Supplementary Material for manuscript:

Multimodal Hypersensitivity Derived from Quantitative Sensory Testing Predicts Pelvic Pain Outcome: an Observational Cohort Study

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Annual Questionnaire Attrition was Approximately Random

A common concern among longitudinal designs is the impact of attrition on study conclusions. Given our >50% attrition rate across four years of annual questionnaires (Baseline *n*=200; Year 1 *n*=143; Year 2 *n*=129, Year 3 *n*=97, Year 4 *n*=87), we evaluated potential loss to follow up effects in several different ways. First, a chi-square test of independence determined that loss to follow-up did not depend on recruited participant groups (i.e., dysmenorrhea, pain-free controls, chronic pain, bladder pain syndrome), χ^2 (16) = 4.58, p = .998. Second, we found that baseline pelvic pain did not differ between participants who submitted a year 4 questionnaire (M = 14.72, SD = 14.7) versus those that dropped out of the study (M = 16.28, SD = 18.8), t (198) = .60, p = .55. Third, we tested whether baseline sensory testing composites and PCs differed depending on the years of annual data submitted (see Figure 0.1). We computed six one-way between-subject analysis of variance (ANOVAs)—one ANOVA for each dependent variable/ measure (i.e., QST, Bladder Test, Audio/Visual, PC1 (*MMH*), PC2 (*PPT S-R*), PC3 (*bladder hypersensitivity*)—as a function of five participant groups that were separated based on the number of years of submitted annual data (i.e., complete data; 0; 1; 2; 3 years). All ANOVAs were not significant except for PC3 *bladder hypersensitivity* (see Table 0.1). We performed *post hoc* follow up testing using pairwise Tukey honest significant difference tests; however, none of these pairwise tests were significant after correction (see Table 0.2.). Together, these analyses suggest that longitudinal data were missing at random and did not selectively depend on recruited participant groups, pelvic pain outcome, nor predictor variables of interest calculated either via sensory testing composites or PCA.

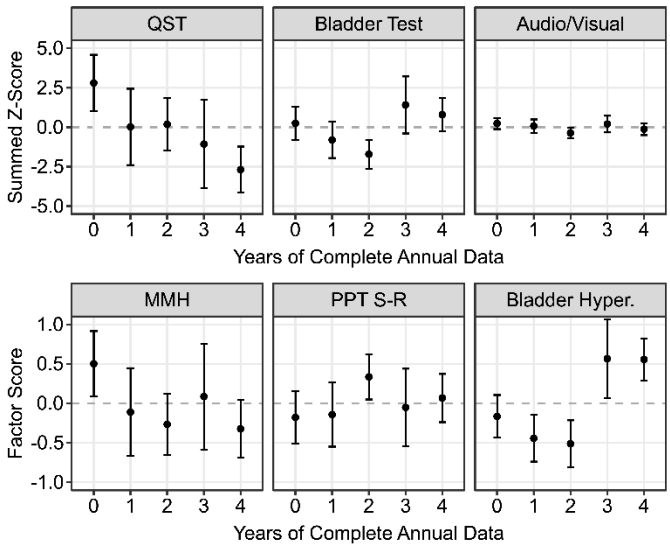

Figure 0.1. Predictor variables derived from baseline testing remain stable across annual questionnaire. Scores were generated for all participants over time to evaluate the impact of loss follow up. Mean summated Z-scores and factor scores for each predictor variable are plotted for each group of participants that completed 0 to 4 (complete data) years of annual questionnaires. Error bars are standard error of the mean.

Table 0.1. One-way Analysis of Variance Results of Longitudinal Attrition Across Predictor Variables.

