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Association between pelvic pain bothersomeness and pain sensitivity: A community-based cross-sectional study of young adult females in the Raine Study

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Abstract

Objective: Pelvic pain has been associated with augmented nociceptive processing, but large studies controlling for multiple potential confounding factors are lacking. This study investigated the association between pelvic pain bothersomeness and pain sensitivity in young adult women, accounting for potential confounding factors.

Design: Cross-sectional study.

Setting: Community-dwelling sample.

Population: The Raine Study Gen2-22 year follow-up ($n = 475$).

Main outcome measures: The experience of bothersomeness related to pelvic pain was determined from a question in the Urogenital Distress Inventory short form. Pain sensitivity was measured using pressure pain and cold pain thresholds. Potential confounding factors included ethnicity, marital status, highest level of education, income, waist–hip ratio, level of activity, sleep quality, smoking, comorbidity history, C-reactive protein level, musculoskeletal pain experience and psychological distress.

Results: Three hundred and sixty-two women (76.2%) reported no pelvic pain bothersomeness, 74 (15.6%) reported mild pelvic pain bothersomeness and 39 (8.2%) reported moderate–severe pelvic pain bothersomeness. After adjusting for marital status (and test site), moderate–severe pelvic pain bothersomeness was associated with a lower pressure pain threshold (i.e. greater pressure pain sensitivity) (coefficient −51.46, 95% CI −98.06 to −4.86, $p = 0.030$). After adjusting for smoking, moderate–severe pelvic pain bothersomeness was also associated with a higher cold pain threshold (i.e. greater cold pain sensitivity) (coefficient 4.35, 95% CI 0.90–7.79, $p = 0.014$).

Conclusions: This study suggests augmented nociceptive processing as a contributing factor in pelvic pain bothersomeness for some women. Thorough assessment of women who present clinically with pelvic pain should consider pain sensitivity as a potential contributing factor to their presentation.

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1 | INTRODUCTION

Pelvic pain (PP) occurs in the lower abdominal region below the umbilicus, and includes the pelvis, pelvic organs and genitalia. Pelvic pain may be linked to specific and non-specific disorders of the gynaecological and urinary systems, digestive system, peripheral or central nervous systems and/or the musculoskeletal system.[1–3] It can be provoked or unprovoked (without a direct stimulus), and in females can be cyclic (with pain fluctuating across the menstrual cycle) or non-cyclic.[1,2] Pelvic pain may affect as many as one in four women of reproductive age worldwide.[4,5] It is associated with significant individual burden, including reduced physical function, negative psychological consequences, reduced socialisation and impacted sexual function, and negatively impacts work.[6,7] It presents a significant societal burden through the cost of medical care and lost work productivity.[8]

Consistent with the potential involvement of several body systems many factors are associated with PP,[9] with multiple suggested mechanisms.[10,11] One proposed contributing factor is changes in nociceptive processes reflected by heightened pain sensitivity.[10,12,13] Quantitative sensory testing (QST) has been utilised in clinical practice and research to assess pain sensitivity.[14,15] A systematic review incorporating 29 articles across multiple PP presentations suggested the presence of generalised heightened pain sensitivity in people with PP.[12] That review highlighted heterogeneity in the measures of pain sensitivity across studies, and suggested that changes in nociceptive processing are likely to occur at various levels of the nervous system, both peripherally and centrally. This association between PP and pain sensitivity has been supported elsewhere.[11,13,16–18] However, for non-cyclical PP in particular, there is a lack of large population-based studies investigating the association between PP and pain sensitivity that allow for an array of potential confounding factors.[12] The ability to control for confounding factors is important given the complex combination of factors associated with PP. Being able to investigate PP and pain sensitivity while accounting for potential confounding factors could improve our understanding and characterisation of PP.

The aim of this study was to assess the association between PP and pain sensitivity in young female participants of the Raine Study, adjusting for potential confounding factors. In this study, PP was defined by how much women were bothered by pain or discomfort in the lower abdomen/genital region. In the Raine Study Gen2 22-year follow-up,[19] more intense cyclical PP has been associated with heightened pain sensitivity.[20] However, it is not known if this holds for all presentations of PP in this cohort.

