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A CASE-CROSSOVER STUDY OF UROLOGIC CHRONIC PELVIC PAIN SYNDROME FLARE TRIGGERS IN THE MAPP RESEARCH NETWORK

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Abstract

Purpose—Although many factors have been proposed to trigger symptom exacerbations (“flares”) in patients with interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome, few studies have investigated these factors empirically. Therefore, we embedded a case-crossover study in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain longitudinal study to evaluate a range of patient-reported triggers.

Materials and methods—Exposure to proposed triggers (diet, physical activities, sedentary behaviors, stress, sexual activities, infection-like symptoms, and allergies) was assessed by questionnaire a maximum of three times when participants reported flares and at three randomly-selected times. Participants’ pre-flare to -non-flare exposures were compared by conditional logistic regression.

Results—In our full analytic sample (n=292 participants), only two factors, recent sexual activity (odds ratio (OR)=1.44, 95% confidence interval (CI): 1.06–1.96) and symptoms of a urinary tract infection (OR=3.39, 95% CI: 2.02–5.68), which may overlap with those of flares, were associated with flare onset. In sub-analyses restricted to flares with specific, suspected triggers, additional positive associations were observed for some (certain dietary factors, abdominal muscle exercises, and vaginal infection-like symptoms and fever), but not other (e.g., stress) factors.

Conclusions—With the exception of sexual activity, our findings suggest that patient-reported triggers may be either individual/group-specific or may not contribute to flares. These findings suggest caution in following rigid, global flare prevention strategies and support additional research to develop evidence-based strategies.

Key words/MeSH terms

Epidemiology; interstitial cystitis; precipitating factors; prostatitis; symptom flare-up

INTRODUCTION

Interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), collectively referred to as urologic chronic pelvic pain syndrome (UCPPS), are chronic, idiopathic conditions characterized by persistent bladder and/or pelvic pain, and urologic symptoms, such as urgency and frequency. Both conditions are common – ranging in prevalence from 1–7%¹ – and difficult to diagnose and treat. They are also burdensome to patients, contributing to decreased physical and mental health, sexual functioning, and work participation.^{2,3}

One particularly troubling aspect of UCPPS are symptom exacerbations or “flares”. These vary in manifestation, but some can be extremely painful, long-lasting, and unpredictable.^{4,5} Although numerous factors have been proposed to trigger flares (e.g., diet, stress^{5–13}), very few studies have evaluated these factors empirically to determine their influence on patients’ symptoms.^{14–17} These types of studies are important to help patients prevent flares while also minimizing the restrictions that avoiding multiple suspected triggers can impose.⁵ Therefore, we embedded a case-crossover study – a study comparing exposures before flares to exposures before times without flares from the same participant¹⁸ – in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Epidemiology and Phenotyping Study to identify factors associated with flare onset.

MATERIALS AND METHODS

Study population and design

The MAPP Epidemiology and Phenotyping Study was a one-year, multi-site longitudinal study designed to characterize the usual-care natural history of UCPPS, and to identify subgroups with possible differing etiology and clinical course.^{19,20} Participants completed an extensive battery of questionnaires at bi-annual clinic visits and a brief set at bi-weekly online assessments.²⁰

As part of the case-crossover study, we asked participants about their current flare status at each clinic and bi-weekly assessment (“Are you currently experiencing a flare of your urologic or pelvic pain symptoms [i.e.,] symptoms that are much worse than usual?”). If participants responded affirmatively, they were directed to an additional questionnaire – the brief flare risk factor questionnaire (BFRFQ; Appendix 1) – that inquired about pre-flare exposures. We administered this questionnaire a maximum of three separate times when participants reported a flare and at three randomly selected assessments without a flare (one per 4-month period). We did not administer the BFRFQ at baseline because this visit was deemed too lengthy for an additional questionnaire.

This study was approved by the Institutional Review Boards at each site. All participants provided written informed consent.

Flare trigger assessment

On the BFRFQ,²⁰ participants were asked about their exposures in the three days (diet, physical activities, sedentary behaviors, and stress) or week (sexual activities, and infection and allergy symptoms) before their flare (flare assessment) or the date of questionnaire completion (non-flare assessment). Participants were also asked about their flare onset date, symptom intensity, and beliefs about current flare triggers in pre-specified categories to: 1) identify new flares in the past two weeks; 2) inform the quality of recalled pre-flare information; 3) categorize flares by duration and pain intensity, as these might have differing etiology; and 4) explore the possibility of recall bias, as participants’ responses might be influenced by both their knowledge of their flare status and trigger beliefs.

Possible triggers were selected based on the published literature,^{6–10,14–16,21} Interstitial Cystitis Association website, and clinical expert opinion. Questionnaire items were based on

the Harvard 131-item food frequency questionnaire,²² the International Physical Activity questionnaire,²³ occupational sitting questions,²⁴ the Perceived Stress Scale-4,²⁵ and clinical and epidemiologic expertise. We selected a three day/one week exposure period based on clinical expertise, and chose a lengthier period for sexual activities and infections because we suspected these factors might take longer to trigger a flare.

Statistical analyses

Only participants with at least one flare and one non-flare assessment were included in the analyses to allow for within-person comparisons. We used descriptive statistics and generalized estimating equations to describe participants' flare experiences and changes in symptoms during flares, and conditional logistic regression to calculate matched odds ratios (ORs), 95% confidence intervals (CIs), and p-values for interaction in stratified analyses. We explored each possible trigger by the presence of any exposure (any versus none), as a trend for increasing level of exposure (ordinal), and as individual levels (categorical). Because all three yielded similar results, we present the ordinal variable findings only. We also performed several pre-specified restricted and stratified analyses to evaluate possible biologic differences in flare etiology (e.g., by sex) and recall bias, and to identify sub-groups of participants/flares more likely to be influenced by certain triggers (Appendix Table 2 describes all sub-analyses).