Predictor Variable	Term	*df*	*SS*	*MS*	*F*	*p*
QST	Years of Annual Data	4	865	216	1.47	.21
	Residuals	195	28717	147		
Bladder Test	Years of Annual Data	4	206	51	0.97	.43
	Residuals	195	10391	53		
Audio/Visual	Years of Annual Data	4	10	2	0.39	.82
	Residuals	195	1236	6		
PC1 (MMH)	Years of Annual Data	4	23	6	0.70	.60
	Residuals	195	1616	8		
PC2 (PPT S-R)	Years of Annual Data	4	7	2	0.34	.85
	Residuals	195	983	5		
PC3 (Bladder Hypersensitivity)	Years of Annual Data	4	41	10	2.67	.03
	Residuals	195	741	4		

Note. MMH=multimodal hypersensitivity; QST=quantitative sensory testing; PC=principal component; PPT S-R=pressure point threshold stimulus-response

Table 0.2. One-way Analysis of Variance Results of Longitudinal Attrition for PC3 Bladder Hypersensitivity: Post-Hoc Follow Up Tukey Testing.

			95% CI		
Predictor Variable	Comparisons (Year-to-Year)	Mean Difference	*LL*	*UL*	*p*
PC3 (Bladder Hypersensitivity)	1-0	-0.28	-1.46	0.91	.97
	2-0	-0.35	-1.49	0.80	.92
	3-0	0.73	-0.64	2.10	.59
	4-0	0.72	-0.30	1.74	.30
	2-1	-0.07	-1.37	1.24	1.00
	3-1	1.01	-0.50	2.52	.35
	4-1	1.00	-0.20	2.19	.15
	3-2	1.08	-0.40	2.55	.26
	4-2	1.07	-0.09	2.22	.09
	4-3	-0.01	-1.39	1.37	1.00

Note. PC=principal component; CI=confidence interval; LL=lower level; UL=upper level.

Table S1. Descriptive Statistics of Pelvic Pain Outcome

	Year				
	Baseline	1	2	3	4
Mean	15.6	15.5	13.5	12.4	11.0
SD	18.3	17.8	15.1	14.9	12.6
95% CI [LL UL]	[13.1 18.1]	[12.6 18.5]	[10.9 16.1]	[9.4 15.3]	[8.3 13.6]
Min - Max	0 - 77	0 - 95	0 - 68	0 - 72	0 - 54
Median	7.8	9.3	8.0	7.0	5.7
SEM	1.3	1.5	1.3	1.5	1.4
n	200	143	129	97	87