2 | METHODS

2.1 | Population

This cross-sectional study evaluated data from the Raine Study Gen2-22 year follow-up (www.rainestudy.org.au).[19] The Raine Study is a multigenerational observational community-dwelling cohort study investigating health and wellbeing across the lifespan. The initial cohort consisted of 2868 live births that have been regularly followed since before they were born (Gen2, with Gen1 being the parents of these children). The participants who have remained in the Raine Study cohort have retained a comprehensive representation of the general population.[21] At the 22 year follow-up, 2086 participants were still active in the cohort, 1414 of which were female. Only females who had answered the Urogenital Distress Inventory short form (UDI-6) and had a minimum of one valid pain sensitivity measure were eligible for inclusion in this study.

Study-specific patient/public involvement was not completed for this project. However, the Raine Study Community Advisory Committee provides input into the research priority setting of the study and have indicated pain and women's health issues should be considered priority areas for research.

2.2 | Data collection

Data were obtained from questionnaires and anthropometric/physical measures performed at the Gen2-22 year follow-up. All assessments were completed by qualified Raine Study research personnel who had extensive training.[19] Core outcome measure sets were not consulted, although these are in development for chronic PP.[22]

2.3 | Pelvic pain

The UDI-6 was used to gather a combined estimate of the prevalence and bothersomeness of PP.[23] The specific question used to determine the presence of PP was: 'Do you experience, and, if so, how much are you bothered by, pain or discomfort in the lower abdomen/genital area (urogenital pain)?' The response options were 'not at all', 'slightly', 'moderately' or 'greatly'. A detailed analysis of the full UDI-6 questionnaire outcomes from the Raine Study Gen2-22 year follow-up is described elsewhere.[24]

2.4 | Pain sensitivity measures

Pain sensitivity was determined via QST consisting of pressure pain thresholds (PPTs) and cold pain threshold (CPT). These measures were collected according to a standardised protocol,[25] and following current best practice.[14] The PPTs were tested before the CPT. Detailed descriptions of pain sensitivity in the Raine Study are described elsewhere.[26–28]

2.4.1 | Pressure pain threshold

Pressure data were obtained following a standardised protocol,[26] using a pressure algometer (Somedic AB, Sösdala, Sweden) with 1-cm^2 contact area applied perpendicularly to the skin, with a ramp rate of 50 kPa/s. Standardised instructions were given to the participants to stop the test at the first onset of discomfort or pain. The pressure was interrupted at 1000 kPa for safety purposes. The locations assessed were: the wrist, at the middle of the dorsal aspect of the wrist joint line; the leg, at muscle belly of tibialis anterior, approximately 2.5 cm lateral and 5 cm distal to the tibial tubercle; the neck, at the upper trapezius, tested at the mid-point between the C7 spinous process and the lateral acromion; and the lumbar spine, at the erector spinae, 2 cm lateral to the L4/L5 interspinous space.

2.4.2 | Cold pain threshold

The Modular Sensory Analyser thermal stimulator (Somedic AB, Sösdala, Sweden) with a 12.5-cm^2 (25 mm × 50 mm) probe was used to collect the CPT at one standardised body site, on the wrist at the middle of the dorsal aspect of the wrist joint line. The initial temperature started at 32°C with a cut-off temperature of 5°C. The temperature was reduced at 1°C/s and standardised instructions were given to the participants to stop the test at the first moment when the temperature felt uncomfortable or painfully cold.

2.5 | Additional measurement

Additional demographic/potential confounding factors and women's health variables were collected (Tables 1 and 2). Potential confounding factors were selected based on their relationship with PP and/or pain sensitivity in prior Raine Study analyses and the broader literature, and included ethnicity, marital status, waist–hip ratio, C-reactive protein level, psychological distress, sleep quality, level of activity, smoking prevalence, highest level of education, income, musculoskeletal pain experience and medical co-morbidities (Table 1). High-sensitivity C-reactive protein level was taken from blood samples collected at the time of follow-up as a representation of subclinical inflammation.[29] Measures above 10 mg/L were removed as they were

likely to indicate acute inflammation or a current infection, rather than a chronic inflammatory state.[30] Psychological distress was measured with the Depression Anxiety Stress Scale short form (21-item) total score,[31] a commonly used measure for this purpose with the total score displaying good psychometric properties.[32,33] Sleep quality was measured using the Pittsburgh Sleep Quality Index,[34] which has been recommended for use in assessing sleep quality.[35] Physical activity and sedentary behaviour were objectively measured over a 1-week period using a GT3X accelerometer (ActiGraph, Pensacola, FL, USA), worn continuously on the right hip during all waking time other than during bathing or aquatic activities.[36] Musculoskeletal pain experience was derived from the Orebro Musculoskeletal Pain Screening Questionnaire,[37] used to capture musculoskeletal pain experiences across the concepts of chronicity, severity and number of pain sites.[27] Medical comorbidities were constructed as a count of the presence of self-reported health professional diagnosed disorders that included eating disorder/weight problems, diabetes, menstrual problems, migraine or severe headache, arthritis or joint problems and respiratory disorders. More information on how these demographics/potential confounding variables were collected are provided in Appendix S1.

