et al.* 2002, Gao *et al.* 2019, Mandar *et al.* 2020 and Mehik *et al.* 2001, Wallner *et al.* 2009).

Comparability

Chung *et al.* (2013) used a conditional logistic regression (conditioned on the age group, geographic region, urbanization level, and index year). Collins *et al.* (2002) adjusted odds ratio by age. Gao *et al.* (2019) did not show adjusted data. Mandar *et al.* (2020) and Mehik *et al.* (2001) adjusted for age, nightshift work, worrying personality type, CNS disorders, and depression. Wallner *et al.* (2009) estimated age-adjusted odds ratios in logistic regression models.

Assessment of outcome (prostatitis)

Chung *et al.* (2013) included patients who had received a CP/CPPS diagnosis by a urologist. Collins *et al.* (2002) considered subjects self-reporting an history of prostatitis. Gao *et al.* (2019) assessed CP/CPPS by evaluation of expressed

prostatic secretions and NIH-CPSI score. *Mandar et al.* (2020) and *Mehik et al.* (2001) administered two standardized prostatitis questionnaires. *Wallner et al.* (2009) assessed subjects with a comprehensive urologic examination.

Association with psychologic disorders

Chung et al. (2013) found cases with anxiety disorders (based on ICD-9-CM codes) in 11.5% of cases and 5.7% of controls. OR for prior anxiety disorders was 2.10 (95% CI = 1.92~2.29, $p < 0.001$). *Collins et al.* (2002) observed that subjects reporting stress at home or work had 1.5- and 1.2-fold greater odds of moderate or severe lower urinary tract symptoms. *Gao et al.* described greater OR for anxiety (OR: 2.24, CI: 1.57-2.69), depression (OR: 2.04, CI: 1.33-2.71), loss of sleep (OR: 1.56, CI: 1.03-3.35) and decline in memory (OR: 1.87, CI: 1.45-2.36) in patients with CP/CPPS. *Mandar et al.* (2019) observed higher rate of depression (25.6% vs 11.9%) and consumption of antidepressants, sedative, or sleeping pills (30.4% vs 14.4%) in men with prostatitis-like symptoms. The more common personality type of men with prostatitis-like symptoms was “worrying”. *Mehik et al.* (2001) found that men with prostatitis are more frequently busy, nervous or meticulous. They have more fear of having prostate cancer or a sexually transmitted disease and suicidal tendencies. *Wallner et al.* (2009) reported that poor emotional and physical health, high perceived stress and low social support are associated with an increased risk of prostatitis history.

Scoring of Risk of Bias according to Newcastle-Ottawa score in Cohort studies

Study	SELECTION				COMPARABILITY	EXPOSURE/OUTCOME		
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Assessment of outcome	Follow up length	Adequacy of follow
<i>Chung 2013</i>	*	*	*	*	**	*	*	*
<i>Collins 2002</i>		*			*	*		
<i>Gao 2019</i>		*	*			*		
<i>Mandar 2020</i>	*	*	*		**	*		
<i>Mehik 2001</i>	*	*	*		**	*		
<i>Wallner 2009</i>	*	*	*		*	*		