RESULTS

Of the 424 participants who completed the MAPP study, 292 (176 women, 116 men) were included in the analysis after excluding those with negative responses to all flare questions (n=79), those who reported a flare at baseline but none later during follow-up (n=28), and those who did not complete at least one flare and non-flare assessment (n=25; Appendix Table 3 describes participant characteristics). Approximately 7.9% of participants completed one non-flare assessment, 11.3% completed two, and 80.8% completed three (total=797 assessments). For flares, 39.7% of participants completed one, 21.2% completed two, and 39.0% completed three assessments (total=582 assessments). Compared to non-flare assessments, participants' pelvic pain was higher during flare assessments by a mean of 2.7 points (95% CI=2.5–2.9), their urgency by 1.9 points (95% CI=1.6–2.1), and their frequency by 1.7 points (95% CI=1.5–1.9) on scales of 0–10. Participants' flares started a median of 5 days (interquartile range=3–8) before their flare assessment. When asked what they believed triggered their flares, participants provided one response for 67.9% of flares, two for 17.9%, and 3 for 14.2%. Female participants ($P=0.0006$), those diagnosed with IC/BPS ($P=0.032$), and those who provided >1 response for a previous flare ($P<0.0001$) were more likely to provide >1 response for their current flare. The most common responses were stress, diet, and “don't know” (Table 1).

Diet

In our full sample, no associations were observed for diet in the past three days and flare onset. Null results or inconsistent patterns were observed in most sub-analyses, except for those restricted to flares with suspected dietary triggers. In those analyses, positive findings

were observed for tomatoes, yogurt, spicy foods, alcohol, and caffeinated, carbonated beverages, and suggestive positive findings were observed for onions (Table 2).

Physical activities and sedentary behaviors

No associations were observed for riding a bicycle, motorcycle, horse, or small motorized vehicle, or for sitting for long periods of time in the past three days and flare onset. A suggestive positive association was observed for abdominal exercises in the main and most sub-analyses, which strengthened when the analyses were restricted to flares with suspected physical activity triggers (Table 3). Restricted analyses could not be performed for flares with suspected sedentary triggers because these were not queried on the BFRFQ.

Stress

Perceived stress in the past three days was not significantly associated with flare onset in any analyses (Table 3).

Sexual activities

In the full sample, no associations were observed for any of the individual sexual activities in the past week and flare onset. However, suggestive positive associations were observed for vaginal intercourse without a condom and for receiving oral intercourse with flares suspected to have been caused by sexual activity. Positive associations were also observed when all activities were combined and for engaging in sexual activities with a new partner in the main and most sub-analyses, particularly those restricted to flares with suspected sexual activity triggers (Table 4).

Infection-like symptoms and allergies

No associations were observed for symptoms of infection, including vaginal, respiratory, and gastrointestinal, as well as for fever and allergies in the past week in the main and most sub-analyses. Exceptions were suggestive positive associations for vaginal infection-like symptoms and fever with flares suspected to have been caused by infection, and for urinary tract infection (UTI)-like symptoms with all types of flares. Finally, no association was observed for infection, fever, or allergy symptoms combined, once UTI and vaginal infection-like symptoms were removed (Table 4).

DISCUSSION

In our large case-crossover analysis, only recent sexual activities and UTI-like symptoms were positively associated with flares. In sub-analyses restricted to flares suspected to have been caused by specific triggers, additional positive associations were observed for some (tomato; yogurt; spicy food; alcohol; caffeinated, carbonated beverage; and possibly onion intake; abdominal exercises; and recent vaginal infection-like symptoms and fever), but not other proposed triggers (e.g., citrus, stress).

Our findings for sexual activities are consistent with several patient reports suggesting that sexual activities trigger flares.^{5–7,13} However, how these activities trigger flares – whether through local physical trauma, acquisition of a genitourinary infection, or modification of

the genitourinary flora – is unknown and difficult to discern from our findings. For instance, although our suggestive positive findings for vaginal intercourse without, but not with, a condom and for receptive oral intercourse are consistent with a possible infectious mechanism, our findings for new sexual partners might be explained by either exposure to a new flora²⁶ or lack of adaptation to a new sexual partner/practice. This possibility was raised by previous focus group participants who mentioned developing methods to continue engaging in sexual activities without triggering a flare (e.g., medications before sexual activities⁵). Further exploration of mechanisms underlying our observed associations might help to extend these prevention strategies.

Similar to sexual activities, our findings for UTI- and vaginal infection-like symptoms are consistent with patient reports indicating that flares are frequently similar in sensation to genitourinary infections.^{5,13,16} Additionally, although our findings differ from those from studies that examined culturable, bacterial uropathogens and flares,^{16,17} they are consistent with those from a recent MAPP analysis that observed a greater prevalence of non-culturable *Candida* and *Saccharomyces* species in women experiencing flares,²⁷ suggesting that fungal species, such as those that cause vaginal infections, may contribute to flares. However, as we did not perform laboratory testing in our analysis, we cannot comment on whether participants' urogenital flora triggered their flares or whether flares and infections simply have similar symptoms. This question will be addressed in future MAPP studies comparing flare to non-flare assessments.

In contrast to our findings for sexual activities and infections, our findings for other suspected triggers, such as diet and stress, differ from those from most previous patient surveys,^{6–13} and medical and lay recommendations. These differences may be explained by several possible reasons, encompassing both the validity of our study design, as well as that of previous patient surveys. One major assumption of our study was that triggers take one day to one week to contribute to a flare. We based this time frame on clinical opinion and epidemiologic principles (i.e., ensuring that exposures clearly preceded flares), as little data existed to guide our decision. However, based on some earlier articles^{14,21} and our own recent focus group study,⁵ a more relevant exposure period for some triggers (e.g., diet) may be the hours rather than day(s)/week before a flare. This possible mis-specification of the exposure period may have contributed to non-differential misclassification and a bias towards the null for some, but not all, triggers. Other possible sources of misclassification are our trigger categories, which may have been too broad to capture susceptibility to one, but not another, sub-category (e.g., wine but not beer⁵); and random errors in pre-flare/non-flare exposure recall. However, why any of these concerns – mis-specification of the exposure period, broad exposure categories, and random recall errors – would apply only to null study findings in the full sample, and not to positive findings in restricted samples, is unclear because these should have been consistent across analyses. Additionally, studies of other pain conditions have detected trigger associations using a similar approach (i.e., examining self-reported exposures on the day(s) before a migraine).^{28,29}

Another major assumption of our study that may explain differences with previous patient surveys was that a sufficiently large proportion of participants are susceptible to triggers to detect them as statistically significant associations in our full sample (Appendix Table 4

summarizes susceptibility estimates from the literature). However, in a study comparing $n=1$ to population-level analyses of migraine patients, the authors estimated that 10% of participants must be susceptible to a trigger for it to be detectable in population-level analyses.³⁰ Other assumptions that may have influenced our power were that triggers contribute to flares a large proportion of the time in susceptible individuals, and that each individual has only a limited number of triggers. However, if flare triggers vary widely both across and within participants, then we may not have had sufficient power to detect associations in our full sample. As a further consideration, if participants who knew their flare triggers either avoided these triggers or engaged in self-care to mitigate flare symptoms (e.g., post-trigger medications⁵), then these activities may have further reduced our power. Finally, it is also possible that triggers contribute to some types of flares but not others, as we recently identified a broader spectrum of flares than previously reported in the literature (e.g., mild to painful flares).^{4,5} This possible heterogeneity in flare etiology may have further reduced our power.

