

CLINICAL ARTICLE

Expanded Physiological Testing of the Lower Urinary Tract in Asymptomatic Women and Those With Urgency Urinary Incontinence: Findings From the LURN-Organ Study

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ABSTRACT

Purpose: To investigate sensory and motor function of the bladder and urethra in women with and without urgency urinary incontinence (UUI).

Materials and Methods: Treatment-seeking women with UUI and healthy, asymptomatic, nontreatment seeking controls enrolled in the Symptoms of Lower Urinary Tract Dysfunction Research Network Organ-Based study (LURN-Organ) and underwent a single session of physiological testing. Testing included rapid-fill cystometry before and after lidocaine administration, urethral pressure profiles, pelvic floor contraction (Kegel) testing, and tuning fork sensation testing at the urethral meatus.

Results: Data were collected from 31 asymptomatic controls and 56 women with UUI. Women with UUI were more likely to demonstrate detrusor overactivity (DO) (32% vs. 10% in controls, $p = 0.019$). In addition, women with UUI on average generated 25% lower active urethral closure pressures during maximal contraction ($p = 0.0016$) and reported sensations at lower volumes

Abbreviations: AIC, Akaike information criterion; AUC, area under the receiver-operating characteristic (ROC) curve; BMI, body-mass index; CV, controlled variables; DO, detrusor overactivity; FDV, first desire to void; IQR, inter-quartile range; KUCP, Kegel urethral closure pressure; LUT, lower urinary tract; MCC, maximum cystometric capacity; MUCP, maximum urethral closure pressure; Pclo, pressure calculated by subtracting Pves from Pura; Pura, pressure measured on the urethral pressure sensor; Pves, pressure measured on the bladder/vesical pressure sensor; SDV, strong desire to void; UPP, urethral pressure profile; UUI, urgency urinary incontinence.

For a complete list of the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) Study Group, see the Acknowledgments section.

during cystometry (34% lower for first desire to void, $p = 0.028$; 34% lower for strong desire to void, $p = 0.0017$; and 32% lower for maximum cystometric capacity, $p = 0.0047$). Women with UI demonstrated diminished urethral sensation on the tuning fork test (median of 7 vs. 8 in controls) though the difference was not significant ($p = 0.054$). Considerable overlap in all findings occurred between cases and controls in each parameter. While individual component comparisons revealed some differences, additional multivariable analysis demonstrated prominently the physiological heterogeneity of women with UI.

Conclusions: Women with UI demonstrated varying amounts of bladder sensory dysfunction, urethral motor dysfunction and bladder motor dysfunction. Considering the function of lower urinary tract components in combination may reveal UI phenotypes, highlighting the need to study UI from a multifactorial perspective.

Clinical Trial Registration: [ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: NCT04557748.

1 | Introduction

Treatments for urgency urinary incontinence (UI) have primarily focused on treating suspected detrusor overactivity (DO), a motor aspect of bladder function. However, it is well known that not all women with UI demonstrate DO on urodynamic testing [1], and some healthy controls demonstrate DO but do not leak [2]. These observations suggest an incomplete understanding of the pathophysiology of UI and that additional factors are involved. This is supported further by the lack of therapeutic response in many individuals to UI treatments designed to reduce detrusor contractility [3, 4]. The Organ Function Testing project within the Symptoms of Lower Urinary Tract Dysfunction Research Network II (LURN II) [5], was designed to study lower urinary tract (LUT) physiology in women with UI symptoms.

In this study we tested the null-hypothesis that UI is exclusively related to abnormal bladder motor function, and that it does not involve bladder sensory or urethral dysfunction. We undertook examining urethral sensory and motor function, together with bladder sensory and motor function, comparing findings between women with and without UI. Our objective was to identify functional differences, individually and in combination, to define different physiological phenotypes of women with UI. Unlike previous studies, our study utilized age-matched, nontreatment seeking controls and assessed urethral as well as bladder behavior. Additionally our interest for this study is specifically with reference to women with UI, rather than the more general symptom-complex of overactive bladder, where the diversity of symptoms complicates interpretation of the physiology.