Women's health variables were used to profile the study participants more broadly in this area. These included the use of single questions for frequency of menstrual period, pain related to menstrual period and intercourse, medication use for pelvic cramps or pain, oral contraceptive use and parity (Table 2). Single items of the UDI-6 (other than the pelvic pain question used for participant categorisation above) were also used to report the presence and bothersomeness of urogenital distress symptoms (Table 2). A priori we decided not to include these additional women's health variables as potential confounding factors because of the likelihood of multicollinearity. For information on how these women's health variables were collected, refer to Appendix S2.

2.6 | Power calculation

The sample size was predetermined by the number of participants in the Raine Study Gen2-22 year follow-up ($n = 584$ with a valid response to the UDI-6). Of the 584 participants, 134 reported lower abdominal/genital pain or discomfort. Adequate power to detect a standardised effect size of ≥0.27 could be stated based on the estimated number in each group with a significance of 0.05 and a power of 0.8.

2.7 | Statistical analysis

The participants' answers to the UDI-6 question used to determine the presence of bothersome PP were categorised into three groups: 'not bothered by PP', for the 'not at all' response; 'mild bothersomeness', for the 'slightly' response; and 'moderate–severe bothersomeness' combining the

TABLE 1 Demographic, potential confounding factors and pain sensitivity measures

	Whole cohort (n = 475)	Pelvic pain bothersomeness			p for group differences
		Not bothered (n = 362)	Mild (n = 74)	Moderate–severe (n = 39)	
Ethnicity (white)[a]	429 (90.5)	332 (91.7)	63 (86.3)	34 (87.2)	0.270
Marital status[b]					
Single	187 (39.6)	158 (43.9)	19 (25.7)	10 (26.3)	<0.001[r]
In relationship but not living together	176 (37.3)	135 (37.5)	30 (40.5)	11 (28.9)	
In relationship living together/married	109 (23.1)	67 (18.6)	25 (33.8)	17 (44.7)	
Waist–hip ratio[c]	0.8 (0.1) [0.61–1.04]	0.8 (0.1) [0.61–0.99]	0.8 (0.1) [0.67–1.04]	0.8 (0.1) [0.67–1.00]	0.782[s]
C-reactive protein level (mg/L, for cases ≤10 mg/L)[d]	1.26 [0.5–2.93]	1.41 [0.48–3.17]	0.97 [0.53–2.18]	1.11 [0.56–2.07]	0.275[t]
Psychological distress (DASS-21 total score)[e]	18 [10–36]	16 [8–30]	24 [12–46]	36 [16–56]	0.001[t]
Sleep quality (PSQI total score)[f]	5.2 (2.5) [0–17]	4.9 (2.3) [0–12]	5.9 (3.2) [2–17]	6.6 (2.8) [1–13]	<0.001[s]
Activity levels (ActiGraph GT3X+)[g]					
Awake wear time (min/day)	902 (90) [619–1134]	900 (91) [619–1105]	910 (85) [622–1092]	906 (91) [710–1134]	0.674[s]
MVPA (min/day)	27 [16–40]	27 [16–39]	31 [17–43]	25 [15–38]	0.848[t]
Sedentary time (%)	65 (9) [29–89]	65 (9) [29–89]	64 (8) [44–80]	66 (7) [54–78]	0.434[s]
Smoking (yes)[h]	62 (13.1)	40 (11.1)	12 (16.2)	10 (25.6)	0.027
Highest level of education[i]					
Secondary school	226 (49)	178 (50.7)	31 (43.1)	17 (44.7)	0.570
Technical college	94 (20.4)	68 (19.4)	19 (26.4)	7 (18.4)	
University	141 (30.6)	105 (29.9)	22 (30.6)	14 (36.8)	
Income[j] (total usual pay/week after tax)					
≤A$604 per week	264 (59.5)	206 (61.0)	37 (55.2)	21 (53.8)	0.517[r]
≥A$605 per week	180 (40.5)	132 (39.0)	30 (44.8)	18 (46.2)	
Musculoskeletal pain experience[k]					
No–low pain	295 (63.3)	238 (66.8)	44 (60.3)	13 (35.1)	0.001[r]
Moderate–high pain	171 (36.7)	118 (33.2)	29 (39.7)	24 (68.9)	
Medical comorbidities					
No comorbidity	303 (63.8)	247 (68.2)	40 (54.0)	16 (41.0)	<0.001[r]
1 comorbidity	123 (25.9)	89 (24.6)	21 (28.4)	13 (33.3)	
2 or more comorbidities	49 (10.3)	26 (7.2)	13 (17.6)	10 (25.6)	
PPT lumbar spine (kPa)[l]	368 (182) [69–1000]	372 (186) [69–1000]	375 (170) [76–909]	325 (162) [99–706]	0.306[s]
PPT tibialis anterior (kPa)[m]	380 (180) [74–1000]	384 (186) [74–1000]	390 (159) [93–796]	326 (151) [84–731]	0.134[s]
PPT upper trapezius (kPa)[n]	236 (116) [25–669]	243 (121) [61–669]	229 (102) [44–508]	196 (87) [25–421]	0.046[s]
PPT wrist (kPa)[o]	354 (143) [40–791]	361 (145) [85–791]	352 (138) [122–687]	294 (120) [40–609]	0.019[s]
CPT (°C)[p]	14.3 (8.5) [5–30.3]	14.0 (8.5) [5–30.3]	14.5 (8.2) [5–29.1]	17.4 (8.2) [5–29.1]	0.078[u]