Recognizing these concerns, we performed several sub-analyses to increase our ability to detect associations. These included analyses: 1) stratified by factors believed to identify differing UCPS sub-types, and 2) restricted to sub-groups of participants more likely to experience flare triggers (e.g., less knowledgeable participants), flares more likely to have been caused by certain triggers (e.g., those with suspected triggers), and more bothersome flares (e.g., painful flares). Although most of these findings were null, positive or more strongly positive results were observed for flares suspected to have been caused by specific triggers, raising the possibility that these exposures contribute to flares in a subset of participants. Furthermore, the fact that these associations were observed for some, but not all, possible triggers (e.g., tomatoes but not citrus), reduces, but does not completely eliminate, the possibility of recall bias as an explanation for our findings. This possibility should be ruled out in future studies, such as observational studies with prospective exposure assessment or randomized controlled trials of trigger elimination.

Despite some of the above-described limitations, our study has several strengths that distinguish it from most previous studies. These include its large sample size, investigation of a wide range of possible triggers, extensive characterization of participants to allow for numerous sub-analyses, and most importantly, empirical approach. These strengths lend credence to a final possible interpretation that some reported triggers may not, in fact, contribute to flares, or that they may do so in a much smaller proportion of patients than initially believed. Pursuing this possible explanation for our findings further is important to reduce the restrictions that avoiding multiple suspected triggers can impose on patients' lives.⁵

CONCLUSIONS

In one of the first studies to test flare triggers empirically, we found that only recent sexual activities and UTI-like symptoms were associated with flare onset in our full sample. Findings in our sub-analyses suggest the possibility that other reported triggers, such as diet, abdominal exercises, vaginal infection-like symptoms and fever, apply to only a subset of patients, or that our findings were susceptible to recall bias. Finally, null findings for other

proposed triggers in our main and sub-analyses raise questions about the validity of other triggers. These possibilities should be explored further to inform evidence-based flare prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key of Definitions for Abbreviations

MAPP	Multidisciplinary Approach to the Study of Chronic Pelvic Pain
CI	Confidence Interval
OR	Odds Ratio
UCPPS	Urologic Chronic Pelvic Pain Syndrome
BFRFQ	Brief Flare Risk Factor Questionnaire
UTI	Urinary Tract Infection

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Appendix

Pin # _____
	Discovery Site: _____ Clinical Center: _____
	CRF Date: ____/____/____ Visit #: _____

Brief Flare Risk Factor Questionnaire
Participant completes at Follow-up Contacts as needed.

Instructions for Research Coordinator:

- For reported symptom flares:** This questionnaire is to be completed at each of the first three instances when the Participant reports a symptom flare that has started in the past two weeks. If a reported symptom flare did not start in the past two weeks, please complete Q.#1 only. Please note, when this questionnaire is being completed after a reported symptom flare, the questions below apply to symptoms "today" and subsequent sections refer to "the 3 days before your flare began" or "the week before your flare began".
- For non-flares:** This questionnaire is also to be completed at randomly assigned intervals when the Participant reports NOT experiencing a symptom flare. When this questionnaire is completed at these intervals, please skip Q.#s 1-3 and begin this questionnaire at Q.#5a. Please note, when this questionnaire is being completed for a non-flare the questions below apply to symptoms "today" and subsequent sections refer to "the previous 3 days before today" or "the previous week before today".

- Did your flare start in the past two weeks? ☐ Yes ☐ No
If "Yes", continue with this questionnaire. If "No", please stop here.
- How many days have you been experiencing your current flare? _____ days
- What do you think caused your flare?
(please check all that apply)

☐ I don't know/not sure
☐ Eating a certain food or drinking a certain beverage
☐ Performing a certain physical activity
☐ Performing a certain sexual activity
☐ Getting an infection
☐ Stress
☐ Other

(Specify: _____)

Pain, Urgency, Frequency Severity Scales

3a. Think about the pain, pressure, and discomfort associated with your bladder/prostate and/or pelvic region. On average, how would you rate these symptoms today?

No pain or pressure or discomfort	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Most severe discomfort I can imagine
0	1	2	3	4	5	6	7	8	9	10	

3b. Urgency is defined as the urge or pressure to urinate. On average, how would you rate the urgency that you have felt today?

No urgency	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Most severe urgency I can imagine
0	1	2	3	4	5	6	7	8	9	10	

3c. Think about your frequency of urination. On average, how would you rate your frequency of urination today?

Totally normal	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Most severe frequency I can imagine
0	1	2	3	4	5	6	7	8	9	10	

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FLARE

The questions in the sections below refer to **"the 3 days before your flare began or the previous 3 days before today"**. Please note that if you **are** experiencing a flare, these questions refer to the **"3 days before your flare began"**. If you are **not** experiencing a flare, these questions refer to **"the previous 3 days before today"**.

For each of the foods and beverages listed below, please indicate how many servings or drinks you consumed **in the 3 days before your flare began, (or if not experiencing a flare, the previous 3 days before today)**. For instance, if you drank one glass of orange juice every morning in the 3 days before your flare began or the previous 3 days before today for a total of three glasses of orange juice in 3 days before your flare began or the previous 3 days before today, then you would check the box for "2 or more" servings.

If some of the foods or drinks you consumed in the 3 days before your flare began or the previous 3 days before today contain more than one of the options listed below, please check all the options that apply. For instance, if you had a salad that contained approximately one tomato and 1-2 Tablespoons of salad dressing, then you would check the box for "one" serving of tomatoes and "one" serving of salad dressing.

