Adverse Childhood Experiences and Symptoms of Urologic Chronic Pelvic Pain Syndrome: A Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network Study

Andrew Schrepf, PhD[1] • Bruce Naliboff, PhD[2,3] • David A. Williams, PhD[1] • Alisa J. Stephens-Shields, PhD[4] •
J. Richard Landis, PhD[4] • Arpana Gupta, PhD[5] • Emeran Mayer, MD, PhD[5] • Larissa V. Rodriguez, MD[6] •
Henry Lai, MD[7,8] • Yi Luo, MD, PhD[9] • Catherine Bradley, MD[10,11] • Karl Kreder, MD[9] •
Susan K. Lutgendorf, PhD[12]; for the MAPP Research Network*

Andrew Schrepf
aschrepf@med.umich.edu

[1] Chronic Pain and Fatigue Research Center, Department of Anesthesiology, University of Michigan, Ann Arbor, MI, USA

[2] Department of Medicine, University of California, Los Angeles, CA, USA

[3] Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA, USA

[4] Department of Biostatistics and Epidemiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

[5] Oppenheimer Center for Neurobiology of Stress, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA

[6] Department of Urology, University of Southern California, Los Angeles, CA, USA

[7] Division of Urologic Surgery, Department of Surgery, Washington University School of Medicine, St. Louis, MO, USA

[8] Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO, USA

[9] Department of Urology, University of Iowa, Iowa City, IA, USA

[10] Department of Obstetrics and Gynecology, University of Iowa, Iowa City, IA, USA

[11] Department of Urology, University of Iowa, Iowa City, IA, USA

[12] Department of Psychological and Brain Sciences and Urology, University of Iowa, Iowa City, IA, USA

*See MAPP Masthead for full list of participants

Abstract

Background Adverse Childhood Experiences (ACEs) such as sexual and physical violence, serious illness, and bereavement have been linked to number of chronic pain conditions in adulthood, and specifically to urologic chronic pelvic pain syndrome (UCPPS).

Purpose We sought to characterize the prevalence of ACEs in UCPPS using a large well-characterized cohort in comparison with a group of healthy controls. We also sought to determine the association of ACE severity with psychological factors known to impact pain and to determine whether ACEs are associated with patterns of improvement or worsening of symptom over a year of naturalistic observation.

Methods For longitudinal analyses we used functional clusters identifying broad classes of (a) improved, (b) worsened, and (c) stable groups for genitourinary pain and urinary symptoms. We employed a mediation/path analysis framework to determine whether ACEs influenced 1 year outcomes directly, or indirectly through worse perceptions of physical well-being.

Results ACE severity was elevated in UCPPS ($n = 421$) participants compared with healthy controls ($n = 414$; $p < .001$), and was most strongly associated with factors associated with complex chronic pain, including more diffuse pain, comorbid functional symptoms/syndromes, and worse perceived physical well-being (all $p < .001$). Finally, worse physical well-being mediated the relationship between ACE severity and less likelihood of painful symptom improvement (OR = .871, $p = .007$)) and a greater likelihood of painful symptom worsening (OR = 1.249, $p = .003$) at 1 year.

Conclusions These results confirm the association between ACEs and UCPPS symptoms, and suggest potential targets for therapeutic interventions in UCPPS. *Clinical Trial registration* NCT01098279.

Keywords Interstitial Cystitis/Painful Bladder Syndrome • Chronic Prostatitis with Chronic Pelvic Pain Syndrome • Psychological Trauma • Sexual Abuse

Introduction

For more than three decades, researchers have investigated the association between the presence of chronic pain conditions and adverse childhood experiences (ACEs) such as sexual abuse, neglect, and family upheaval. The preponderance of case-control studies supports a relationship between self-reported ACEs and chronic pain conditions, a relationship since confirmed through meta-analysis [1, 2]. In addition to this evidence from retrospective designs, prospective analyses have found that ACEs are associated with a higher incidence of somatic and painful symptoms in adulthood [3, 4] though not all studies have confirmed this relationship [5]. Chronic pelvic pain in particular has been linked to multiple forms of ACEs [6–13]. For instance, a meta-analysis of case-control studies places the incidence of sexual abuse in pelvic pain at nearly three times that of control group [14].

A number of interleaving hypotheses have been advanced to explain the relationship between chronic pain and a history of ACEs, largely focusing on the concepts of biological embedding [15] in early life and the psychological sequelae of trauma. Biological embedding suggests that developmental trajectories change in response to trauma, perhaps by promoting a pro-inflammatory phenotype [16, 17]. ACEs have been consistently linked with increased levels of negative emotionality in adulthood [18, 19] and negative emotionality has been independently associated with painful symptoms and chronic pain conditions [20–28]. Concepts like pain catastrophizing and increased levels of perceived stress may be indicative of a stress reactive phenotype in chronic pain [29]. Similarly, the burden of somatic symptoms has been previously linked to greater pain sensitivity independently of depressive and anxious symptoms [30]. However, the vast majority of studies have considered the relationship between ACEs and chronic pain in a relatively static manner, and have not considered the broad range of potential associations between psychological and physical constructs and ACEs in the context of chronic pelvic pain.