Note: Data reported as mean (standard deviation) [range], median [interquartile range] or number (%).

Abbreviations: CPT, cold pressure threshold; DASS-21, Depression Anxiety Stress Scale 21; MVPA, moderate–vigorous physical activity; PPT, pressure pain threshold; PSQI, Pittsburgh sleep quality index.

Missing data (for whole cohort): [a]1, [b]3, [c]2, [d]84, [e]2, [f]34, [g]115, [h]3, [i]3 missing +11 dropped that reported 'other', [j]31, [k]9; [l]9, [m]6, [n]5, [o]5, [p]8.

[q]Sedentary time, as a percentage of non-MVPA time during wake time.

[r]χ^2 test.

[s]Linear regression.

[t]Kruskal–Wallis.

[u]Tobit regression.

TABLE 2 Women's health variables

	Whole cohort (n = 475)	Pelvic pain bothersomeness			p for group differences[j]
		Not bothered (n = 362)	Mild (n = 74)	Moderate–severe (n = 39)	
Frequency of menstrual period[a]					
Never	14 (3.0)	10 (2.8)	3 (4.1)	1 (2.6)	0.129
Very irregular	48 (10.2)	30 (8.4)	9 (12.3)	9 (23.1)	
Less than once a month	71 (15.1)	53 (14.8)	13 (17.8)	5 (12.8)	
At least once a month	337 (71.7)	265 (74.0)	48 (65.8)	24 (61.5)	
Pain experience during menstrual cycle (yes)[b]	422 (94.6)	323 (94.2)	64 (94.1)	35 (100)	0.340
Pelvic pain not during menstrual cycle (yes)[c]	75 (16.6)	43 (12.4)	15 (21.4)	17 (46.0)	<0.001
Pain during intercourse[d]					
Yes	57 (12.6)	36 (10.4)	8 (11.4)	13 (34.2)	<0.001
Not applicable	56 (12.4)	50 (14.5)	3 (4.3)	3. (7.9)	
Medications for pelvic cramps/pain[e]	111 (24.6)	82 (23.7)	15 (21.7)	14 (37.8)	0.138
Present oral contraceptive pill usage[f]	228 (48.3)	180 (50.1)	29 (39.2)	19 (48.7)	0.229
Parity (yes)[g]	19 (4.0)	12 (3.3)	4 (5.4)	3 (7.7)	0.335
Urogenital distress (UDI-6)					
Frequent urination					
Not at all	277 (58.3)	239 (66.0)	26 (35.1)	12 (30.8)	<0.001
Mild	121 (25.5)	79 (21.8)	29 (39.2)	13 (33.3)	
Moderate–severe	77 (16.2)	44 (12.2)	19 (25.7)	14 (35.9)	
Urine leakage related to urgency					
Not at all	391 (82.3)	315 (87.0)	50 (67.6)	26 (66.7)	<0.001
Mild	64 (13.5)	35 (9.7)	22 (29.7)	7 (17.9)	
Moderate–severe	20 (4.2)	12 (3.3)	2 (2.7)	6 (15.4)	
Urine leakage with activity					
Not at all	382 (80.4)	303 (83.7)	55 (74.3)	24 (61.5)	0.004
Mild	76 (16.0)	48 (13.3)	17 (23.0)	11 (28.2)	
Moderate–severe	17 (3.6)	11 (3.0)	2 (2.7)	4 (10.3)	
Small volume of urine leakage (drops)[h]					
Not at all	379 (80.0)	304 (84.0)	53 (72.6)	22 (56.4)	<0.001
Mild	74 (15.6)	46 (12.7)	18 (24.7)	10 (25.6)	
Moderate–severe	21 (4.4)	12 (3.3)	2 (2.7)	7 (18.0)	
Difficulty emptying your bladder/urinating[i]					
Not at all	416 (87.9)	338 (93.6)	55 (74.3)	23 (60.5)	<0.001
Mild	43 (9.1)	19 (5.3)	17 (23.0)	7 (18.4)	
Moderate–severe	14 (3.0)	4 (1.1)	2 (2.7)	8 (21.0)	