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CASE-CONTROL STUDIES

Author	Population & Controls	Measures	Outcome
Ahn 2012	<p>Case-control study</p> <p>55 military personnel suffering from CP/CPPS</p> <p>58 military personnel without CP/CPPS symptoms working at the Military Capital Hospital</p>	<p>NIH-CPSI</p> <p>Hospital Anxiety and Depression (HAD) scale</p> <p>Social Readjustment Rating Scale</p> <p>Global Assessment of Recent Stress (GARS) scale</p> <p>Weisman Coping Strategy Scale</p>	<p>in CP/CPPS</p> <p>Anxiety and Depression domain of the HAD significantly higher</p> <p>Social Readjustment Rating Scale no difference</p> <p>Higher GARS score correlated with the pain, quality of life, and total NIH-CPSI</p> <p>Weisman Coping Strategy Scale intellectualization, redefinition, and flexibility were higher fatalism, externalization, and self-pity were lower</p>
Anderson 2009	<p>Case-control study</p> <p>60 men with NIH-CPSI total score = > 12 & non-zero score pain domain</p> <p>30 healthy male volunteers with no history of genitourinary disease or symptoms</p>	<p>Perceived Stress</p> <p>Beck Anxiety</p> <p>Type A personality test</p> <p>Brief Symptom Inventory (distress)</p> <p>Trier Social Stress Test (hypothalamic-pituitary-adrenal axis function with serum ACTH + cortisol during acute stress)</p> <p>Positive and Negative Affective Scale (emotions)</p>	<p>Patients with chronic pelvic pain</p> <p>More anxiety</p> <p>More perceived stress</p> <p>Higher profile of global distress in all Brief Symptom Inventory domains (p 0.001)</p> <p>Blunted plasma ACTH response curve 30% less vs controls (p < 0.038)</p> <p>No differences in any cortisol responses</p> <p>Less emotional negativity after the test</p>
Aubin 2008	<p>Case-control study</p> <p>72 men diagnosed with CPPS and 98 men without any pain condition</p>	<p>Short Form-36 (SF-36) physical health composite score (PCS) and mental health composite score (MCS)</p> <p>Center for Epidemiologic Studies–Depression Scale (CES-D)</p> <p>Survey of Pain Attitudes (SOPA)</p> <p>Perceived stress scale (PSS)</p> <p>Childhood trauma questionnaire (CTQ)</p>	<p>CPPS patients below the mean scores SF-36 (44.4 vs. 50.7 for physical) SF-36 (44 vs. 51.1 for mental)</p> <p>Below the threshold score CES-D (14.1 vs. 19.0)</p> <p>Slightly below SOPA Control (1.56 vs. 1.71 and 1.78) scale Emotion (1.80 vs. 1.94 and 1.99) scale</p> <p>More than half perceived that stress worsened their pain (PSS)</p> <p>Mean scores comparable to normal scores (22.2 vs. 22.4)</p> <p>None to minimal history of sexual and physical abuse behavior directed at them</p>

<i>Clemens 2008</i>	Case-control study Male patients with chronic prostatitis/chronic pelvic pain syndrome (N=174) Control men (N=72)	Patient Health Questionnaire (depression and panic disorder)	Mental health disorders were identified in 13% of CPPS patients Medications for anxiety, depression taken by 18% of CPPS patients vs 7% of male controls
<i>De la Rosette 1993</i>	Case-control study 50 chronic prostatitis patients 50 patients seen for a vasectomy	Personality inventory (NVM, Dutch short form of the MMPI) Symptom checklist (SLC-90) Depression inventory (IDD)	Significant differences between the groups Chronic prostatitis patients scoring consistently higher
<i>Egan 1994</i>	Case-control study 20 men from Prostatitis Clinic 20 men from Pain Clinic for chronic low back pain.	Minnesota Multiphasic Personality Interview Structured psychological interviews	Prostatitis patients Less interference with work activity More interference with sexual/romantic relationships Back pain patients primary interference with work less interference with marital relationships more somatically focused, depressed, and anxious
<i>Krieger 2015</i>	Case-control study Urological chronic pelvic pain syndromes vs urological chronic pelvic pain syndromes plus chronic functional nonurological associated somatic syndrome. N=132 vs N=59 MAPP Research Network	Male Genitourinary Pain Index (MGUPI) domains BPI HADS-anxiety and depression PANAS -positive and negative PSS stress CSQ catastrophizing IPIP personality	Participants with associated nonurological somatic syndrome More severe symptoms longer duration Higher rates of depression and anxiety
<i>Li 2008</i>	Case-control study 258 CP/CPSS patients 87 healthy (HC) controls	NIH-CPSI Leukocyte count in EPS Self-rating anxiety scale (SAS) Self-rating depression scale (SDS)	SAS in CP/CPSS vs HC 42.8 +/- 11.43 vs 32.12 +/- 9.68 SDS 48.15 +/- 11.49 vs 35.12 +/- 10.81 (P < 0.01) Anxiety, depression and anxiety and/or depression in the CP/CPSS group were 25.97, 21.71 and 34.50 % higher than in the control group (P < 0.01) Rate of introversion higher rate of extroversion lower (P < 0.01)
<i>Mo 2014</i>	Case-control study 600 type IIIa CP patients 40 normal man	NIH-CPSI IIEF-5 Symptom Checklist 90-R	Type IIIa CP patients Depression anxiety somatization obsessive-compulsive interpersonal sensitivity