The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network is a multi-center study designed to provide information of symptomology and mechanisms of Urologic Chronic Pelvic Pain Syndrome (UCPPS) through deep phenotyping of patients [31, 32]. UCPPS is characterized by painful symptoms in the bladder or pelvic region (e.g., pain as the bladder fills) and urinary symptoms relating to a frequent or urgent need to urinate and/or getting up to urinate at night (e.g., needing to urinate less than 2 h after last urination) [33]. Recent investigations through the MAPP Network have examined longitudinal symptom patterns and uncovered novel risk factors for improvement and worsening of painful and urinary symptoms 1 year after study entry [34]. Specifically, a worse perception of physical well-being was associated with less favorable medium-term outcomes for UCPPS pain [34]. Perceived physical well-being is a composite measure of several aspects of perceived physical health including limitations in physical functioning, limitations in physical roles in work, interference and severity of bodily pain, energy or vitality, and general health [35]. The measure is related to both objective measures of physical fitness [36] and affective/cognitive processes [37]. The perception of physical well-being may have particular importance in the context of chronic pain, because worse perceived physical health is associated with less engagement in preventative health-related behaviors [38]. However, it is not yet known how a history of ACE relates to medium-term (i.e., 1 year) likelihood of improvement or worsening. Because UCPPS symptoms tend to be persistent [39, 40], any factors related to short- and medium-term change are important to understand for planning treatments and determining necessary windows of observation to determine treatment effectiveness.

The aim of this study is to determine how self-reported ACE severity is associated with painful and urinary symptoms in UCPPS, comorbid factors relating to physical and psychological health, including a variety of measures of negative mood and stress, somatic/functional symptoms, and the likelihood of symptom improvement/worsening at 1 year. We hypothesized that ACE severity is associated with both painful and urinary symptoms at study entry, greater levels of negative emotionality, more functional and somatic symptoms, and less likelihood of improvement over time. We also hypothesize that perceived physical well-being, previously shown to be associated with medium-term symptom outcomes [34], may mediate the effect of ACE severity on symptom improvement/worsening.

Methods

Participants

Inclusion/exclusion

UCPPS participants were recruited from clinics and local advertisements and healthy control participants were recruited at each MAPP Network Discovery Site. Complete information about the MAPP Network inclusion/exclusion criteria is available [31, 32]. Briefly,

participants were eligible if they were at least 18 years of age and reported chronic pain/pressure/ discomfort associated with the bladder or pelvic region in the preceding 3 months in the presence of negative urine cultures for uropathogens. Exclusion criteria included pregnancy if female and conditions that might result in tissue damage to areas relevant to UCPPS symptomology (e.g., history of urethral stricture, neurological disorder affecting the bladder or bowel). UCPPS Participants were enrolled in a longitudinal study of symptom changes related to pelvic pain and urinary symptoms. Participants completed demographic and symptom information during a baseline visit following which genitourinary pain and urinary symptom data were collected biweekly for 48 weeks via an online module (25 time points, including baseline). At study entry, participants had a physical examination, urine collection, blood draw, and completed questionnaires regarding symptoms, and nonurologic factors such as mood, coping, and childhood adversity that are fully described elsewhere [32]. The same broad medical comorbidity exclusions were applied to healthy controls. In additon, healthy controls could not report any pain in the pelvic or bladder region or pain in more than one of the 42 nonurologic body regions on a body map or meet criteria for a chronic pain condition (described under the subsection 'comorbid conditions') [32]. At baseline the final sample consisted of 421 UCPPS participants (232 women) who completed the measure of ACE severity and 414 (233 women) healthy controls who completed measures of ACE severity. The final sample for longitudinal analyses included 421 (232 women) UCPPS participants. The study was approved by Institutional Review Boards at all participating sites.

Measures

Adverse childhood experiences

The Childhood Traumatic Events Scale (CTES) examines traumatic events that occurred before the age of 17 in the following categories: death of a close family member or friend, parental separation, physical abuse including sexual assault, serious illness, and other. For each category, severity of the trauma, age at the time of the trauma, and extent of confiding in others is assessed [41]. Each ACE is rated either 0 ("no trauma") or from 1 ("not at all traumatic") to 7 ("extremely traumatic"). The total CTES severity score is a simple sum of the severity rating for each ACE category (possible range 0–42). We used this summary measure rather than individual ACE categories (e.g., sexual trauma) as the primary predictor, as cumulative ACE burden across multiple domains, including bereavement and serious illness, has

been shown to strongly predict complex symptoms in adulthood even when controlling for specific categories of ACE and particular ACE characteristics, such as age of exposure [42, 43].

Functional symptoms

Functional symptoms were assessed using the Complex Medical Symptoms Inventory checklist [44], a 41 item measure assessing symptoms commonly reported in functional syndromes. The checklist assesses symptoms present at least 3 months out of the preceding year, using binary responses. A sum of nonurinary symptoms (e.g., dry eye, photo-sensitivity, palpitations) was used as an assessment of the cumulative burden of these symptoms.

Genitourinary pain and urinary symptoms

Pain and Urinary Severity was assessed using a composite measure derived from the genitourinary pain index (GUPI) [45], and Interstitial Cystitis Symptom Index (ICSI) [46], based on psychometric analyses performed on MAPP baseline data, suggesting that pain and urinary symptoms should be measured separately. In this analysis the urinary and symptom severity scores were correlated ($r = .56$) [33]. Pain severity scores range from 0 to 28 (MAPP sample Cronbach's $\alpha = .92$) and urinary severity scores range from 0 to 25 (MAPP sample Cronbach's $\alpha = .89$).