Note: Data reported as number (%).

Abbreviation: UDI-6, Urogenital Distress Inventory short form.

Missing data (for whole cohort): [a]5, [b]29, [c]22, [d]22, [e]23, [f]3, [g]1, [h]1, [i]2.

[j]χ^2 test used for all group comparisons.

'moderately' and 'greatly' responses. This is consistent with how these data had previously been handled in this cohort.[24] The average of the three PPT and CPT measures were calculated and used for analyses.

Descriptive statistics were calculated for demographics/potential confounding factors, pain sensitivity variables (PPTs/CPT) and the women's health variables for the whole cohort and the three PP bothersomeness groups. Frequency

distributions were used for categorical and ordinal variables. Means and standard deviations or medians and interquartile ranges were used for continuous variables, determined by normality tests. Data were checked for missing values or outliers, and the missing data for the whole cohort were reported. Between-group comparisons were performed on these variables for the different PP groups, using the chi-square test for categorical variables and linear regression or Kruskal–Wallis for continuous variables (except for CPT, where tobit regression was used because of the censored nature of the CPT data, with the lower limit of the thermal stimulator being 5°C).

Next, a series of univariable regression analyses were performed to analyse the relationship between each potential confounding factor with PPTs and CPT. Regression models using generalised estimating equations were used for assessing the association between PP bothersomeness and PPTs. These models were adjusted for the site that the PPT was recorded from. Tobit regression models were used for assessing the association between PP bothersomeness and CPT. For both PPTs and CPT, activity level variables, moderate to vigorous physical activity and sedentary time were adjusted for awake wear time.

From the univariable regression result, potential confounding factors identified to have a univariable association of $p < 0.15$ were included in a multivariable analysis with the PP bothersomeness groups and pain sensitivity measures (except for musculoskeletal pain experience). The potential confounding factors were sequentially removed if not found to be significant in the multivariable model ($p > 0.05$). A final model was estimated using the factors identified as significant in the multivariable analysis to provide the adjusted association between PP bothersomeness and pain sensitivity. The final models were created using regression models utilising generalised estimating equations for PP bothersomeness and PPTs and tobit regression model for PP bothersomeness and CPT. Given the known relationship between musculoskeletal pain experience and the pain sensitivity measures,[27] an interaction analysis was performed between PP bothersomeness groups and musculoskeletal pain experience.

Interpretation of the results was based on effect sizes, confidence intervals, p-values and plausibility of any identified associations. The data were analysed using Stata/IC 16.1 software (StataCorp).

3 | RESULTS

In the Gen2-22 year follow-up, 475 of 1414 females active in the cohort responded to the UDI-6 and also had at least one valid QST pain sensitivity measure. The mean (SD) age of all participants was 22.1 years (0.6 years) with a range of 20.7–24.4 years. Of these, 362 (76.2%) reported no PP bothersomeness, 74 (15.6%) reported mild PP bothersomeness and 39 (8.2%) reported moderate–severe PP bothersomeness.