	Number of servings/drinks in the 3 days before your flare began, (or if not experiencing a flare, the previous 3 days before today)		
Fruit and Fruit Juices:			
4. Citrus fruits (1 serving: 1 orange, clementine, tangerine, mandarin, or ½ grapefruit; or 1 glass of orange or grapefruit juice)	☐ None	☐ 1 One	☐ 2 2 or more
5. Pineapple (1 serving: 1 cup of pineapple or 1 glass of pineapple juice)	☐ None	☐ 1 One	☐ 2 2 or more
6. Cranberry (1 serving: 1 glass of cranberry juice)	☐ None	☐ 1 One	☐ 2 2 or more
Vegetables and Vegetable Juices:			
7. Tomato (1 serving: 1 tomato, 1 glass of tomato juice, or ½ cup of tomato sauce)	☐ None	☐ 1 One	☐ 2 2 or more
8. Onion (1 serving: 1 raw slice or ½ cup cooked)	☐ None	☐ 1 One	☐ 2 2 or more
Dairy Products:			
9. Aged, usually strong-tasting cheese (1 serving: 1 slice or 1 oz. of cheese, such as Blue cheese, aged cheddar, or Brie. Do not include mild cheeses, such as cottage cheese, or processed American cheese.)	☐ None	☐ 1 One	☐ 2 2 or more
10. Sour cream (1 serving: 1 Tbsp)	☐ None	☐ 1 One	☐ 2 2 or more
11. Yogurt (1 serving: 1 cup or 1 small container (~6-8 oz))	☐ None	☐ 1 One	☐ 2 2 or more
Other Foods and Drinks:			
12. Beans (1 serving: ½ cup of beans, such as fava beans, lima beans, or soy beans)	☐ None	☐ 1 One	☐ 2 2 or more
13. Nuts (1 serving: 1 small packet or 1 oz. of nuts, such as peanuts or almonds, or 1 Tbs of peanut butter)	☐ None	☐ 1 One	☐ 2 2 or more
14. Vinegar, salad dressing (1 serving: 1-2 Tbs)	☐ None	☐ 1 One	☐ 2 2 or more

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15. Spicy food (1 serving: 1 meal containing hot peppers, chili peppers, hot sauce or other spicy ingredients)	☐ None	☐ 1 One	☐ 2 2 or more
16. Chocolate (1 serving: 1 small chocolate bar or 3-4 pieces of chocolate)	☐ None	☐ 1 One	☐ 2 2 or more
Other Drinks:			
17. Alcoholic drinks (1 serving: 1 beer, glass of wine, cocktail, or shot)	☐ None ☐ 1-3 (1/day) ☐ 4-11 (2-3/day) ☐ 12-20 (4-6/day) ☐ 21 or more (7 or more/day)		
18. Caffeinated coffee or tea (1 serving: 1 cup)	☐ None ☐ 1-3 (1/day) ☐ 4-11 (2-3/day) ☐ 12-20 (4-6/day) ☐ 21 or more (7 or more/day)		
19. Caffeinated carbonated drinks (1 serving: 1 glass, can or bottle of drinks, such as Coke, Pepsi, or Mountain Dew)	☐ None ☐ 1-3 (1/day) ☐ 4-11 (2-3/day) ☐ 12-20 (4-6/day) ☐ 21 or more (7 or more/day)		
20. Non-caffeinated carbonated drinks (1 serving: 1 glass, can or bottle of drinks, such as 7-Up, or Sprite)	☐ None ☐ 1-3 (1/day) ☐ 4-11 (2-3/day) ☐ 12-20 (4-6/day) ☐ 21 or more (7 or more/day)		

In the 3 days before your flare began, (or if not experiencing a flare, the previous 3 days before today), how much time did you spend doing the following activities?

It may be helpful to think about how much time you usually spend doing the following activities and then think about whether 3 days before your flare began, or if not experiencing a flare, the previous 3 days before today were different. For instance, if 3 days before your flare began or the previous 3 days before today were work days, and you usually sit eight hours a day at work, and 3 days before your flare began or the previous 3 days before today were no different than usual, then you sat at work for 24 hours, and you would check the box marked "12-26 hrs (4-8 hrs/day)".

	Time of activity in the 3 days before your flare began, (or if not experiencing a flare, the previous 3 days before today)
Physical Activities:	
21. Driving/sitting in a car, truck, bus, train or plane (Do not include bicycle or motorcycle riding).	☐ No Time ☐ 1-5 hrs (1 hr/day) ☐ 6-11 hrs (2-3 hrs/day) ☐ 12-26 (4-8 hrs/day) ☐ 27 or more hrs (9 or more hrs/day)

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22. Sitting at work (if you work outside the home; do not include sitting while driving if your job involves driving).
23. Sitting at home (e.g., watching TV, reading, having dinner), visiting friends or doing coursework.
24. Riding a bicycle, exercise bicycle, horse, or smaller motorized vehicles, such as motorcycles, mopeds, lawn mowers, or tractors.
25. Doing exercises that work your stomach muscles, such as sit-ups, crunches, push-ups, heavy lifting, or Pilates.

- ☐ No Time
☐ 1-5 hrs (1 hr/day)
☐ 6-11 hrs (2-3 hrs/day)
☐ 12-26 (4-8 hrs/day)
☐ 27 or more hrs (9 or more hrs/day)
- ☐ No Time
☐ 1-5 hrs (1 hr/day)
☐ 6-11 hrs (2-3 hrs/day)
☐ 12-26 (4-8 hrs/day)
☐ 27 or more hrs (9 or more hrs/day)
- ☐ No Time
☐ Less than 1 hour
☐ 1 hour
☐ 2 hours
☐ 3 hours
☐ 4 or more hours
- ☐ No Time
☐ Less than 1 hour
☐ 1 hour
☐ 2 hours
☐ 3 hours
☐ 4 or more hours

Stress:

Please indicate how often you felt or thought a certain way in **the 3 days before your flare began, (or if not experiencing a flare, the previous 3 days before today)**

26. Felt unable to control the important things in your life.
27. Felt confident about your ability to handle your personal problems.
28. Felt that things were going your way.

- ☐ Never
☐ Almost never
☐ Sometimes
☐ Fairly often
☐ Very often
- ☐ Never
☐ Almost never
☐ Sometimes
☐ Fairly often
☐ Very often
- ☐ Never
☐ Almost never
☐ Sometimes
☐ Fairly often
☐ Very often

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29. Felt difficulties were piling up so high that you could not overcome them.

- ☐ Never
☐ Almost never
☐ Sometimes
☐ Fairly often
☐ Very often

Sexual Activities

The next set of questions is about your recent sexual activity. We realize that these questions may be sensitive. If you do not feel comfortable answering them, you may skip to the next section.