			Correlation depression and anxiety with erectile dysfunctions no correlation with premature ejaculation and ejaculatory pain
Naliboff 2015	Case-control study Men with Urologic Chronic Pelvic Pain Syndromes N=191 Male healthy controls N=182 from 6 academic medical centers in the United States MAPP Research Network	Quality of Life (GUPI-QoLImpact SF12 physical health SF12 mental health, BPI, SEAR) Mood (SYMQ Mood, HADS-Anxiety, HADS-Depression, PANAS positive, PANAS negative) Life stress (CTES, PSS) Coping skills (CSQ, BPCQ) Personality traits (BPI, CMSI) Cognitive skills MASQ	CPSS vs healthy Greater negative affect Higher levels of current and lifetime stress Poorer illness coping Increased self-report of cognitive deficits More widespread pain symptoms
Smith 2006	Case-control study 38 patients with CP/CPPS and their female partners 37 control couples	Center for Epidemiologic Studies Depression Scale (CES-D) International Index of Erectile Function (IIEF) Female Sexual Function Index (FSFI) Golombok-Rust Inventory of Sexual Satisfaction (GRISS) Dyadic Adjustment Scale (DAS)	CP/CPPS more sexual dysfunction and symptoms of depression Not decreased sexual satisfaction Correlation of depression and sexual dysfunction Partners of men with CP/CPPS more pain upon intercourse, vaginismus, and depressive symptoms (compared to control females) Patients with CP/CPPS and their partners not different with regard to sexual functioning and satisfaction, relationship functioning, and symptoms of depression
Tripp 2013	Case-control study Forty-four CP/CPPS diagnosed men and their spouses	Depression, anxiety, pain, disability, and catastrophizing compared to spouses	In patients and spouses physical QoL both increased over the study period Mental QoL increased over time, but patients reported lower QoL Patients reported more depression and anxiety, but both measures remained stable In patients disability did decrease over time but pain and catastrophizing showed stability
Zhang 2011	Case-control studies 77 patients and 37 age-matched healthy men	NIH-CPSI Hospital anxiety and depression scale (HADS)	Patients with CP/CPPS, 48 (62.3%), 5 (6.5%), and 1 (1.2%) had anxiety symptoms, depression symptoms, or both anxiety and depression symptoms, respectively HADS anxiety and depression scores in patients were 14.5 ± 6.8 and 5.2 ± 4.5 , both significantly higher than in controls

Characteristics of case-control series (N = 13)

Definition and representativeness of the cases

In some studies (N=4), the definition of cases is based on the presence of symptoms scored with the NIH-CPSI questionnaire and results of laboratory tests.

Ahn *et al.* (2012) considered 55 military personnel suffering from CP/CPSP according to NIH definition and examination of prostate secretion and urinalysis after prostate massage (VB3). Li *et al.* (2008) evaluated 258 CP/CPSP patients included according to NIH-CPSI score and leukocyte count in *expressed prostatic secretion* (EPS). Mo *et al.* (2014) randomly selected patients with NIH-CPSI score > 5 and pre- and post- prostatic massage test to determine bacterial infection and inflammation from multiple clinics in the districts of Tianhe and Huangpu, Guangzhou City (China). Zhang *et al.* (2011) studied 77 men who referred to the Urology Clinic of the People's Hospital Peking University having a NIH-CPSI ≥ 12 and non-zero pain score and exclusion of bacterial prostatitis by with the four-glass test.

In other studies, no information of laboratory tests is provided. Anderson *et al.* (2009) evaluated 60 men with symptoms of CP/CPSP with NIH-CPSI ≥ 12 classified as NIH category III. Aubin *et al.* (2008) included 72 men with CPSP type III from a larger observational study. Clemens *et al.* (2008) considered 174 patients previously diagnosed with CP/CPSP according to ICD-9 coding at the time of the office visit. De la Rosette *et al.* (1993) studied 50 patients with chronic prostatitis. Egan *et al.* (1994) evaluated 20 patients referred by a prostatitis clinic.