Table 1 summarises the demographics/potential confounding factors and values for PPTs and CPT for the whole cohort and for each of the PP bothersomeness groups. Compared with women who reported no PP bothersomeness, women with moderate–severe PP bothersomeness had a higher proportion reporting being in a relationship and living together/being married, reported higher levels of psychological distress,[31] reported poorer sleep quality,[34] had a higher proportion of smokers, had a higher proportion reporting a moderate–high musculoskeletal pain experience and reported a higher number of medical comorbidities.

Table 2 summarises the woman's health variables for the whole cohort and for each of the PP bothersomeness groups. Reporting pain experienced during the menstrual cycle was common (95% of the whole cohort). Reporting pain not during the menstrual cycle was more common in participants in the moderate–severe PP bothersomeness group. Compared with women with no PP bothersomeness, women with moderate–severe PP bothersomeness more commonly reported other urogenital symptoms, including frequent urination, urine leakage and difficulty emptying the bladder.

Univariable associations between pain sensitivity measures and demographics/potential confounding factors are presented in Table 3. For PPTs, marital status along with test site were carried over as potential confounding factors in the multivariable model. For CPT, marital status, waist–hip ratio, C-reactive protein level and smoking were carried over as potential confounding factors in the multivariable model.

Table 4 presents the final models for the association between pain sensitivity measures and PP bothersomeness. After adjusting for marital status (and test site), moderate–severe PP bothersomeness was associated with lower PPTs (greater pressure pain sensitivity) (coefficient −51.46, 95% CI −98.06 to −4.86, $p = 0.030$). Moderate–severe PP bothersomeness was also associated with higher CPT (greater cold pain sensitivity), with only smoking being retained in the final model as a confounding factor (coefficient 4.35, 95% CI 0.90–7.79, $p = 0.014$). There was no interaction effect between PP bothersomeness and musculoskeletal pain experience for either the PPT or CPT models.

4 | DISCUSSION

4.1 | Summary of the main findings

This study investigated the association between the bothersomeness of PP and pain sensitivity in young women living in Australia, adjusted for confounding factors. There was a positive association between moderate–severe PP bothersomeness and increased pressure and cold pain sensitivity. This aligns with the evidence in the literature suggesting that some women with PP have augmented central nociceptive processing, when compared with women without PP,[11,12] and this is related to the severity of the symptoms. Additionally, heightened cold and pressure pain sensitivity was found in the upper extremity, suggesting widespread sensitivity, distant to the area of PP symptoms. This provides evidence that increased sensitivity is

TABLE 3 Univariable associations between pain sensitivity and demographics/potential confounding factors

	Pressure pain threshold[a] Regression coefficient	95% CI	*p*	Cold pain threshold Regression coefficient	95% CI	*p*
Site						
Back	Ref					
Leg	11.89	0.82 to 22.96	0.035	–		
Neck	−131.88	−142.93 to −120.82	<0.001			
Wrist	−13.93	−24.99 to −2.87	0.014			
Ethnicity						
White	Ref			Ref		
Non-white	11.87	−30.52 to 54.26	0.583	1.24	−2.05 to 4.54	0.459
Marital status						
In relationship living together/married	Ref			Ref		
In a relationship but not living together	38.77	5.62–71.91	0.022	−2.60	−5.12 to −0.08	0.043
Single	25.76	−6.95 to 58.46	0.123	−2.07	−4.57 to 0.43	0.104
Waist–hip ratio[b]	−126.66	−303.64 to 50.33	0.161	−11.9	−25.49 to 1.62	0.084
C-reactive protein level (mg/L, for cases ≤10 mg/L)	−2.84	−8.94 to 3.27	0.363	−0.63	−1.10 to −0.15	0.010
Psychological distress (DASS-21 total score)	−0.23	−0.81 to 0.35	0.442	0.01	−0.04 to 0.05	0.767
Sleep quality (PSQI total score)	−1.73	−6.80 to 3.34	0.503	−0.13	−0.53 to 0.25	0.483
Activity levels (ActiGraph GT3X+)[c]						
MVPA (mins/day)[d]	−0.07	−0.67 to 0.53	0.824	0.02	−0.03 to 0.06	0.493
Sedentary time (%)[e]	−93.31	−265.78 to 79.16	0.289	6.09	−7.14 to 19.31	0.366
Smoking						
No	Ref			Ref		
Yes	14.32	−22.70 to 51.34	0.448	−2.52	−0.538 to 0.35	0.085
Highest level of education						
Secondary school	Ref			Ref		
Technical college	−11.13	−44.87 to 22.60	0.518	0.54	−2.01 to 3.09	0.678
University	−7.63	−37.09 to 21.84	0.612	0.71	−1.52 to 2.94	0.533
Income						
≥A$605 per week	Ref			Ref		
≤A$604 per week	−15.48	−41.73 to 10.84	0.249	−1.30	−3.33 to 0.72	0.206
Musculoskeletal pain experience						
No–low pain	Ref			Ref		
Medium–high pain	−18.39	−44.64 to 7.85	0.170	3.11	1.12 to 5.09	0.002
Medical comorbidities						
No comorbidity	Ref			Ref		
1 comorbidity	5.63	−23.38 to 34.64	0.704	−1.18	−3.43 to 1.06	0.300
2 or more comorbidities	−27.84	−69.62 to 13.94	0.192	−1.08	−4.28 to 2.12	0.508