Note. CI=confidence interval; LL=lower level; UL=upper level

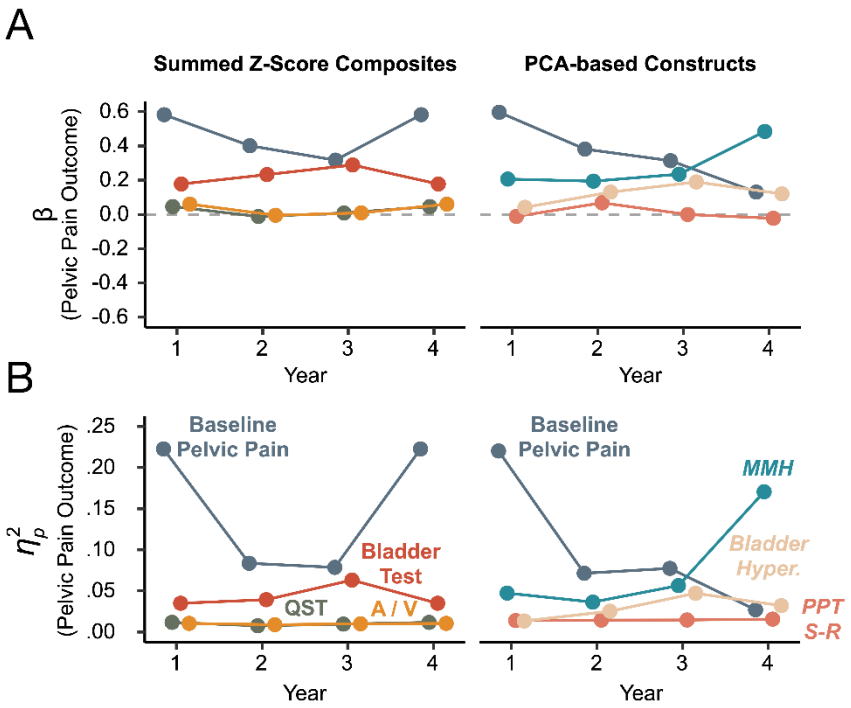

Figure S1. Adjusting for population prevalence rates replicated the observed sample-wise regression results across the sensory composite and PCA models. A) Standardized regression coefficients (β's) are plotted across the collected annual questionnaire period for both the summed Z-score composites (left) and the PCA-based constructs (right). All β values are approximately zero or positive, indicating in general that increased sensitivity resulted in worse pelvic pain outcome. See B for colored labels denoting predictor variables. B) Unique explained variance (η_p^2) in pelvic pain outcome as a function of each predictor is plotted across the collected annual questionnaire period for both the summed Z-score composites (left) and the PCA-based constructs (right). When comparing to the unadjusted regression results, the pattern of change over time is similar, especially in the case of the PCA-based constructs. Namely, MMH increases in predictive strength of pelvic pain outcome over time, while the opposite trend is observed with baseline pelvic pain. Italicized text labels refer to principal components; A/V = Audio/Visual.

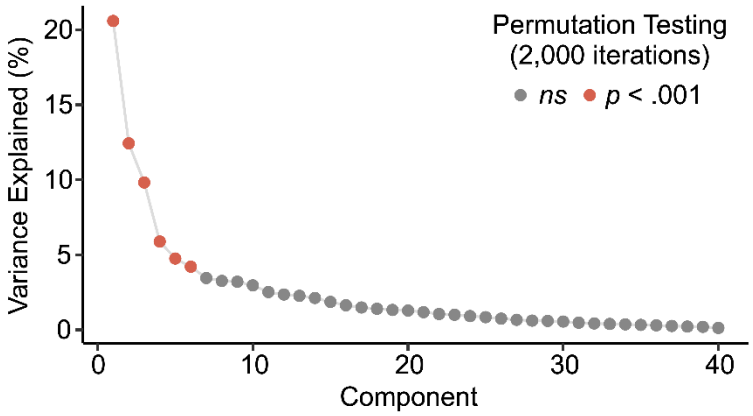

Figure S2. Scree plot supports the first three principal components as significant components that explain total variance. The first three components explain 43% of the variability in multimodal sensory testing. Although components four, five, and six were significant via permutation testing, their geometric factor score plots were not interpretable and likely represented non-meaningful variation. Therefore, we chose to focus on the first three components that we interpreted as representing multimodal hypersensitivity (MMH), pressure pain threshold stimulus-response function (PPT-SR), and bladder pain hypersensitivity, respectively.

Table S2. Principal Component Eigenvalues and Explained Variances Obtained from CRAMPP Multimodal Sensory Testing Data Matrix.

PC	Eigenvalue	Variance (%)	Cumulated (%)	PC	Eigenvalue	Variance (%)	Cumulated (%)
1*	1639	20.6	21	21	93	1.2	90
2*	990	12.4	33	22	84	1.1	91
3*	782	9.8	43	23	80	1.0	92
4*	468	5.9	49	24	73	0.9	93
5*	378	4.8	53	25	67	0.8	94
6*	335	4.2	58	26	59	0.7	95
7	275	3.4	61	27	53	0.7	95
8	259	3.3	64	28	49	0.6	96
9	255	3.2	68	29	47	0.6	96
10	236	3.0	71	30	44	0.5	97
11	200	2.5	73	31	38	0.5	97
12	187	2.4	75	32	34	0.4	98
13	180	2.3	78	33	31	0.4	98
14	169	2.1	80	34	29	0.4	99
15	148	1.9	82	35	26	0.3	99
16	130	1.6	83	36	24	0.3	99
17	118	1.5	85	37	20	0.3	99
18	112	1.4	86	38	17	0.2	100
19	105	1.3	88	39	16	0.2	100
20	102	1.3	89	40	10	0.1	100

Note. PC=principal component; *indicates p=.005 for 2,000 permutation iterations.