Two studies evaluated subjects from a prospective study of *Interstitial cystitis/bladder pain syndrome* (IC/BPS) and CP/CPSP (MAPP network). Krieger *et al.* (2015) studied 132 patients with urological chronic pelvic pain syndromes without any associated chronic functional nonurological associated somatic syndrome. Naliboff *et al.* (2015) considered 191 men with *Urologic Chronic Pelvic Pain Syndromes*.

Finally, two studies included men with CP/CPSP and their partners recruited through the *Outpatient Prostatitis Clinic at Kingston General Hospital, Kingston, Ontario, Canada*. Smith *et al.* (2006) and Tripp *et al.* (2013) reported about 38 and 44 couples, respectively.

Selection and definition of controls

Controls were defined as subjects with no history of disease or with NIH-CPSI scores not indicative of disease.

Some studies selected controls from populations that was not fully representative of the general population. In the Ahn *et al.* (2012) study, controls were 58 military personnel without CP/CPSP symptoms working at the *Military Capital Hospital*. Clemens *et al.* (2008) recruited 73 controls from different sources: friends or family members of patients waiting to be seen in their clinic, individuals in a research registry from a center on aging, and nursing staff from an hospital. Controls in the study of de la Rosette *et al.* (1993) were 50 patients seen for vasectomy.

Other studies recruited subjects from the community with different methods. Controls in the Anderson *et al.* (2009) study were healthy male volunteers with no history of genitourinary disease recruited by advertisement and paid for participation. Aubin *et al.* (2008) recruited controls from advertisements in the community. Inclusion criteria was absence of pelvic pain with a score of 0 on the NIH-CPSI. Naliboff *et al.* (2015) recruited healthy controls from advertisements at each MAPP discovery site. Smith *et al.* (2006) recruited control couples from the general community using posters and newspaper advertisements.

Some studies compared CP/CPSP patients with patients with other pain syndromes. Egan *et al.* (1994) considered as controls 20 men from Pain Clinic for chronic low back pain. Krieger *et al.* (2015) compared urological chronic pelvic pain patients with and without association with chronic functional nonurological somatic syndromes (irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome).

In some studies modality of recruitment of controls was not specified. Mo *et al.* considered 40 normal male volunteers with normal routine urinalysis and NIH-SCPSI < 5; Li *et al.* (2008) 87 healthy controls; Zhang *et al.* (2011) 37 age-matched healthy men.

Finally, Tripp *et al.* (2013) compared 44 CP/CPSP patients with their spouses.

Comparability

Analyses were adjusted for age (Aubin *et al.* 2008, Clemens *et al.* 2008, Egan *et al.* 1994, Krieger *et al.* 2015, Li *et al.* 2008, Naliboff *et al.* 2015, Zhang *et al.* 2014), marital status (Aubin *et al.* 2008), education (Clemens *et al.* 2008, Egan *et al.* 1994), income (Clemens *et al.* 2008, Naliboff *et al.* 2015) race/ethnicity (Clemens *et al.* 2008) and employment (Krieger *et al.* 2015) and symptom duration (Krieger *et al.* 2015).

Association with psychological disorders

Ahn *et al.* (2012) evaluated participants with *Hospital Anxiety and Depression* (HAD) scale, *Social Readjustment Rating Scale*, *Global Assessment of Recent Stress* (GARS) scale and *Weisman Coping Strategy Scale*. CP/CPSP patients showed higher anxiety and depression (HAD) and high level of stress perception (GARS) regardless of equal scores of the frequency of stress event (*Social Readjustment Rating Scale*). More common coping strategies of CP/CPSP patients were intellectualization, redefinition, and flexibility whereas fatalism, externalization, and self-pity were less frequent.