2 | Materials and Methods

This multi-institutional study was approved by a single authorized ethical review board, and all study participants provided written informed consent. Women with UI who had enrolled in the parent LURN II Observational Cohort study who also met specific enrollment criteria for this study (see Table 1 and Supplementary Methods) were recruited. Age-matched nontreatment seeking women without LUTS were enrolled as “controls” in a 2:1 (case:control) ratio.

Incontinence for this study was classified based on questions on the LUTS Tool [6]. Women reporting mixed incontinence

had to have “urgency-predominant” urinary incontinence (see Table S1). Six sites across the US enrolled participants and contributed data.

Participants discontinued medications for urinary symptoms 3 days before testing. The single-visit protocol consisted of four separate sections, conducted in series (Figure 1A).

Physiological testing utilized Laborie urodynamics machines (Laborie Medical Technologies Corp., Portsmouth, NH,) and software (v14). T-DOC (air-charged) 7 Fr dual sensor catheters were used in the bladder and urethra. A single sensor T-DOC catheter to record abdominal pressure was placed in the upper vagina for both comfort and to avoid rectal contractions.

2.1 | Test of Urethral Sensation: Vibration Perception

A 128 Hz Rydel-Seiffer tuning fork, used to diagnose large-fiber neuropathy [7], was used to test urethral vibration sensation. The tuning fork was activated and the base (Figure 1B) placed against the urethral meatus. When the participant no longer reported vibration, the current vibration level was recorded. Three trials were performed, and the numbers averaged (median).

TABLE 1 | Case inclusion and exclusion criteria (summarized).

Inclusion:
1. Women ages 18–80 with UI, who fulfilled the criteria for entry into the LURN Observational Cohort study.
2. Completed LUTS Tool questionnaire:
<i>Urgency Urinary Incontinence</i> defined by answer of “sometimes,” “often,” or “always” to the question, “How often in the past month have you ... leaked urine in connection with a sudden need to rush to urinate?”
Exclusion:
1. All the exclusion criteria of the LURN Observational Cohort Study
2. Post-void residual > 150 mL as identified on baseline physical exam
3. Greater than Stage 2 prolapse as identified on baseline physical exam