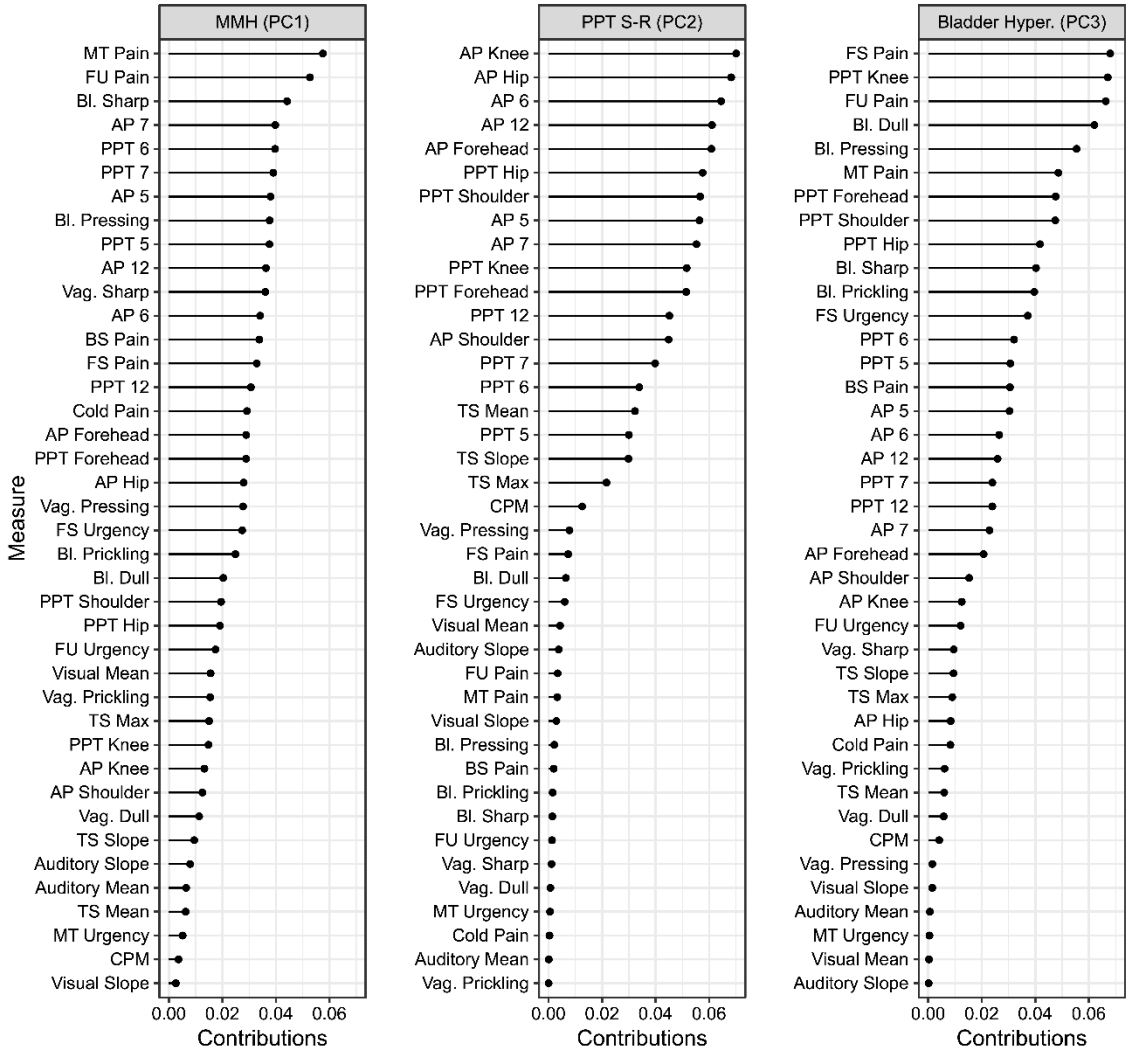

Figure S3. Sensory testing measure contributions across the first three principal components. Greater values indicate a greater contribution/importance of that measure to a component. BS=baseline; FS=first sensation; FU=first urge; MT=max. tolerance; PPT=pressure pain threshold; TS=temporal summation; AP=after-pain; CPM=conditioned pain modulation; Bl.=bladder; Vag.=Vaginal; numbers denote clock face positions (e.g., 6=6 o'clock).