Anderson *et al.* administered questionnaires including *Perceived Stress*, *Beck Anxiety*, *Type A behavior* and *Brief Symptom Inventory* and submitted participants to the *Trier Social Stress Test* for measuring hypothalamic-pituitary-adrenal axis function. Subjects were studied during acute stress by measurement of serum adrenocorticotropin hormone and

cortisol. Patients with pelvic pain had significantly more anxiety, perceived stress and a higher profile of global distress in all Brief Symptom Inventory domains. Patients showed an altered hypothalamic pituitary adrenal axis function in response to acute stress with blunted plasma adrenocorticotropin hormone response curve but no differences in cortisol response. Patients with pelvic pain had less emotional negativity after the test than controls.

Aubin *et al.* (2008) measured psychological traits in CPPS patients using the Short Form-36 (SF-36) *physical health composite score* (PCS) and *mental health composite score* (MCS), the *Center for Epidemiologic Studies—Depression Scale* (CES-D), the *Survey of Pain Attitudes* (SOPA), the *perceived stress scale* (PSS) and the *childhood trauma questionnaire* (CTQ). Scores were compared to values of normative samples because psychological scores were not measured in controls. Scores of physical (PCS) and mental health (MCS) were lower than the normative population, and were below the threshold score for depression (CES-D). More than half of patients perceived that stress worsened their pain (PSS) and the majority did not believe to have been either physically or sexually abused.

Participants to the study of Clemens *et al.* (2008) replied to a questionnaire including the *Patient Health Questionnaire* (PHQ)15 to assess for mental health disorders (nine-item depression module + five-item anxiety module). Mental health disorders were diagnosed in 13% of CPPS patients which also took medications for anxiety and depression in 18% of cases vs 7% of controls.

De la Rosette *et al.* (1993) administered a personality inventory (NVM, Dutch short form of the MMPI), a *symptom checklist* (SLC-90), and a *depression inventory* (IDD). Results showed statistically significant higher scores in chronic prostatitis patients.

In the study of Egan *et al.* (1994), participants completed the *Minnesota Multiphasic Personality Interview* before being evaluated by a structured interview. Both groups in the study met DSM-III criteria for major depression in a high rate of cases, respectively 60% for prostatitis and 56% for chronic low back pain. In patients with prostatitis pain caused less interference with work activity but more with sexual/romantic relationships.

Krieger *et al.* (2015) assessed anxiety and depression (HADS-anxiety and depression), affective style (PANAS -positive and negative characteristic), stress (PSS), *catastrophizing* (CSQ), and personality (IPIP-neuroticism, extroversion, openness, agreeableness, conscientiousness). They showed that participants with a non-urological associated somatic syndrome presented higher rates of depression and anxiety.

Li *et al.* (2008) reported about *self-rating anxiety scale* (SAS) and *self-rating depression scale* (SDS). Rate of anxiety, depression and anxiety and/or depression were higher in the CP/CPPS group than in the control group. Rate of introversion was also higher in CP/CPPS patients.

Mo *et al.* (2014) administered the Symptom Checklist 90-R for assessing psychological problems of type IIIa CP patients. They demonstrated higher scores for depression, anxiety, somatization, obsessive-compulsive and interpersonal sensitivity.

Naliboff *et al.* (2015) evaluated participants with a comprehensive battery of psychosocial and illness impact measures including measures of Quality of Life (*GUPI-QoL Impact*, *SF12 physical health*, *SF12 mental health*, *BPI*, and *SEAR*), mood (*SYMQ Mood*, *HADS-Anxiety*, *HADS-Depression*, *PANAS positive*, *PANAS negative*), life stress (*CTES*, *PSS*), coping skills (*CSQ*, *BPCQ*) and personality traits (*BPI*, *CMSI*). In CP/CPPS they show greater negative affect, higher levels of current and lifetime stress, poorer illness coping, and increased self-report of cognitive deficits.

Smith *et al.* (2006) administered the *Center for Epidemiologic Studies Depression Scale* (CES-D) as a measure of depression in patients with CP/CPPS and their female partners. More sexual dysfunction and symptoms of depression were observed in CP/CPPS and their partners compared to control couples.