Health, medical, and demographic information

Health, medical, and demographic information (e.g., age, duration of symptoms, use of medication) was collected by self-report. A 45 site body map was also administered (42 nonpelvic sites) and the sum of sites checked as painful, using binary responses, was used as an indication of the burden of widespread pain [47]. Headache was indicated by any of four head sites being checked as painful.

Comorbid conditions

Comorbid Conditions were assessed using standardized self-report criteria for fibromyalgia (FM) [48], chronic fatigue syndrome (CFS) [49], irritable bowel syndrome (IBS) [50], vulvodynia (VVD; females only) [44], and temporomandibular disorder (TMD) [51].

Perceived stress

The Perceived Stress Scale (PSS) is a 10-item scale (MAPP sample Cronbach's $\alpha = .93$) measuring the degree to which situations are perceived as being unpredictable, uncontrollable, and overwhelming during the last month. Responses range from 0 ("never") to 4 ("very often"). Higher scores indicate more stress [52].

Catastrophizing

Catastrophizing refers to the appraisal of one's pain as overwhelmingly awful and the extent to which a person believes that their pain will lead to catastrophic consequences. The 6-item (MAPP sample Cronbach's $\alpha = .88$) Catastrophizing subscale from the Coping Strategies Questionnaire (CSQ) was used to measure this characteristic, with higher scores indicating worse catastrophizing. Responses range from 0 ("never do that") to 6 ("always do that") when the participant feels pain [53].

Sleep and fatigue

Sleep (8 items; MAPP sample Cronbach's $\alpha = .95$) and fatigue (7 items; MAPP sample Cronbach's $\alpha = .80$) were assessed with the NIH Patient Reported Outcomes Measurement Information System (PROMIS) questionnaires. Responses range from 1 ("never") to 5 ("always") for each symptom experienced in the last 7 days [54].

Anxiety and depression

Anxiety (7 items; MAPP sample Cronbach's $\alpha = .88$) and depression (7 items; MAPP sample Cronbach's $\alpha = .88$) were measured using the Hospital Anxiety and Depression Scale (HADS). Responses range from 0 (e.g., "not at all") to 3 (e.g., "most of the time") for each item experienced over the last week [55].

Perceived physical and mental well-being

Perceived physical and mental well-being were measured using the SF-12 physical components score (PCS; a composite of all physical health subscales), and mental components score (MCS). These measures are scored using a proprietary algorithm. Responses range from 1 ("all of the time") to 4 ("none of the time"). Higher scores indicated better physical and mental well-being [56].

Statistical Analyses

Statistical analyses were performed using SPSS v. 24, MPLUS v 5.2. Descriptive statistics were generated for each of the six CTES subscales and compared between the longitudinal MAPP UCPPS ($n = 421$) and healthy cohorts by analysis of variance (ANOVA) for severity scores and psychosocial/physical health characteristics, and Pearson χ^2 difference testing for binary ACE categories. Total number of ACE types endorsed and total severity scores were also compared by ANOVA. Pearson correlation analyses were conducted between ACE severity scores and each of the psychosocial and physical health measures in each cohort. We also examined these relationships stratified by cohort and sex.

UCPPS severity outcome groupings

As described in a previous publication, a functional clustering algorithm was employed to classify subjects according to symptom trajectory status on pain and urinary severity at 48 weeks (improve, stable, worse) [34]. Briefly, an initial clustering step Ward's minimum variance was used to assign each subject to a cluster based on a treatment of all the longitudinal data from weeks 4 to 48. In the second iterative classification step, one subject is removed and new mixed effects models are estimated by K-mixture functional mixed effects models [57]. The posterior probability of the excluded subject belonging to one of the groups is then calculated, and the steps are repeated until group assignments for each subject are stable. The number of clusters is selected based on Kullback–Leibler (KL) criterion [58].

In previous analyses it was determined that large study entry or regression to the mean type effects were present in this cohort [59], and that classification of "improved" or "worse" changed substantially when the first 4 weeks of data were excluded. For these reasons, the "baseline" measure of symptoms occurred at week four. The algorithm subsequently produced three broad classifications of symptom change: "improved," "stable," and "worse."

For pain severity outcomes at 1 year, 87 (21.9%) were classified as improved, 230 (57.9%) as stable, and 80 (20.1%) as worse. For urinary severity 83 (20.9%) improved, 261 (65.7%), remained stable, and 53 (13.3%) were worse.

Mediation/path analysis

To address the question of how levels of ACE severity might be related to changes in in genitourinary pain and urinary symptoms at 1 year, we conducted mediation/path analyses using perceived physical well-being (the SF-12 PCS scale) as the mediator of interest. Model building procedures in our previous work using univariate then multivariate analyses identified the SF-12 PCS as the only significant predictor of pain and urinary functional outcomes [33].

All models controlled for patient age. Sex was not used as a covariate because it was not found to be associated with UCPPS symptom outcome group membership [33]—in secondary analyses we confirmed that sex did not influence the model. For the mediation/path analyses, a parallel mediation model was conducted to control for any relationships between ACEs, baseline pain or urinary severity, and UCPPS symptom outcome status. This was owing to the established association between baseline severity and UCPPS symptom outcome status [34] as well as association between ACE severity and baseline symptom severity (pain severity, $r = .156$, $p < .001$; urinary severity, $r = .194$, $p < .001$). A logistic regression

framework was employed, with separate models tested for improvement status ("improved" vs. "worse/stable") and worse status ("worse" vs. "stable/improved"). We chose this approach as each outcome may have unique associations that would not be captured by proportional odds models. Indirect effects were tested through the construction of bias-corrected 95% confidence intervals (20,000 resamples).