30. **In the week before your flare began, (or if not experiencing a flare, the previous week before today)** did you have any sexual activity (oral, vaginal or anal sexual intercourse)?

- ☐ Yes ☐ No

31. If **"Yes"**, **in the week before your flare began, (or if not experiencing a flare, the previous week before today)** did you do any of the following sexual activities? (please check all that apply)

For Males

Had vaginal sexual intercourse:

- with a condom ☐
 without a condom ☐
 with a diaphragm ☐
 Received oral intercourse ☐
 Received anal intercourse ☐
 Had insertive anal intercourse where you put your penis into someone else's anus/bum:
 with a condom ☐
 without a condom ☐

For Females

Had vaginal sexual intercourse:

- with a condom ☐
 without a condom ☐
 with a diaphragm ☐
 Received oral intercourse ☐
 Received anal intercourse:
 with a condom ☐
 without a condom ☐

32. **In the week before your flare began, (or if not experiencing a flare, the previous week before today)** did you have any new sexual partners?

- ☐ Yes ☐ No

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Infections

33. *In the week before your flare began, (or if not experiencing a flare, the previous week before today) did you have any of the following infections or additional symptoms? (please check all that apply)*

- ☐ Vaginal infection (symptoms include vaginal itching or burning, unusual vaginal discharge or change in odor) (females only)
- ☐ Urinary tract infection (symptoms include burning during urination, frequent urination, sudden urge to urinate, or blood in your urine)
- ☐ Cold, flu, sinus infection, pneumonia, bronchitis, or other respiratory tract infection (symptoms include sore throat, cough, earache, sinus congestion or pain, or a runny nose)
- ☐ Gastroenteritis or "the stomach flu" (symptoms include nausea, vomiting or diarrhea)
- ☐ Symptoms of hay fever (such as itchy watery eyes, or sneezing), or an allergic reaction
- ☐ Fever
- ☐ Other infections (Specify: _____)

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FLARE**Appendix Table 2**

Pre-specified restricted and stratified analyses^a performed to evaluate possible biologic differences in flare etiology and recall bias, and to identify sub-groups of participants or flares more likely to have been influenced by flare triggers

Restricted/stratified analysis	Purpose	Rationale	Analytic sample
Longer-lasting flares ^b	Explore biologic differences in flare etiology	More bothersome type of flare for patients ^{1,2}	All longer-lasting flares and all non-flare assessments from participants with these types of flares
Painful flares ^c	Explore biologic differences in flare etiology	More bothersome type of flare for patients ^{1,2}	All painful flares and all non-flare assessments from participants with these types of flares
Pain widespread-ness phenotype	Explore biologic differences in flare etiology	Believed to identify UCPPS subtypes ³	All flare and non-flare assessments from participants with this phenotype
Presence of chronic overlapping pain conditions	Explore biologic differences in flare etiology	Believed to identify UCPPS subtypes ⁴	All flare and non-flare assessments from participants with these conditions
Presence of bladder hypersensitivity	Explore biologic differences in flare etiology	Believed to identify UCPPS subtypes ⁵	All flare and non-flare assessments from participants with this phenotype
Presence of sensory hypersensitivity ^d	Explore biologic differences in flare etiology	Participants with sensory hypersensitivity might be	All flare and non-flare assessments from

Restricted/stratified analysis	Purpose	Rationale	Analytic sample
	Identify sub-groups of participants or flares more likely to be influenced by possible flare triggers	more susceptible to flare triggers.	participants with this phenotype
Female versus male sex	Explore biologic differences in flare etiology	Possible differences by sex or IC/BPS versus CP/ CPPS diagnosis	All flare and non-flare assessments from participants of the same sex
	Explore recall bias	Greater potential for recall bias among women because of greater exposure to the IC/BPS literature	
	Identify sub-groups of participants or flares more likely to be influenced by possible flare triggers	Men possibly less knowledgeable about flare triggers/prevention (and thus possibly more likely to experience a trigger-related flare) because of lesser exposure to the IC/BPS literature	
IC/BPS versus CP/ CPPS diagnosis	Explore biologic differences in flare etiology	Possible differences by IC/BPS 4versus CP/ CPPS diagnosis	All flare and non-flare assessments from participants with the same diagnosis
	Explore recall bias	Greater potential for recall bias among participants diagnosed with IC/BPS because of greater exposure to the IC/BPS literature	
	Identify sub-groups of participants or flares more likely to be influenced by possible flare triggers	CP/ CPPS patients possibly less knowledgeable about flare triggers/prevention (and thus possibly more likely to experience a trigger-related flare) because of lesser exposure to the IC/BPS literature	
Condition duration (2 versus <2 years)	Explore recall bias	Greater potential for recall bias among those with a longer condition duration because of a greater length of time to research flare triggers and/or develop flare trigger beliefs	All flare and non-flare assessments from participants with the same condition duration
	Identify sub-groups of participants or flares more likely to be influenced by possible flare triggers	Participants with a shorter condition duration may be less knowledgeable about flare triggers/prevention (and thus possibly more likely to experience a trigger-related flare) because of less time to research flare triggers/ develop flare trigger beliefs	
Flare suspected to have been caused by a certain trigger	Explore recall bias	Participants may report exposures differently	All flares suspected to have been caused by a

Restricted/stratified analysis	Purpose	Rationale	Analytic sample
	Identify sub-groups of participants or flares more likely to be influenced by possible flare triggers	given knowledge of their flare status and their flare trigger beliefs Flares suspected to have been caused by a certain trigger may be more likely to have actually been caused by that trigger	certain trigger and all non-flare assessments from participants with these flares
Presence of irritable bowel syndrome	Identify sub-groups of participants or flares more likely to be influenced by possible flare triggers	Participants in our previous focus group study reported that diet triggered their bowel symptoms, which in turn triggered their UCPPS symptoms. ²	All flare and non-flare assessments from participants with irritable bowel syndrome
Removing flare and non-flare assessments with other possible triggers (i.e., sexual activities)	Identify sub-groups of participants or flares more likely to be influenced by possible flare triggers	Flares triggered by one risk factor might be less likely to be triggered by other possible risk factors at the same time.	Excluding all flares and non-flares with a report of any sexual activity in the previous week
	Explore recall bias	Lesser potential for recall bias because of lesser exposure to the BFRFQ	
First flare during follow-up	Identify sub-groups of participants or flares more likely to be influenced by possible flare triggers	Possibly less knowledgeable about flare triggers/prevention (and thus possibly more likely to experience a trigger-related flare) because of lesser exposure to the BFRFQ	The first flare and non-flare assessment during follow-up

BFRFQ=brief flare risk factor questionnaire; CP/CPPS=chronic prostatitis/chronic pelvic pain syndrome; IC/BPS=interstitial cystitis/bladder pain syndrome; UCPPS=urologic chronic pelvic pain syndrome

^aDespite our large number of statistical tests, we used an α -level of 0.05 for each test because of the exploratory nature of our study, which is the first to evaluate many of these factors empirically; and our focus on: 1) previously-reported triggers from the literature; and 2) patterns of findings rather than individual findings.