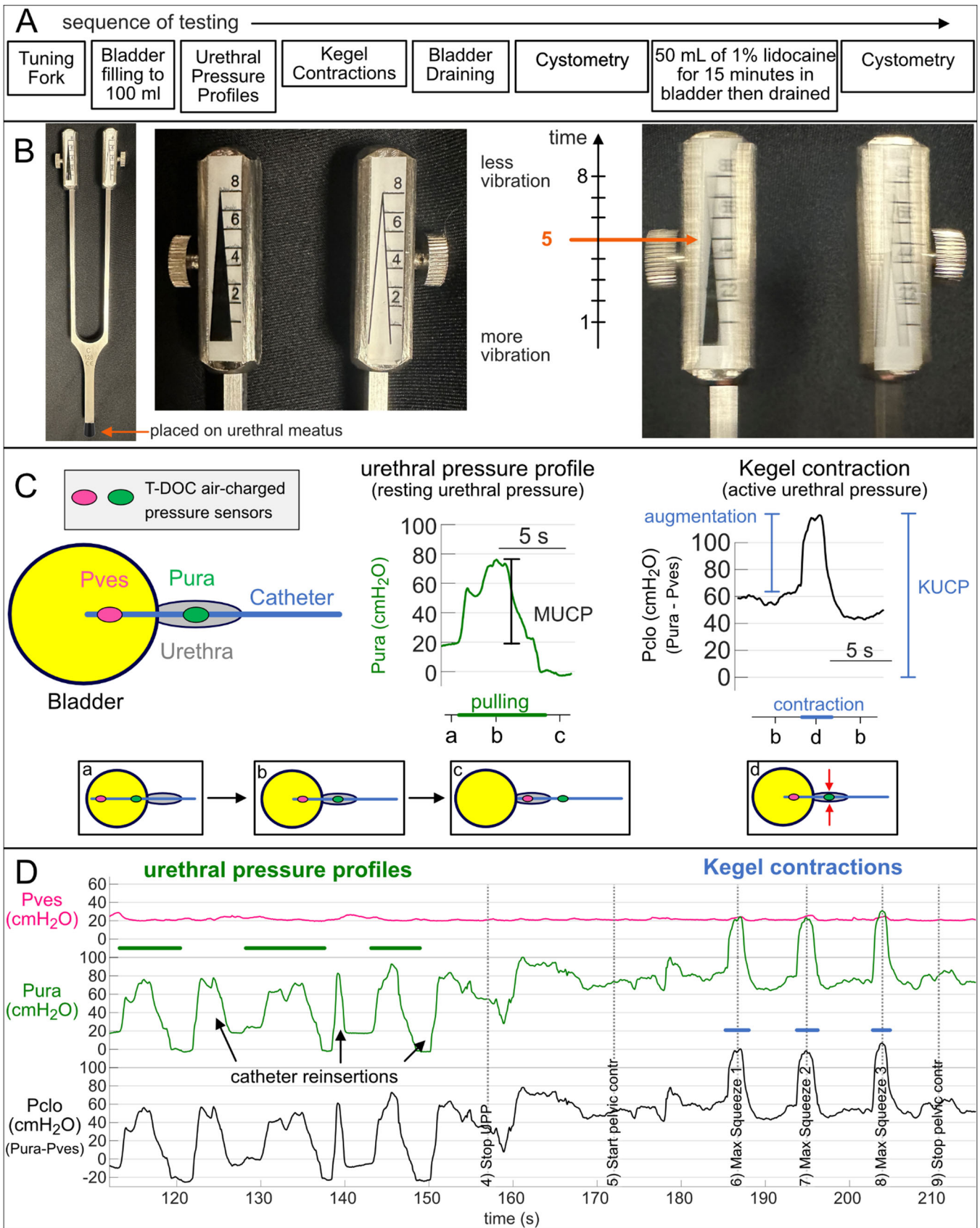


FIGURE 1 | Legend on next page.

2.2 | Tests of Urethral Motor Function: Urethral Pressure Profilometry (UPP)

UPP measurements were made in the semi-recumbent/low lithotomy position. After zeroing pressures outside the body, the single sensor abdominal catheter tip was positioned in the upper vagina, and the dual-sensor catheter was placed into the bladder. The bladder was filled with 100 mL of room temperature saline. With both vesical catheter sensors in the bladder, the operator manually withdrew the catheter out of the bladder at approximately 1 cm/s until the urethral sensor exited the meatus (Figure 1C). The procedure was performed three times (Figure 1D). Maximum urethral closure pressures (MUCPs) were identified and averaged (mean).

2.3 | Tests of Urethral Motor Function: Maximal Voluntary Sphincter Contraction Strength

The urethral sensor was repositioned at the MUCP point within the urethra. Participants were instructed to squeeze their pelvic floor muscles as tightly as possible ('Kegel maneuver') for several seconds. This was done three times, with a brief rest (~5–10 s) between squeezes. The highest closure pressure (KUCP) and largest pressure increase (augmentation, Figure 1C) were noted.

2.4 | Tests of Bladder Sensory and Motor Function: Cystometry, Before and After Lidocaine Instillation

Before filling, the bladder was emptied via voiding or aspiration. With the participant in the semi-recumbent lithotomy position, the urethral sensor was positioned at the MUCP point. Bladder filling with room temperature saline commenced at 70 mL/min through the filling lumen. The fast fill rate was selected to make provoking DO more likely [8]. DO was defined by a > 10 cmH₂O rise in detrusor pressure, with or without sensation to void. The participant was prompted to report first sensation of filling, first desire to void, strong desire to void, and maximum cystometric capacity. At either capacity or 750 mL (whichever came first), filling was stopped and the participant allowed to void.

Fifty mL of lidocaine 1% was then instilled into the bladder. After 15 min, the bladder was drained. Cystometry was then repeated (post-lidocaine trial).

2.5 | Statistical Analysis

Between group differences were analyzed using linear regression (controlling for age, BMI, and vaginal parity, selected a priori for associations with UII), signed-rank tests, or Fisher's exact test, as appropriate. *p*-values less than 0.05 were considered statistically significant. Logistic regression models were fit to assess the discriminability of UII versus controls as a function of one or more physiological measurements or clinical covariates (details in Methods S1). To minimize distractions important statistics and model parameters are included in Tables S2 and S3. Some data were not analyzable and were marked so before analysis.