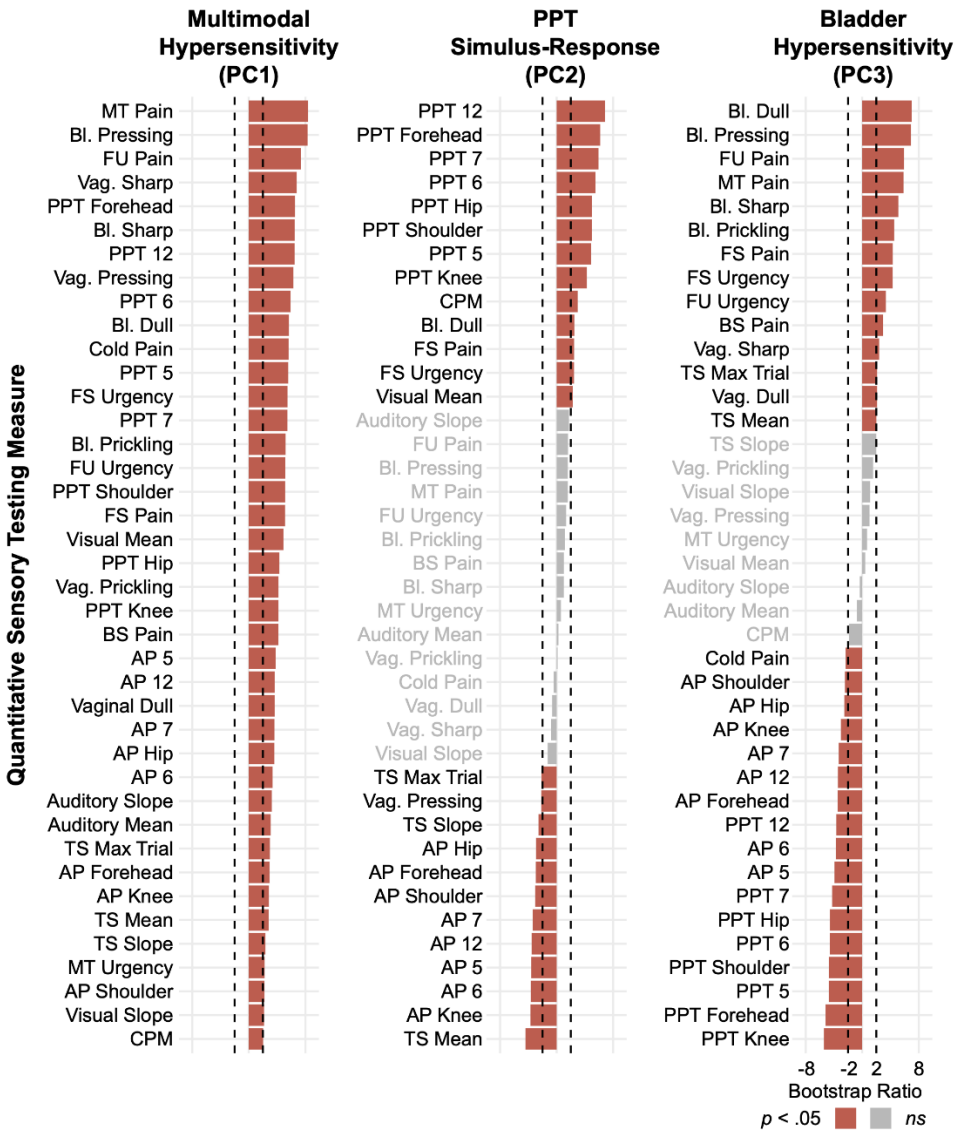

Figure S4. Bootstrap ratios for each sensory testing measure across the first three principal components (PCs). A 2,000 iteration bootstrapping procedure calculated bootstrap ratios that are interpreted like Student's t-value and indicate the extent to which they significantly contributed to the variance of a PC. BS=baseline; FS=first sensation; FU=first urge; MT=max. tolerance; PPT=pressure pain threshold; TS=temporal summation; AP=after-pain; CPM=conditioned pain modulation; Bl.=bladder; Vag.=Vaginal; numbers denote clock face positions (e.g., 6=6 o'clock).