^bDefined as median duration of 5 days.

^cDefined as: 1) median intensity of 6 on a scale of 0–10; or alternatively as 2) occurring near in time to when participants sought medical care for their symptoms as a marker of flare severity.

^dDefined as self-reported sensitivity to chemicals (e.g., perfumes, laundry detergents, gasoline), sound, odor, or bright lights.

Appendix Table 3

Baseline demographic and clinical characteristics of participants in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain flare trigger case-crossover study, 2009–2013.

All participants (n=292)	
Demographic characteristics:	
Age (years, mean (SD))	43.2 (15.1)
Female (%)	60.3
Caucasian (%)	92.8
Hispanic ethnicity (%)	5.1
Clinical characteristics:	

All participants (n=292)	
Duration of symptoms (years, mean (SD))	8.4 (10.0)
Duration of symptoms <1 year (%)	10.7
Age at diagnosis of IC/BPS (years, mean (SD))	41.5 (13.5)
Age at diagnosis of CP/CPPS (years, mean (SD))	36.4 (14.2)
Medication class (%)	
Central acting medication (e.g., pregabalin, tricyclics)	44.9
Peripheral acting medication (e.g., pentosan polysulfate)	18.2
Opioids	12.3
No medications	24.7
Chronic overlapping pain conditions (%)	
Chronic fatigue syndrome	11.3
Irritable bowel syndrome	31.2
Temporomandibular joint pain	24.0
Fibromyalgia	9.3
Vulvodynia	11.0
Migraine headache	24.3
More than one condition	39.4
Urologic and pelvic pain intensity (mean (SD))	
Pelvic pain (0–10)	5.1 (2.1)
Overall urologic or pelvic pain symptoms (0–10)	5.3 (2.3)
Genitourinary Pain Index pain score (0–23)	12.7 (4.4)
MAPP composite pain score (0–28) ⁶	15.3 (5.5)
Urinary symptom intensity (mean (SD))	
Urinary frequency (0–10)	5.1 (2.5)
Urgency (0–10)	4.9 (2.6)
Genitourinary Pain Index urinary score (0–10)	5.4 (3.0)
MAPP composite urinary score (0–25) ⁶	12.9 (6.3)
American Urological Association Symptom Index (0–35)	15.9 (8.7)
Composite pain and urinary symptom scores (mean (SD))	
Interstitial Cystitis Symptom Index (0–20)	10.1 (4.7)
Interstitial Cystitis Problem Index (0–16)	8.7 (4.4)
Genitourinary Pain Index total score (0–45)	25.9 (8.5)

CP/CPPS=chronic prostatitis/chronic pelvic pain syndrome; IC/BPS=interstitial cystitis/bladder pain syndrome;
SD=standard deviation.

Appendix Table 4

Prevalence estimates of susceptibility to proposed flare triggers from the published literature

Proposed flare trigger	Prevalence estimates of susceptibility (% of participants)
Diet	
Citrus fruits	19–90 ^{7–11}
Pineapple	16–79 ^{10,11}

Proposed flare trigger	Prevalence estimates of susceptibility (% of participants)
Cranberry	73–79 ^{9,10}
Tomato	80–85 ^{9,10}
Onion	13 ¹¹
Aged cheese	12 ⁸
Sour cream	-----
Yogurt	-----
Beans	-----
Nuts	15 ⁸
Vinegar, salad dressing	83 ⁹
Spicy foods	23–88 ^{7–11}
Chocolate	22–29 ^{7,8,11}
Alcoholic beverages	19–87 ^{7–9,11}
Caffeinated beverages	26–91 ^{7–11}
Carbonated beverages	26–86 ^{7,8,10,11}
Physical or sedentary activities	
Riding a bicycle, exercise bicycle, horse, or smaller motorized vehicle	-----
Doing exercises that work abdominal muscles	-----
Driving/sitting in a car, truck, bus, train, or plane	-----
Sitting at work or home	-----
Stress	61–85 ^{7,8,10}
Any sexual activities	50–82 ^{7,8,12}
Allergies	28 ¹⁰

Proportions were calculated for references ⁹ and ¹¹.

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Table 1

Patient-reported triggers of urologic chronic pelvic pain syndrome flares; Multidisciplinary Approach to the Study of Chronic Pelvic Pain flare trigger case-crossover study, 2009–2013.

Reported trigger	Number of reported triggers per flare		
	One reported trigger (n=392 flares, %)	Two reported triggers (n=103 flares, %)	Three or more reported triggers (n=83 flares, %)
Stress	10.5	67.0	85.4
Diet	12.2	34.9	69.5
Sexual activities	4.3	17.5	40.2
Physical activities	4.9	15.5	35.4
Infection	4.1	9.7	19.5
Menstrual cycle ¹	4.0	7.0	9.5
New or increasing dose of medications or medical procedures	3.3	2.9	7.3
Stopped taking medications or undergoing therapies	2.0	1.9	3.7
Bowel movements/constipation	1.3	2.9	1.2
Dehydration	0.0	1.9	3.7
Don't know	51.0	30.1	47.6
Other ²	4.1	10.7	12.2

¹Percentage of flares among female participants only.

²Other responses included: winter weather; plane travel; soap; having a massage; tighter workout clothes; lack of exercise and hot baths; lack of pelvic exercises; more sitting than usual; more driving than usual; fatigue/poor sleep; cooking and standing for >10 hours over 2–3 days; falling down the stairs; pelvic injury; kidney stone; Hunner's ulcer; ruptured ovarian cyst; pregnancy; back pain; diarrhea and bloating; and bearing down when going to the bathroom, leading to semen drippage.