Tripp *et al.* (2014) assessed QoL using the SF12 (*Medical Outcomes Study Short Form 12*), chronic pain interference with life activity using the *Pain Disability Index* (PDI) state anxiety by the *State-Trait Anxiety Inventory* (STAI), depression by the *Center for Epidemiological Studies for Depression scale* (CES-D), current pain severity using the *Short-Form McGill Pain Questionnaire* (SF-MPQ) and catastrophic thinking in relation to pain by the *Pain Catastrophizing Scale* (PCS). Patients reported worse mental QoL, depression, and anxiety compared to spouses.

Zhang *et al.* (2011) administered hospital anxiety and depression scale (HADS) in CP/CPPS who showed higher anxiety and depression scores than in controls.

Scoring of Risk of Bias according to Newcastle-Ottawa score in Case control studies

	SELECTION				COMPARABILITY	EXPOSURE/OUTCOME		
	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate
Ahn 2012	*	*		*		*	*	*
Anderson 2009	*	*	*	*		*	*	*
Aubin 2008	*	*	*	*	**	*	*	*
Clemens 2008	*	*		*	**	*	*	*
De la Rosette 1993	*	*		*		*	*	*
Egan 1994	*	*			*	*	*	*
Krieger 2015	*	*	*	*	**	*	*	*
Li 2008	*	*	*	*	**	*	*	*
Mo 2014	*	*	*	*		*	*	*
Naliboff 2015	*	*	*	*	**	*	*	*
Smith 2006	*	*	*	*		*	*	*
Tripp 2013	*	*	*	*		*	*	*
Zhang 2011	*	*	*	*	*	*	*	*

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CLINICAL SERIES

Author	Population & Controls	Measures	Outcome
<i>Drannik 2017</i>	Clinical series 27 patients with CP/CPPS	NIH-CPSI Patient Health Questionnaire-9 (PHQ-9) for depression Cytokine levels and testosterone levels in semen	Positive correlations between NIH-CPSI total scores and PHQ-9 alone Negative correlation between anti-inflammatory cytokines (IL-10, TGF- β) and depression and symptoms of CP/CPPS
<i>Koh 2014</i>	Clinical series Outpatient prostatitis clinic Clinical diagnosis of CP/CPPS based on an NIH consensus regarding CP/CPPS symptoms N=66	NIH-CPSI Patient Health Questionnaire-9 (PHQ-9) to assess depression and somatization EuroQol Questionnaire-5 Dimensions (EQ-5D), (utility index and visual analog scale to assess quality of life) Personality traits 44-item Big Five Inventory (BFI)	Neuroticism poorer treatment response and higher levels of depression and somatization Extraversion, agreeableness, and conscientiousness some influence on clinical characteristics Openness did not affect overall symptoms or the
<i>Ku 2002</i>	Clinical series 87 men	NIH-CPSI Beck Depression Inventory State-Trait Anxiety Inventory Bem Sex Role Inventory	Pain and urinary symptoms correlated depression ($p < 0.001$ and $p = 0.01$) State and trait anxiety not correlated Masculinity scores not correlated to pain but correlated to urinary symptoms ($p = 0.042$) Femininity scores not correlated
<i>Lee 2007</i>	Clinical series University of Sciences Malaysia Chronic Prostatitis Cohort 332 cases	Self-reported history of disease	Psychiatric diseases 20/332 (6%)
<i>McNaughton Collins 2001</i>	Clinical series Chronic Prostatitis Cohort (CPC) study Six clinical research centers across the United States and Canada N=278	Short Form 12 (SF-12) Mental Component Summary (MCS) and Physical Component Summary (PCS) (NIH-CPSI)	CPC subjects' MCS scores (44.0 ± 9.8) were lower than those observed in the most severe subgroups of patients with congestive heart failure and diabetes mellitus PCS scores (46.4 ± 9.5) were worse than those among the general U.S. male population. Decreasing scores were seen in both domains with worsening symptom severity ($P < .01$).
<i>Naliboff 2017</i>	Clinical series 221 female and 176 male patients with urological chronic pelvic pain syndromes from 6 academic medical centers in the United States	Symptom, psychosocial and illness-impact measures Biweekly symptom reports, a functional clustering procedure classified participant outcome as worse, stable or improved on pain and urinary symptom severity	Anxiety, depression and general mental health were not significant predictors of outcomes but pain catastrophizing and self-reported stress were associated with pain outcome