Results

Demographics

UCPPS participants were 43 (15 +/− SD) years old on average. Of the sample, 55% were female, 93% were non-Hispanic, 88% were Caucasian, and 65% were college graduates. Approximately 30% of the sample was using a pain medication at the time of study entry. Demographic information on the trans-MAPP cohort has been previously published [60].

ACEs and Psychosocial/Physical Health

Compared with the healthy control group, UCPPS participants had elevated levels of depression, anxiety, perceived stress, pain catastrophizing, functional symptoms, painful body map sites, fatigue, sleep disturbance, head pain, and worse physical and mental health (all $p < .001$; see Table 1). Similarly, UCPPS participants reported experiencing more categories of ACEs than the control group and greater ACE severity (both $p < .001$). Comparing specific ACE categories, UCPPS participants were more likely to endorse sexual ACE, physical violence, illness/injury, and "other trauma" than healthy controls (all $p < .01$), while death of family members/close friends and parental separation/divorce were not more common for UCPPS participants (both $p < .13$). In addition, there was a significant effect of sex on ACE severity across both cohorts, such that women had higher ACE severity scores than men ($p < .001$) and significant group X sex interaction, such that women with UCPPS had higher ACE severity scores than healthy women and men from both groups ($p < .001$; see Fig. 1). UCPPS participants with one or more comorbid pain conditions had significantly higher ACE severity scores (UCPPS only, mean 0= 7.24, SD = 6.94; UCPPS comorbid, mean = 9.81, SD = 8.96; $p = .001$).

In the UCPPS cohort, ACE severity was associated with higher levels of baseline depression, anxiety, perceived stress, pain catastrophizing, functional symptoms, painful body map sites, fatigue, sleep disturbance, and perceived physical well-being (all $r > .108$, all $p < .05$; see Table 2). The strongest relationships were with

Table 1. Trauma and psychological characteristics of UCPPS and healthy control participants

| Characteristic mean (SD)	UCPPS ($n = 421$)	Healthy controls ($n = 414$)	F value	DF	p
Depression (HADS-D)	5.42 (4.20)	1.80 (2.34)	235.25	1,832	< .001
Anxiety (HADS-A)	7.70 (4.54)	3.63 (3.15)	226.37	1,832	< .001
Catastrophizing (CSQ)	12.63 (8.80)	2.58 (4.58)	421.23	1,826	< .001
Perceived stress (PSS)	16.48 (7.89)	10.44 (6.27)	149.19	1,830	< .001
Physical health (SF-12 PCS)	47.34 (10.31)	57.14 (4.29)	307.96	1,799	<.001
Mental health (SF-12 MCS)	43.76 (10.42)	53.76 (6.99)	250.470	1,799	<.001
Number of functional symptoms	8.74 (6.87)	1.58 (2.80)	386.98	1,833	<.001
Number of painful body map sites	5.02 (6.47)	1.24 (2.05)	128.64	1,833	<.001
Fatigue (PROMIS-fatigue)	19.12 (5.67)	13.05 (3.74)	333.09	1,833	<.001
Sleep disturbance (PROMIS –sleep disturbance)	24.19 (7.75)	15.09 (5.56)	379.00	1,833	<.001
Adverse Childhood Experiences (ACEs) severity (CTES)	8.63 (8.16)	6.08 (6.68)	24.51	1,833	<.001
ACE # categories	1.69 (1.41)	1.29 (1.22)	32.81	1,833	<.001
	Frequency (%)		Pearson χ^2		p
Body map head pain	118 (28)	47 (11)	36.61		<.001
ACEs					
Death of family member/close friend	209 (50)	184 (45)	2.17		.14
Divorce/separation of parents	126 (30)	123 (30)	.002		.96
Traumatic sexual experience	85 (20)	41 (10)	17.37		<.001
Victim of violence	65 (15)	39 (9)	6.94		.008
Extremely ill or injured	82 (20)	48 (12)	10.06		.002
Other trauma	143 (34)	102 (25)	9.04		.003
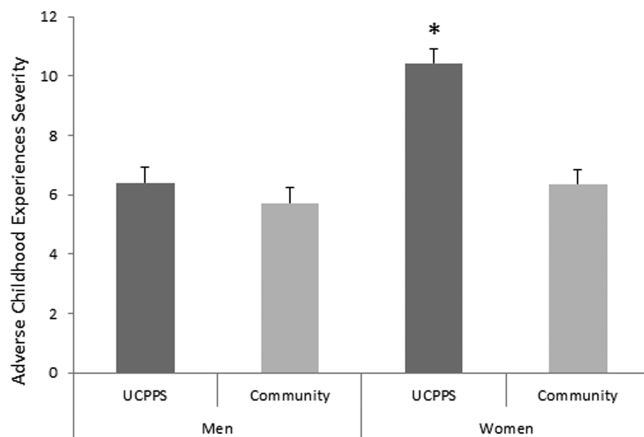
Fig. 1. Means and S.E.s of ACE severity scores for men and women with UCPPS and healthy controls. *After adjustment for multiple comparisons with Sidak correction UCPPS women had higher ACE severity compared with all other groups (all $p < .001$), while no other groups differed significantly from one another (all $p > .9$).

stress, pain catastrophizing, functional symptoms, painful body map sites, fatigue, sleep disturbance, and mental health (all $r > .108$, all $p < .05$) but not head pain ($r = .059$, $p = .228$) or perceived physical well-being ($r = −.087$, $p = .084$). There were some apparent sex differences, with females showing slightly stronger associations between ACE severity and some psychosocial variables.