Table 2

Associations between consumption of specific foods and beverages in the past three days and urologic chronic pelvic pain syndrome flare onset; Multidisciplinary Approach to the Study of Chronic Pelvic Pain flare trigger case-crossover study, 2009–2013.

	All participants						Female participants	Male participants	Sample restricted to flares with suspected dietary triggers
	Pre-flare servings (%)								
	Pre-non-flare servings (%)								
	0	1	2	0	1	2	OR (95% CI) ^{1,2}	OR (95% CI) ^{1,4,5}	OR (95% CI) ^{1,6}
Fruit and fruit juices									
Citrus fruits	67.5	18.4	13.4	64.9	19.9	14.8	0.91 (0.75–1.11)	0.98 (0.75–1.26)	0.83 (0.54–1.29)
Pineapple	86.3	9.5	3.3	85.8	9.8	3.8	0.87 (0.67–1.13)	0.92 (0.67–1.26)	1.32 (0.81–2.15)
Cranberry	87.6	6.7	4.3	88.2	7.5	3.6	1.17 (0.87–1.59)	1.31 (0.87–1.98)	1.28 (0.69–2.39)
Vegetables, and vegetable juices and sauces									
Tomato products	45.2	30.6	23.0	49.2	30.5	19.4	1.12 (0.95–1.33)	1.13 (0.91–1.40)	1.57 (1.11–2.20)
Onion	47.3	31.6	20.3	46.5	34.8	17.7	1.07 (0.88–1.29)	1.08 (0.84–1.38)	1.36 (0.96–1.91)
Dairy products									
Aged cheese	61.3	21.6	16.2	58.8	24.0	16.6	0.91 (0.76–1.09)	0.96 (0.75–1.23)	0.95 (0.66–1.36)
Sour cream	75.3	16.3	7.4	75.7	17.6	5.5	1.17 (0.92–1.49)	1.19 (0.88–1.62)	1.09 (0.71–1.68)
Yogurt	61.7	15.3	21.6	63.5	16.7	18.3	1.14 (0.93–1.39)	1.06 (0.83–1.35)	1.47 (1.02–2.11)
Other foods									
Beans	62.5	22.2	14.3	59.2	26.6	13.4	0.92 (0.76–1.11)	0.99 (0.76–1.27)	1.00 (0.69–1.44)
Nuts	34.0	28.4	36.8	35.8	30.2	33.2	1.07 (0.90–1.27)	0.97 (0.78–1.20)	1.05 (0.76–1.45)
Vinegar, salad dressing	49.1	33.5	16.3	47.2	31.7	19.8	0.89 (0.73–1.08)	0.87 (0.68–1.11)	1.03 (0.71–1.51)
Spicy foods	59.1	25.3	14.4	57.3	25.1	17.1	0.99 (0.81–1.22)	1.08 (0.83–1.41)	1.67 (1.13–2.48)
Chocolate	29.2	32.1	37.5	30.7	34.5	34.0	1.08 (0.90–1.30)	0.97 (0.77–1.23)	1.35 (0.93–1.95)
Other beverages									
Alcoholic beverages	60.5	28.0	10.8	59.8	28.5	11.0	1.09 (0.84–1.43)	1.01 (0.71–1.44)	1.61 (1.01–2.55)

	All participants						Female participants	Male participants	Sample restricted to flares with suspected dietary triggers
	Pre-flare servings (%)								
	Pre-non-flare servings (%)								
	0	1	2	0	1	2	OR (95% CI) ^{1,2}	OR (95% CI) ^{1,4,5}	OR (95% CI) ^{1,6}
Caffeinated coffee or tea	45.2	37.6	16.2	42.5	40.4	16.2	1.01 (0.77–1.32)	1.04 (0.74–1.44)	1.20 (0.71–2.09)
Caffeinated, carbonated beverages	63.2	28.0	7.7	62.0	31.6	5.8	1.16 (0.88–1.54)	1.31 (0.89–1.92)	2.19 (1.28–3.75)
Non-caffeinated, carbonated beverages	70.3	25.1	3.6	70.9	24.0	3.6	1.01 (0.77–1.31)	0.92 (0.65–1.31)	1.19 (0.75–1.90)

Statistically significant associations ($p < 0.05$) are indicated in bold.

CI=confidence interval; OR=odds ratio.

¹OR for increasing number of servings calculated by conditional logistic regression to compare pre-flare to -non-flare values from the same participant.

²Includes 292 participants with 582 flare assessments and 797 non-flare assessments.

³Includes 176 participants with 363 flare assessments and 471 non-flare assessments.

⁴Includes 116 participants with 219 flare assessments and 326 non-flare assessments.

⁵None of the findings for male participants were statistically significantly different than those for female participants (all p -values for interaction > 0.1).

⁶Restricted to flares with suspected dietary triggers ($N=92$ participants with 141 flare assessments and 257 non-flare assessments).

Table 3

Associations between engaging in specific physical activities and sedentary behaviors, and perceived stress in the past three days and urologic chronic pelvic pain syndrome flare onset; Multidisciplinary Approach to the Study of Chronic Pelvic Pain flare trigger case-crossover study, 2009–2013.

	All participants						Female participants	Male participants	Sample restricted to flares with suspected triggers
	Pre-flare duration or intensity (%)			Pre-non-flare duration or intensity (%)					
	0 hrs	0.1–1 hr	1 hr	0 hrs	0.1–1 hr	1 hr			
Physical activities									
Riding a bicycle, exercise bicycle, horse, or smaller motorized vehicle	76.6	9.8	12.9	74.3	10.8	14.2	0.90 (0.74–1.10)	0.93 (0.71–1.23)	0.88 (0.66–1.17)
Doing exercises that work abdominal muscles, such as sit-ups or pilates	53.4	23.5	22.3	54.6	25.5	18.8	1.17 (0.97–1.42)	1.15 (0.90–1.46)	1.22 (0.89–1.68)
Sedentary behaviors									
	0 hrs	1–5 hrs	6 hrs	0 hrs	1–5 hrs	6 hrs			
Driving/sitting in a car, truck, bus, train, or plane	9.3	63.6	26.5	9.4	65.6	24.2	1.08 (0.86–1.35)	1.10 (0.82–1.46)	1.05 (0.73–1.52)
Sitting at work or home	1.4	13.1	84.9	1.9	13.9	83.7	1.13 (0.82–1.54)	1.19 (0.79–1.79)	1.05 (0.65–1.69)
Stress									
	0–7	8	9–16	0–7	8	9–16			
Perceived stress (<i>on a scale of 0–16</i>)	24.7	34.0	38.5	27.6	35.6	33.8	1.12 (0.95–1.32)	1.19 (0.97–1.47)	1.02 (0.79–1.32)
									1.17 (0.89–1.55)

Statistically significant associations ($p < 0.05$) are indicated in bold.