Rodriguez 2019	Clinical series 233 female and 191 male UCPPS subjects baseline data from the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAAPP)	Hospital Anxiety and Depression HAD Scale (depression and anxiety) Perceived Stress Scale	Symptom duration was not associated with mental health comorbidities
Schaeffer 2002	Clinical series Health Chronic Prostatitis Cohort (CPC) study 488 men with chronic prostatitis/the chronic pelvic pain syndrome	RAND Medical Outcomes Survey (SF-12) Physical Component Summary (PCS) Mental Component Summary (MCS)	history of psychiatric disease almost 25% Depression (21%), eating disorder (1%), anxiety/panic attacks (14%) and attempted suicide (2%) 138 (29%) Not significantly associated with NIH-CPSI scores at the 1% level
Tripp 2004	Clinical series National Institutes of Health (NIH) Chronic Prostatitis Cohort Study from seven clinical centres (six in the USA and one in Canada) 463 men	Depressive symptoms score (i.e. 'how often have you felt downhearted/blue in the past 4 weeks' on a 0-6 scale, where 0 is all the time and 6 none of the time) From Short Form-12	Predictive models for NIH-CPSI QoL and pain intensity score For 1-point decrease in depressive symptoms, QoL score increased by 0.381 points ($P < 0.001$). Urinary scores and depressive symptoms significant predictors ($P < 0.001$) of pain
Tripp 2006	Clinical series CP/CPPS n = 253 Chronic Prostatitis Cohort Study (6 US and 1 Canadian centers)		Overall pain predicted by depression (beta = .24), and helplessness catastrophizing (beta = .29) Affective pain predicted by depression (beta = .39) and helplessness catastrophizing (beta = .44) Sensory pain predicted by helplessness catastrophizing (beta = .37)
Ulrich 2015	Clinical series Men with nonbacterial prostatitis/pelvic pain N = 224	Perceived stress Pain intensity Pain-related disability	perceived stress correlated with pain intensity ($p = .03$) and disability ($p = .003$)
Wang X 2013	Clinical series 147 patients with clinical diagnosis of CP/CPPS	SCL-90 International Index of Erectile Function 5 (IIEF-5)	Somatization, depression, anxiety and psychosis of patients were significantly higher than normal reference values ($P < 0.05$)
Weninger 1996	Clinical series 39 patients with chronic prostatitis	Sickness impact on quality of life score	Mean sickness impact profile total score similar to score for patients suffering myocardial infarction, angina or Crohn's disease. Pain significantly contributed Psychological symptoms added significantly to the amount of predicted variance

Wu 2006 Chinese	Clinical series 1500 cases of CP patients.	Zung self-rating depression scale (SDS) NIH-CPSI IIEF-5 Self-designed questionnaire	SDS (44.24 +/- 10.20) higher than that of the domestic norm (P = 0.000) 309 (21.7%) depression (>53) 176 (12.3%) mild 114 (8.0%) moderate 19 (1.3%) severe
Zeng 2008	Clinical series Patients with refractory chronic prostatitis N = 232	NIH scales of chronic prostatitis symptoms, anxiety, depression and erectile function	Refractory vs medical chronic prostatitis groups Anxiety and depression significantly higher Erectile function significantly lower (P < 0.01) Negative correlation between the erectile scores and anxiety and depression scores

Characteristics of clinical series (N = 15)

A total of 15 studies presenting clinical series were considered

Some studies reported on large series of patients with CP/CPPS who were extensively evaluated in outpatient prostatitis clinic.