Functional Outcomes at One Year

Total effect of ACE severity

The total effect of ACE severity was not significantly associated with changes in painful or urinary symptoms, adjusting for age (all $p > .25$; see Table 3).

Mediation/path analysis—painful symptoms

ACE severity was associated with less likelihood of improvement in pain symptoms at 1 year indirectly through worse perceived physical well-being (OR = .871, 95% CI = .777, .950, $p = .007$; see Fig. 2). This indicates that a 1 standard deviation increase in ACE severity is associated with an approximately 13% lower probability of 1-year improvement in pain scores through SF-12 PCS scores. The direct effect of ACE severity was not significant ($p = .18$), while the sum of the direct and indirect effect was significant (OR = .725, 95% CI = .542, .943, $p = .023$).

more functional symptoms ($r = .370$, $p < .001$), worse physical health ($r = −.277$, $p < .001$) and more painful body map sites ($r = .267$, $p < .001$). ACE severity was also associated with greater genitourinary pain severity ($r = .118$, $p = .016$) and urinary symptoms ($r = .139$, $p = .005$) at the time of study entry, though these associations were not significant after correction for multiple comparisons. In healthy controls, ACE severity was associated with worse depression, anxiety, perceived

Table 2. Pearson correlations between psychosocial and physical health measures and adverse childhood experiences severity (CTES), for all participants in each group and stratified by sex

Measure	UCPPS	HC	UCPPS		HC	
	r	r	r		r	
	All	All	Female	Male	Female	Male
Depression (HADS-D)	.171[b]	.138	.200[b]	.165	.181	.109[a]
Anxiety (HADS-A)	.205[b]	.162[b]	.248[b]	.128[a]	.110[a]	.219[b]
Catastrophizing (CSQ)	.199[b]	.108	.209[b]	.095[a]	.098	.111[a]
Perceived stress (PSS)	.246[b]	.175[b]	.279[b]	.138[a]	.159	.191
Perceived physical well-being (SF-12 PCS)	−.277[b]	−087[a]	−243[b]	−.222[b]	−.096[a]	−.076[a]
Perceived mental well-being (SF-12 MCS)	−.102	−148	−.149	−.028[a]	−.184	−.110[a]
Number of functional symptoms (CMSI)	.370[b]	.203[b]	.347[b]	.305[b]	.224[b]	.183
Number of painful body map sites	.267[b]	.133	.280[b]	.078[a]	.082[a]	.207
Fatigue (PROMIS- fatigue)	.249[b]	.188[b]	.251[b]	.130[a]	.175	.197
Sleep disturbance (PROMISsleep disturbance)	.221[b]	.175[b]	.267[b]	.068[a]	.133	.231[b]
Body map head pain	.109	.059[a]	.088[a]	.001[a]	.012[a]	.121[a]
Genitourinary pain (Pain severity)	.118	N/A	.051[a]	.144	N/A	N/A
Urinary symptoms (Urinary severity)	.139	N/A	.082[a]	.110[a]	N/A	N/A

All $p < .05$ unless otherwise noted

[a] $p > .05$

[b] $p < .05$ after correction for multiple comparisons

Table 3. Relationship between adverse childhood experiences (ACE) severity and functional outcomes adjusting for age

| Obs. used: 397	Estimate	Standard Error	Estimate/ Standard Error	p	Odds Ratio	95% Confidence Interval, Lower Limit	Upper Limit
Pain improvement							
ACE severity	−0.148	0.130	−1.142	0.253	0.862	0.659	1.094
Age	0.006	0.008	0.840	0.401	1.006	0.991	1.021
Pain worsening							
ACE severity	−0.023	0.121	−0.186	0.852	0.978	0.761	1.225
Age	−0.016	0.009	−1.745	0.081	0.984	0.967	1.002
Urinary improvement							
ACE severity	−0.113	0.116	−0.972	0.331	0.893	0.706	1.119
Age	−0.003	0.008	−0.440	0.660	0.997	0.981	1.012
Urinary worsening							
ACE severity	0.080	0.150	0.503	0.596	1.083	0.798	1.438
Age	0.008	0.010	0.843	0.399	1.009	0.988	1.028
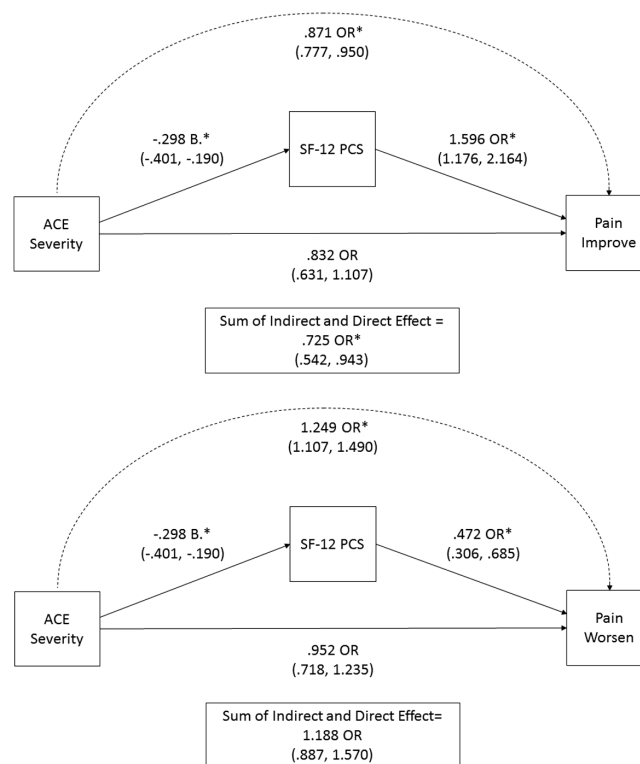
Fig. 2. Mediation analyses showing the direct and indirect effects of ACE severity on pain functional outcomes. Odds ratios represent the increase or decrease in the likelihood of each pain outcome associated with a one standard deviation increase on the ACE severity measure. The association between ACE severity and SF-12 PCS scores is reported in standardized units. The sum of direct and indirect effects includes the mediated effect (by SF-12 PCS scores), and the direct effect of ACE severity on pain outcomes. Both models control for relationships between ACEs and early symptom severity and the effect of age (not shown). *p < .05.