CI=confidence interval; OR=odds ratio

¹ OR for increasing duration/intensity calculated by conditional logistic regression to compare pre-flare to -non-flare values from the same participant.

² Includes 292 participants with 582 flare assessments and 797 non-flare assessments.

³ Includes 176 participants with 363 flare assessments and 471 non-flare assessments.

⁴ Includes 116 participants with 219 flare assessments and 326 non-flare assessments.

⁵ None of the findings for male participants were statistically significantly different than those for female participants (all p -values for interaction > 0.3).

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Restricted to flares with suspected physical activity (N=51) participants with 64 flare assessments and 134 non-flare assessments) and stress triggers (N=123 participants with 180 flare assessments and 334 non-flare assessments), as appropriate. Analyses restricted to flares with suspected sedentary triggers could not be performed because these possible triggers were not queried on the brief flare risk factor questionnaire.

Table 4

Associations between engaging in sexual activities, infection-like symptoms, and allergies in the past week and urologic chronic pelvic pain syndrome flare onset; Multidisciplinary Approach to the Study of Chronic Pelvic Pain flare trigger case-crossover study, 2009–2013.

Sexual activities	All participants			Female participants		Male participants		flares with suspected triggers
	Pre-flare activities/symptoms (%)	Pre-non-flare activities/symptoms (%)		OR (95% CI) ^{1,2}	OR (95% CI) ^{1,3}	OR (95% CI) ^{1,4,5}	OR (95% CI) ^{1,6}	
Vaginal intercourse with a condom	8.2		8.9	0.92 (0.55–1.56)	1.06 (0.56–2.03)	0.70 (0.28–1.74)	0.79 (0.29–2.16)	
Vaginal intercourse without a condom	37.3		37.4	1.25 (0.90–1.75)	1.05 (0.68–1.63)	1.62 (0.95–2.75)	6.58 (1.85–23.37)	
Receptive oral intercourse	16.8		15.6	1.29 (0.88–1.91)	1.51 (0.89–2.57)	1.07 (0.60–1.91)	2.00 (0.92–4.34)	
Anal intercourse	2.1		2.3	0.95 (0.35–2.55)	1.68 (0.45–6.33)	0.40 (0.07–2.21)	1.42 (0.17–11.78)	
Any sexual activities	50.5		48.3	1.44 (1.06–1.96)	1.27 (0.86–1.89)	1.76 (1.07–2.90)	7.31 (2.45–21.82)	
New sexual partner	3.3		1.8	2.53 (1.10–5.83)	1.44 (0.42–4.91)	4.15 (1.24–13.88)	7.73 (1.51–39.42)	
Infection-like symptoms/allergies								
Vaginal infection symptoms (e.g., vaginal itching or burnings, unusual discharge or change in odor)	6.0		4.6	1.25 (0.71–2.18)	1.25 (0.71–2.18)	-----	3.45 (1.18–10.05)	
Urinary tract infection symptoms (e.g., burning during urination, frequent urination, sudden urge to urinate, or blood in urine)	9.8		4.0	3.39 (2.02–5.68)	3.88 (2.04–7.40)	2.62 (1.10–6.21)	42.94 (5.71–322.79)	
Respiratory tract infection symptoms (e.g., sore throat, cough, earache, sinus congestion or pain, or runny nose)	17.9		16.8	1.08 (0.78–1.49)	1.02 (0.68–1.53)	1.20 (0.69–2.06)	1.19 (0.45–3.19)	
Gastroenteritis symptoms (e.g., nausea, vomiting, or diarrhea)	5.2		3.3	1.47 (0.82–2.63)	1.31 (0.69–2.51)	2.32 (0.61–8.79)	0.81 (0.13–5.00)	
Fever symptoms	2.9		2.5	0.95 (0.44–2.06)	0.86 (0.35–2.12)	1.28 (0.28–5.83)	4.97 (0.91–27.01)	
Other infection symptoms	1.9		2.0	0.81 (0.36–1.84)	0.90 (0.34–2.38)	0.60 (0.12–3.10)	0.74 (0.17–3.16)	
Hay fever or allergic reaction (e.g., itchy, watery eyes or sneezing)	14.1		12.9	1.00 (0.68–1.46)	0.95 (0.60–1.51)	1.11 (0.57–2.16)	0.95 (0.26–3.44)	
Any symptoms of infection or allergy	42.1		36.3	1.30 (1.00–1.68)	1.31 (0.94–1.81)	1.28 (0.84–1.95)	6.83 (2.26–20.62)	

<i>Sexual activities</i>	All participants			Female participants		Male participants		flares with suspected triggers	
	Pre-flare activities/symptoms (%)	Pre-non-flare activities/symptoms (%)	OR (95% CI) ^{1,2}	OR (95% CI) ^{1,3}	OR (95% CI) ^{1,4,5}	OR (95% CI) ^{1,6}	OR (95% CI) ^{1,6}	OR (95% CI) ^{1,6}	OR (95% CI) ^{1,6}
Any symptoms of infection or allergy except genitourinary infections	33.0	31.2	1.04 (0.79, 1.36)	1.16 (0.83–1.61)	1.10 (0.70–1.72)	1.14 (0.47, 2.76)			

Statistically significant associations ($p < 0.05$) are indicated in bold.

CI=confidence interval; OR=odds ratio.

¹ Calculated by conditional logistic regression to compare pre-flare to -non-flare values from the same participant.

² Includes 292 participants with 582 flare assessments and 797 non-flare assessments.

³ Includes 176 participants with 363 flare assessments and 471 non-flare assessments.

⁴ Includes 116 participants with 219 flare assessments and 326 non-flare assessments.

⁵ None of the findings for male participants were statistically significantly different than those for female participants (all p -values for interaction > 0.1).

⁶ Restricted to flares with suspected sexual activity ($N=53$ participants with 68 flare assessments and 148 non-flare assessments) and infection/allergy triggers ($N=36$ participants with 42 flare assessments and 96 non-flare assessments), as appropriate.