Table S3. Descriptive Statistics of Self-Report Measures.

Measure	*Mean*	*SD*	*Min*	*Max*	*n*
PROMIS					
Pain Interference	11.0	5.7	6	29	200
Pain Behavior	18.3	7.7	7	35	200
Depression	15.6	6.7	8	37	200
Anxiety	17.2	6.0	7	35	200
Menstrual Pain (0-100 VAS)					
Without NSAIDs	64.8	25.8	0	100	194
Interstitial Cystitis					
Symptom Index (ICSI)	5.7	4.1	0	18	200
Problem Index (ICPI)	3.5	3.8	0	15	200
GUPI					
Urinary	3.5	2.7	0	10	200
Quality of Life	2.9	2.9	0	12	200
Pain	5.2	5.2	0	20	200
Total	11.6	9.6	0	41	200
CMSI (for 3 months)					
During the last year	5.7	6.8	0	30	192
During your lifetime	5.0	6.7	0	34	192
Global Mental Health	3.7	0.9	1	5	199
Global Physical Health	3.4	0.9	1	5	199
BSI (Somatic Symptoms)	3.1	3.4	0	21	200
GSS Brief	1.2	1.6	0	8	192

Note. Global mental/physical health have opposite directionality (i.e., increased score denotes better health); PROMIS scores are raw short form scores; PROMIS=Patient Reported Outcomes Measurement Information System; NSAIDs=Non-Steroidal Anti-Inflammatory Drugs; GUPI=Genitourinary Pain Index; CMSI=Complex Medical Symptoms Inventory; BSI=Brief Symptom Inventory; GSS=Generalized Sensory Sensitivity.

Table S4. Regression Models of Pelvic Pain Outcome Including the GSS Brief.

Year	Parameter	*b*	*SE*	*B*	η_p^2	*SS*	*MSE*	*F*	*p*
1	Intercept	16.3	1.2		.58	36427	197	185.1	< .001
	Baseline Pelvic Pain	0.5	0.1	0.53	.23	7718		39.2	< .001
	GSS Brief	-0.4	0.8	-0.04	.002	43		0.2	.64
	MMH	1.2	0.5	0.18	.04	983		5.0	.03
2	Intercept	14.2	1.3		.52	24346	189	128.7	< .001
	Baseline Pelvic Pain	0.3	0.1	0.30	.06	1557		8.2	.005
	GSS Brief	-0.3	0.9	-0.04	.001	28		0.1	.70
	MMH	1.5	0.6	0.26	.06	1423		7.5	.01
3	Intercept	13.4	1.4		.52	16201	167	96.9	< .001
	Baseline Pelvic Pain	0.2	0.1	0.25	.04	698		4.2	.04
	GSS Brief	1.1	1.0	0.11	.01	180		1.1	.30
	MMH	1.6	0.6	0.31	.09	1382		8.3	.01
4	Intercept	11.9	1.3		.53	11473	129	88.8	< .001
	Baseline Pelvic Pain	0.04	0.1	0.05	.002	21		0.2	.69
	GSS Brief	0.7	1.0	0.09	.01	75		0.6	.45
	MMH	1.9	0.5	0.41	.13	1567		12.1	.001

Note. The *df* for each model were: Year 1 (1, 134), Year 2 (1, 119), Year 3 (1, 89), Year 4 (1, 80). MMH=multimodal hypersensitivity; GSS=generalized sensory sensitivity