Similarly, ACE severity was associated with a greater likelihood of worsening in pain symptoms at 1 year indirectly through worse perceived physical well-being (OR = 1.249, 95% CI = 1.107, 1.490, p = .003). This indicates that a one standard deviation increase in ACE severity is associated with an approximately 25% greater probability of worsening in pain symptoms at

1 year through SF-12 PCS scores. The direct effect of ACE severity was not significant (p = .71), nor was the sum of the direct and indirect effect (OR = 1.188, 95% CI = .887, 1.570, p = .23).

In summary, greater severity of self-reported ACEs is associated with worse perceived physical well-being, which in turn is associated with less likelihood of

improvement and a greater likelihood of worsening in pain severity at 1 year. In secondary analyses, these relationships remained when sex was included as a covariate (data not shown).

Mediation/path analyses—urinary symptoms

ACE severity was not associated with urinary symptom improvement either directly ($p = .07$) or indirectly through perceived physical well-being (OR = .933, 95% CI = .839, 1.015, $p = .15$). Similarly, ACE severity was not associated with worsening of urinary symptoms either directly ($p = .51$) or indirectly through SF-12 PCS scores (OR = 1.107, 95% CI = .994, 1.241, $p = .10$).

Discussion

Our result show that the cumulative severity of ACEs is associated with substantially worse pain outcomes at 1 year, indirectly, through poorer perceived physical well-being. Identifying distinct pathways that impact symptom outcomes is particularly important when, as in these analyses, there is no clear association between the exposure (ACEs) and symptom outcomes in simple prediction models—this may be owing to the combination of different types of indirect effects not explicitly modeled [61]. These analyses confirm the relationship between ACEs and worse perceived physical well-being [62] and suggest that perceived physical well-being is important to evaluate in UCPPS sufferers with a history of ACEs. To our knowledge this is the first study in UCPPS to examine longitudinal outcomes within the context of ACEs.

These findings are consistent with the notion that stressful early life events could play a role in exacerbation of painful symptomology in UCPPS. On average, the UCPPS participants had experienced 1.7 of 6 ACE categories, and approximately 78% of the sample endorsed at least one ACE. Interpersonal violence (both physical and sexual) was roughly twice as likely to be reported by UCPPS participants compared with healthy controls, a finding consistent with meta-analyses in other chronic pain conditions [2]. Although the cumulative impact of ACEs across domains are clearly associated with worse symptom outcomes in the medium-term, it may be true that ACEs involving personal threats during a critical developmental window are part of the pathogenesis of the syndrome. Longitudinal studies beginning in childhood are necessary to answer this question.

Worse perceived physical well-being appears to play an important role in the relationship between ACEs and worse functional pain outcomes. It has previously been shown that chronic pain patients with worse perceived physical well-being are likely to have experienced pain longer and to have more social difficulties related to their pain [63]. Longitudinal studies have demonstrated that individuals with poorer perceived physical health are less likely to engage in preventative health behaviors such as eating a balanced diet and receiving routine medical care [38], that ACEs prospectively predict more negative health behaviors in adulthood such as tobacco use and alcohol abuse [64] and a reduced sense of internal control around adversity [65]. These findings are consistent with conceptual models in which the link between ACEs and poor perceived physical health is due in part to worse overall health behaviors, worse objective measures of health, and a lack of social integration or support. It is possible then that individuals with a history of ACEs are more likely to engage in harmful health behaviors that exacerbate pain, may have less functional or perceived social support that would facilitate behavioral modification, or may have a reduced sense of control in managing symptoms. Our present findings suggest that in the context of medium-term pain outcomes, factors related to the perception of physical health are at least as important as the perception of mental health in individuals with a history of ACEs.

Extrapolating to estimates of UCPPS (3.3–7.9 million women [66] and .96–3.0 million men) [67] prevalence in the USA, our findings suggest that between 3.3 and 8.5 million UCPPS sufferers have experienced some form of ACE which in turn reduces the likelihood of medium-term improvement. By our estimates, a patient one standard deviation above the mean on ACE severity would be approximately 52% more likely to have pain worsen at 1 year after adjustment for age and baseline severity, and approximately 27% less likely to have pain improve, compared with a patient with no history of ACEs—an effect mediated through worse perceived physical well-being. Although ACE severity was higher in women than in men, levels of ACE severity were similarly associated with poorer perceived physical well-being. This is likely why sex did not appear to alter the mediation/path analysis relationship between ACE severity and 1 year painful outcomes. This also suggests that ACE severity confers vulnerability to worse symptom outcomes in the medium-term for both women and men.