Abbreviations: DASS-21, Depression Anxiety Stress Scale 21; MVPA, moderate–vigorous physical activity; PSQI, Pittsburgh Sleep Quality Index.

[a]All pain pressure thresholds adjusted for site.

[b]Accelerometry variables adjusted for awake wear time.

[c]Coefficient represents the expected change in PPT for a 0.1 change in waist–hip ratio.

[d]Coefficient represents the expected change in CPT for an increase in MVPA of 10 min/day.

[e]Coefficient represents the expected change in CPT for a 10% increase in sedentary time.

TABLE 4   Final multivariable associations between pain sensitivity and pelvic pain bothersomeness

	Pressure pain threshold Regression coefficient	95% CI	p	Cold pain threshold Regression coefficient	95% CI	p
Pelvic pain bothersomeness						
Not bothered	Ref.			Ref.		
Mild	−1.14	−36.11 to 33.83	0.949	0.71	−1.91 to 3.32	0.596
Moderate–severe	−51.46	−98.06 to −4.86	0.030	4.35	0.90 to 7.79	0.014
Site						
Back	Ref.					
Leg	12.22	1.16 to 23.28	0.030			
Neck	−131.33	−142.38 to −120.29	<0.001			
Wrist	−14.19	−25.23 to −3.14	0.012			
Marital status						
In relationship living together/married	Ref.					
In a relationship but not living together	33.86	0.50–67.21	0.047			
Single	20.27	−13.00 to 53.53	0.232			
Smoking[2]						
No				Ref.		
Yes				−2.98	−5.85 to −0.11	0.042

not only a local phenomenon in this cohort of women with moderate–severe PP bothersomeness, consistent with the finding of those specifically reporting menstrual pain and musculoskeletal pain in the same cohort.[20,27] This study expands on those prior results by adding the concept of bothersomeness and capturing both cyclical and non-cyclical aspects of CPP.

4.2 | Strengths and limitations

This study is the first to look at a broader presentation of PP bothersomeness in a relatively large, age-specific group of young adult women with richly characterised phenotypes across an array of biopsychosocial factors and health conditions.[12] The community-based cohort provides a low risk of selection bias, and robust QST measures for pain sensitivity were collected according to international recommendations.[38] A limitation might be that bothersome PP was defined by only one question from a validated measure (UDI-6, Q6). However, when comparing this single item with a broad array of questions related to women's health issues (Table 2), multiple similarities were identified that support the use of this question as a good representative of a broader pain/symptom state. It also reflects the complexity in defining PP, and frequent comorbid involvement of multiple systems, particularly in those with more moderate–severe presentations.[1–3] The single question captures bothersomeness rather than just the presence of symptoms, which may provide a more meaningful measure of the individual level of impact and burden of the disorder. Pain sensitivity

has not been directly related to quality of life though, other than via the bothersomeness concept. Cross-sectional analysis does not allow for the determination of causality. Further prospective research is needed for this purpose.[39]

4.3 | Interpretation in relation to the literature

There is ample support for a relationship between PP and pain sensitivity. This includes a systematic review of 29 observational studies that have investigated PP and pain sensitivity,[12] a further update published a year later,[13] and more recent literature.[17,18,40,41] One purpose of the present study was to understand relationships between non-cyclical PP and pain sensitivity. Severe menstrual (cyclical) pain during young adulthood in the same cohort has been associated with increased pressure and cold sensitivity.[20] In the present study almost all women reported menstrual pain (Table 2). It is not known at what stage of the menstrual cycle the women were in when the sensitivity testing was performed. Further research is needed to fully understand the role of the menstrual cycle in the experience and bothersomeness of PP and how pain sensitivity might change across this cycle.[42] Significantly, more women in the moderate–severe PP bothersomeness group (46%) reported pain present not during the menstrual cycle. More detailed characterisation of PP would be useful, but it would appear for women with more severe presentations of either cyclical or non-cyclical PP,[43] the consideration of pain sensitivity as a contributing factor is necessary.