Four studies reported on the *National Institutes of Health Chronic Prostatitis Cohort* (NIH-CPC) including patients from seven clinical centres (six in the USA and one in Canada). *McNaughton Collins et al.* (2001) administered SF-12 questionnaire to 278 patients of the NIH-CPC evaluating the *Mental Component Summary* (MCS) and *Physical Component Summary* (PCS). Both MCS and PCS scores were worse in CP/CPPS patients than those among the general U.S. male population. *Schaeffer et al.* (2002) presented similar data obtained by administration of SF-12 to 488 men from the same cohort. About 25% of the patients self-reported an history of psychiatric disease such as depression (21%), eating disorder (1%), anxiety/panic attacks (14%) and attempted suicide (2%). *Tripp et al.* (2004) reported that a depressive symptom score obtained from SF-12 questionnaire significantly predicted pain intensity in 463 CP/CPPS patients of NIH-CPC. In 2006, *Tripp et al.* in 253 patients found that depression and helplessness catastrophizing predicted overall pain and both affective pain and sensory pain were predicted by helplessness catastrophizing. Finally, a study compared data from 488 patients of the NIH-CPC with 332 patients from the *University of Sciences Malaysia Chronic Prostatitis Cohort* (*Lee et al.* 2007). Patients self-reported an history of psychiatric disease in 20/332 (6%).

Two studies reported about data from the MAPP network that is a multisite, NIDDK-funded prospective study to study *Interstitial cystitis/bladder pain syndrome* (IC/BPS) and CP/CPPS. *Naliboff et al.* (2017) in 176 male patients with *urological chronic pelvic pain syndromes* (UCPPS) demonstrated that anxiety, depression and general mental health were not significant predictors of pain although pain catastrophizing and self-reported stress were associated with pain outcome. *Rodriguez et al.* (2019) evaluated 191 males with UCPPS by the Hospital Anxiety and Depression HAD Scale and Perceived Stress Scale showing that symptom duration was not associated with mental health comorbidities.

Other studies described larger series. *Ullrich et al.* (2015) evaluated 224 men with nonbacterial prostatitis/pelvic pain from a health maintenance organization. Men completed measures of perceived stress, pain intensity, and pain-related disability after a health care visit with a new diagnosis of non bacterial prostatitis/pelvic pain syndrome. Pain intensity and pain-related disability were related to perceived stress (4-item Perceived Stress Scale). *Wang et al.* (2013) administered the SCL-90 in 147 patients with clinical diagnosis of CP/CPPS and found that somatization, depression, anxiety and psychosis were significantly higher than normal reference values. *Wu et al.* (2006) described higher scores of the Zung self-rating depression scale (SDS) in 1500 patients with chronic prostatitis compared to normal range. Depression was mild in 12.3%, moderate in 8% and severe in 1.3%. *Zeng et al.* (2008) in 232 patients with refractory chronic prostatitis showed significantly higher level of anxiety and depression.

Other studies reported on smaller series. *Drannik* (2017) in a small series (N = 27) of patients clinically diagnosed with CPSS found that a depression score (PHQ-9) was positively associated with intensity of symptoms and level of pro-inflammatory cytokines (IL-1 β , TNF- α , IL-8) whereas a significant negative correlation was seen between anti-inflammatory cytokines (IL-10, TGF- β) and depression. *Koh* (2016) presented a small series of patients with CPSS (diagnosed by NIH-CPSI) (N = 66) who were evaluated before and after treatment with alpha-blockers anti-inflammatory or antibiotics. Response to treatment was evaluated in relation to personality traits of patients according to the 44-item *Big Five Inventory* (BFI). They found that high level of "neuroticism" was associated with poorer treatment response and higher levels of depression (PHQ-9) and somatization. High level of "extraversion", "agreeableness", and "conscientiousness" had

some impact on clinical characteristics whereas “openness” was not influent. Ku (2002) in a small series (N=87) of patients diagnosed by NIH-CPSI found that pain and urinary symptoms correlated with depression (*Beck Depression Inventory*) but not anxiety (*State-Trait Anxiety Inventory*). Androgyny (*Bem Sex Role Inventory*) was not correlated to pain but to urinary symptoms. Wenninger et al. (1996) evaluated the impact of sickness on quality of life in 39 patients with chronic idiopathic prostatitis confirmed by 4-glass urine cultures. Multiple regression analysis showed that psychological symptoms contributed significantly in explaining quality of life.

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