The measures and conditions most strongly associated with ACE severity at study entry—spatial distribution of pain, comorbid functional syndromes, total number of functional symptoms, and poorer perceived physical well-being—are all associated with what is sometimes termed "centralized" pain, in recognition of the prominent role the central nervous system plays in the expression of nonspecific symptoms and widespread pain [68]. Interestingly, these constructs were also those more strongly associated with ACE severity in the UCPPS cohort than in the healthy control group. Hypotheses related to central nervous system disruption

of sensory and affective pathways are strengthened by the exclusion of individuals with medical comorbidities of a known autoimmune or overtly inflammatory character. That UCPPS patients with more functional symptoms and bodily pain at study entry have higher levels of ACE severity is consistent with previous studies indicating that ACEs are both more prevalent in those with chronic pain conditions [1] and that the number/severity of ACEs are associated with a greater number of painful symptoms [69]. The concept of biological embedding has been advanced as a potential explanation for the cluster of physical and psychological symptoms seen in chronic pain patients with a history of ACEs [15], as a variety of neurobiological mechanisms appear to influence both sensory and affective pathways that may be relevant to pain. Along these lines, we have previously demonstrated that provoked immune responses are associated with both centralized pain characteristics [70, 71] and worse longitudinal outcomes in an exploratory MAPP cohort [72].

Our findings confirm previous investigations in chronic pain finding relationships between ACEs and affective vulnerabilities as well—at study entry, ACE severity was associated with higher levels of depression, catastrophizing, anxiety, and perceived stress. The associations between catastrophizing, depression, and ACEs at study entry is important, as previous research has found that both are important independent constructs in relation to pain reports [73]. Functional magnetic resonance imaging (fMRI) studies of pain catastrophizing suggest that neural networks related to pain anticipation, emotional elements of pain, and motor control are related to the construct [74, 75]. fMRI studies have revealed that the depressive symptoms are associated with activation of neural networks related to the emotional/affective salience of pain [76, 77], and that induced depressive symptoms enhance the unpleasantness of pain experienced [78]. These findings may have correlates in neuroimaging studies of individuals with a history of ACEs: limbic hyper-responsiveness to threat [79], hippocampal hyper-responsiveness to sad subliminal images [80], and overall reduced limbic-prefrontal connectivity [81]. Regarding pain processing, ACEs have also been associated with reduced activation in the hippocampus during pain–empathy tasks [82], and reduced activity of the anterior cingulate cortex during a visceral pain task [83] a result subsequently found to be modulated by affective symptoms [77]. It would therefore appear that the association of ACEs with pain may share similar neural pathways as affective vulnerabilities. The fact that the association between ACEs and neuroimaging outcomes was no longer significant once affective symptoms were controlled for supports the close relationship between affective and pain processing circuits, and their involvement in ACE-related pain modulation [77]. A recent

MAPP analysis using resting-state functional connectivity analysis of MRI data on a subset of participants found that a broad frontoparietal network of connectivity predicted improvement and worsening at 3 months with substantial accuracy. A number of affective and pain processing regions were identified as having predictive value, including the hippocampus, parahippocampal gyrus, anterior cingulate cortex, nucleus accumbens, and insula [84].

Limitations

As with all self-reported measures of past events, reporting of ACEs may be subject to recall bias. Comparisons of prospective data on childhood maltreatment and self-report in adulthood reveal that a significant number of individuals do not report or recall previous abuse [85, 86], and while difficult to quantify, false-positive reports may be a non-negligible issue as well. Despite these limitations, there is general consensus to support the usefulness of retrospective reports of adverse early life events [86]. It is possible that affective disturbances such as depression and catastrophizing may influence current reporting and evaluations of ACE incidence and/or severity [87]. ACE severity and perceived physical well-being were measured at the same time point. This study was observational and therefore participants entered at different phases of the disease trajectory using different treatment modalities. A recent analysis of the same longitudinal dataset suggested however that self-reported changes in treatment at baseline appeared to have little impact on symptom trajectories [59].

Conclusions and Future Directions

These findings confirm the importance of ACEs in modulating the severity and persistence of UCPPS symptoms. Perhaps more importantly from a clinical perspective, these analyses suggest that ACEs may be associated with elements of the "centralized" pain phenotype. It remains to be determined if well-documented effects of early adversity on pain perception and stress responsiveness are responsible for these clinical observations. Both the change in inflammatory markers and brain systems modulating pain are being tracked in ongoing MAPP Network projects. In addition, projects are underway to identify the neural correlates of ACE severity in this MAPP Network cohort. Future research in UCPPS may focus on differential effects of common treatments among individuals with a history of ACE, particularly those targeting relevant neurotransmitter systems and cognitive and affective interventions targeting characteristics of chronic pain [88, 89].

Compliance with Ethical Standards

Authors' Statement of Conflict of Interest and Adherence to Ethical Standards The authors declare no conflicts of interest to disclose.

Ethical Approval The study was approved by the Institutional Review Boards of all participating institutions.

Informed Consent All subjects provided informed consent.