The richness of the data in the Raine Study allowed the profiling of participants across multiple biopsychosocial factors. Women with moderate–severe PP bothersomeness reported increased psychological distress, poorer sleep quality, more musculoskeletal pain and a higher number of medical comorbidities (Table 1). This is consistent with findings in older women in Canada (average age 34.5 years, standard deviation 7.6 years, $n = 656$).[44] Interestingly, none of these specific factors were retained in our final models, highlighting the potential for an independent relationship between PP bothersomeness and pain sensitivity. For PPTs, marital status was retained in the final model. Married women and those living with a partner reported more severe PP bothersomeness, in contrast to a prior report.[44] Why marital status would confound the relationship between PP and pain sensitivity (Table 4) is unclear, although this is likely to be related to the complex influence of social factors on pain disorders,[45] and is worth further investigation. Smoking confounded the association between PP bothersomeness and pain sensitivity (Table 4). Smoking has been associated with PP,[9,44] and has been associated with pain sensitivity in the Raine Study Gen2 participants.[26]

Women with moderate–severe PP bothersomeness reported more complaints of moderate–severe musculoskeletal pain (Table 1), which is a common combination.[43] Moderate–severe musculoskeletal pain was associated with CPT in univariable association, but not with PPTs (Table 3), and was not maintained in the final CPT model. Prior examination of the cohort found cold and not pressure pain sensitivity to be related to musculoskeletal pain.[27] It seems that the relationship between PP bothersomeness and pain sensitivity occurs independently of musculoskeletal pain, which is a similar finding to that of a previous investigation of menstrual pain in these women.[20]

5 | CONCLUSION

5.1 | Clinical significance and future research

Given the complexity of CPP, person-centred multimodal management is recommended.[10] The results of the present study support other research in PP that highlight pain sensitivity as one potential contributing factor for some women.[12] This has been integrated into clinical practice guidelines for the management of PP problems,[1] and is included in other narrative reviews on this topic.[3,10,11] A systematic multimodal assessment routine for people with PP has been proposed.[46] Screening for red flags and considering specific disorders, such as endometriosis, should be initial priorities. Clues from the patient interview that might allude to pain sensitivity as a contributing factor include more constant symptoms, bloating and burning feelings, comorbid issues with mood and sleep, reports of spread of symptom (wind-up) and subjective report of tactile sensitivity in the pelvic region.[46] Higher levels of bothersomeness could potentially be added to the list based on the findings of this study. Pain

during intercourse was more common for women who reported moderate–severe bothersomeness, highlighting the need to consider this in any assessment. Further guidance is provided in the convergence PP criteria,[47] which highlight factors associated with lower pain thresholds, temporal distribution, variability in symptoms and comorbidities that might suggest heightened pain sensitivity. This should be supplemented with clinical assessment for both tactile and temperature sensitivity,[46] and it would make sense to assess this locally to the pain and more remotely, given the potential for widespread pain sensitivity. Guidelines for the clinical/bedside assessment of pain sensitivity in people with musculoskeletal pain are likely to apply to PP and thus be useful for clinicians working in this area.[15,48] If pain sensitivity is present, multimodal management might include medication for reducing central sensitisation,[11] although this should be considered as part of a broader approach of patient education, exercise, assistance with sleep problems and managing mood.[15,46] Significant work is required to review the efficacy of these approaches for women with moderate–severe PP bothersomeness where pain sensitivity has been identified as contributing factor. There is some evidence, though, that multimodal approaches can change the sensitivity profiles of these women.[49] Additionally, it is important to understand the presence of pain sensitivity for its potential as a treatment effect modifier.[13,15]

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTERESTS

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Raine Study. Restrictions apply to the availability

of these data, which were used under license for this study. Data are available from the Raine Study with the permission of the Raine Study.

ETHICS STATEMENT

The Raine Study data set is covered by a consolidated ethics committee approval from the University of Western Australia Human Research Ethics Committee (RA/4/20/5722, approved 29 April 2020). This specific project was approved by the Raine Study (project no. MUS0623). Specific ethical approval for this project was obtained from the Curtin University Human Research Ethics Committee (HRE2020-0244, approved 20 May 2020).

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