MAPP Research Network Study Group

***MAPP Network Executive Committee*:** J. Quentin Clemens, MD, FACS, MSci, Network Chair, 2013–; Philip Hanno, MD; Ziya Kirkali, MD; John W. Kusek, PhD; J. Richard Landis, PhD; M. Scott Lucia, MD; Chris Mullins, PhD; and Michel A. Pontari, MD.

***Northwestern University Discovery Site*:** David J. Klumpp, PhD, Co-Director; Anthony J. Schaeffer, MD, Co-Director; Apkar (Vania) Apkarian, PhD; David Cella, PhD; Melissa A. Farmer, PhD; Colleen Fitzgerald, MD; Richard Gershon, PhD; James W. Griffith, PhD; Charles J. Heckman II, PhD; Mingchen Jiang, PhD; Laurie Keefer, PhD; Darlene S. Marko, RN, BSN, CCRC; Jean Michniewicz; Todd Parrish, PhD; and Frank Tu, MD, MPH.

***University of California, Los Angeles Discovery Site and PAIN Neuroimaging Core*:** Emeran A. Mayer, MD, Co-Director; Larissa V. Rodríguez, MD, Co-Director; Jeffry Alger, PhD; Cody P. Ashe-McNalley; Ben Ellingson, PhD; Nuwanthi Heendeniya; Lisa Kilpatrick, PhD; Jason Kutch, PhD; Jennifer S. Labus, PhD; Bruce D. Naliboff, PhD; Fornessa Randal; and Suzanne R. Smith, RN, NP.

***University of Iowa Discovery Site*:** Karl J. Kreder, MD, MBA, Director; Catherine S. Bradley, MD, MSCE; Mary Eno, RN, RA II; Kris Greiner, BA; Yi Luo, PhD, MD; Susan K. Lutgendorf, PhD, ;Michael A. O'Donnell, MD; and Barbara Ziegler, BA.

***University of Michigan Discovery Site*:** Daniel J. Clauw, MD, Co-Director; Network Chair, 2008–2013; J. Quentin Clemens, MD, FACS, MSci, Co-Director; Network Chair, 2013–; Suzie As-Sanie, MD; Sandra Berry, MA; Megan E. Halvorson, BS, CCRP; Richard Harris, PhD; Steve Harte, PhD; Eric Ichesco, BS; Ann Oldendorf, MD; Katherine A. Scott, RN, BSN; David A. Williams, PhD.

***University of Washington, Seattle Discovery Site*:** Dedra Buchwald, MD, Director; Niloofar Afari, PhD, Univ. Of California, San Diego; John Krieger, MD; Jane Miller, MD; Stephanie Richey, BS; Susan O. Ross, RN, MN; Roberta Spiro, MS; T.J. Sundsvold, MPH; Eric Strachan, PhD; Claire C. Yang, MD.

***Washington University, St. Louis Discovery Site*:** Gerald L. Andriole, MD, Co-Director; H. Henry Lai, MD, Co-Director; Rebecca L. Bristol, BA, BS, Coordinator; Graham Colditz, MD, DrPH; Georg Deutsch, PhD, University of Alabama at Birmingham; Vivien C. Gardner, RN, BSN, Coordinator; Robert W. Gereau IV, PhD; Jeffrey P. Henderson, MD, PhD; Barry A. Hong, PhD, FAACP; Thomas M. Hooton, MD, University of Miami; Timothy J. Ness, MD, PhD, University of Alabama at Birmingham; Carol S. North, MD, MPE, Univ. Texas Southwestern; Theresa M. Spitznagle, PT, DPT, WCS; Siobhan Sutcliffe, PhD, ScM, MHS.

***University of Pennsylvania Data Coordinating Core (DCC)*:** J. Richard Landis, PhD, Core Director; Ted Barrell, BA; Philip Hanno, MD; Xiaoling Hou, MS; Tamara Howard, MPH; Michel A. Pontari, MD; Nancy Robinson, PhD; Alisa Stephens, PhD; Yanli Wang, MS.

***University of Colorado Denver Tissue Analysis & Technology Core (TATC)*:** M. Scott Lucia, MD; Core Director, Adrie van Bokhoven, PhD; Andrea A. Osypuk, BS; Robert Dayton, Jr.; Karen R. Jonscher, PhD; Holly T. Sullivan, BS; R. Storey Wilson, MS.

***Additional Sites*:** Drexel University College of Medicine, Garth D. Ehrlich, PhD; Harvard Medical School/Boston Children's Hospital, Marsha A. Moses, PhD, Director; Andrew C. Briscoe; David Briscoe, MD; Adam Curatolo, BA; John Froehlich, PhD; Richard S. Lee, MD; Monisha Sachdev, BS; Keith R. Solomon, PhD; Hanno Steen, PhD.

***Stanford University*:** Sean Mackey, MD, PhD, Director; Epifanio Bagarinao, PhD; Lauren C. Foster, BA; Emily Hubbard, BA; Kevin A. Johnson, PhD, RN; Katherine T. Martucci, PhD; Rebecca L. McCue, BA; Rachel R. Moericke, MA; Aneesha Nilakantan, BA; and Noorulain Noor, BS.

***Queens University*:** J. Curtis Nickel, MD, FRCSC, Director.

***National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH)*:** Chris Mullins, PhD, John W. Kusek, PhD, Ziya Kirkali, MD; and Tamara G. Bavendam, MD.

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