3 | Results

87 women enrolled in the LURN Observational Cohort study from March 2021 to November 2023 enrolled in the LURN-Organ project as controls (*N* = 31) or UII (*N* = 56) participants. Group demographics are shown in Table 2.

3.1 | Individual Component Comparisons, UII vs Control

3.1.1 | Urethral Motor Function

The mean resting urethral closure pressure (MUCP) was 12% lower in women with UII (86 cmH₂O) compared to controls (98 cmH₂O) but was not statistically significant (*p* = 0.068, Figure 2A). The mean urethral closure pressure during Kegel (KUCP) was 25% lower in women with UII (78 cmH₂O) compared to controls (103 cmH₂O) (*p* = 0.0016, Figure 2B). The increase in urethral pressure during Kegel ('augmentation') above MUCP was on average 25% lower as well in women with UII (25 cmH₂O) compared to controls (33 cmH₂O) but was also not statistically significant (*p* = 0.16, Figure 2C). These data suggest that the measurement that most distinguishes women with UII versus controls is the total urethral pressure that a woman is able generate on demand (KUCP). See Table S2 (summary statistics) and Table S3 (details of regression models) for additional details.

FIGURE 1 | Overview of experimental testing. A, Components of the testing arranged by execution order. B, Urethral sensation testing using a tuning fork placed on the urethral meatus after initiating vibration. The participant then reported at what point they no longer felt vibration. An optical illusion of a growing triangle allows quantification of the vibration level which ranged from 0 (high vibration) to 8 (minimal vibration). As shown, the readout would be 5 (black triangle). C, Experimental setup for urethral motor function testing. Values extracted included maximum urethral closure pressure (MUCP), urethral closure pressure during a Kegel maneuver (KUCP), and increase in pressure above MUCP generated by a Kegel contraction (augmentation). D, Example of manometric data for urethral motor function tests. The resting pressure profiles along the length of the urethra are noted by the 3 solid horizontal lines immediately above the Pura tracing. Catheter reinsertion to position the urethral sensor into the bladder is noted. After UPP testing the catheter was adjusted so that the urethral sensor was at the location of maximum urethral pressure and Kegel testing was then performed (blue lines above Pclo to indicate the contractions). Note the constant pressure of the vesical sensor, indicating that the sensor appropriately remained in the bladder throughout the study. Pves = vesical pressure, Pura = urethral pressure, Pclo = closure pressure = Pura minus Pves.

TABLE 2 | Demographic data.

	Control (N = 31)	UUI (N = 56)	p value
Age (years), median (IQR)	63 (54–66)	61 (50–68)	0.86
Age category			0.95
< 44	4 (13%)	7 (13%)	
44–54	5 (16%)	12 (21%)	
54–64	10 (32%)	17 (30%)	
65+	12 (39%)	20 (36%)	
Race			1.00
White	23 (74%)	40 (71%)	
Black	6 (19%)	11 (20%)	
Asian	1 (3%)	1 (2%)	
Other/Multi- racial	1 (3%)	4 (7%)	
Ethnicity^a			0.40
Hispanic/Latino	—	2 (4%)	
Non-Hispanic/ Latino	31 (100%)	52 (96%)	
BMI, median (IQR)	27 (23–32)	33 (28–37)	0.01
BMI category			0.06
BMI < 24	12 (39%)	10 (18%)	
24 ≤ BMI < 30	9 (29%)	15 (27%)	
29 ≤ BMI	10 (32%)	31 (55%)	
Diabetes			0.06
No	28 (90%)	44 (79%)	
Type I	1 (3%)	—	
Type II	2 (6%)	12 (21%)	
# of Vaginal Births, median (IQR)	1 (0–2)	2 (0–2)	0.12
# of Vaginal Births categories			0.08
0	14 (45%)	15 (27%)	
1+	17 (55%)	41 (73%)	

^aN = 2 UUI participants have missing ethnicity data and are excluded by the calculated percentages.

3.1.2 | Bladder Motor Function

There was a higher occurrence of DO in women with UUI compared to controls ($p = 0.019$). However, only 32% of women with UUI had DO on their pre-lidocaine fill and 10% of control women had DO (Table 3).

3.1.3 | Bladder Sensory Function

Women with UUI reported sensations at smaller bladder volumes than controls. Mean volume at first desire to void (FDV)

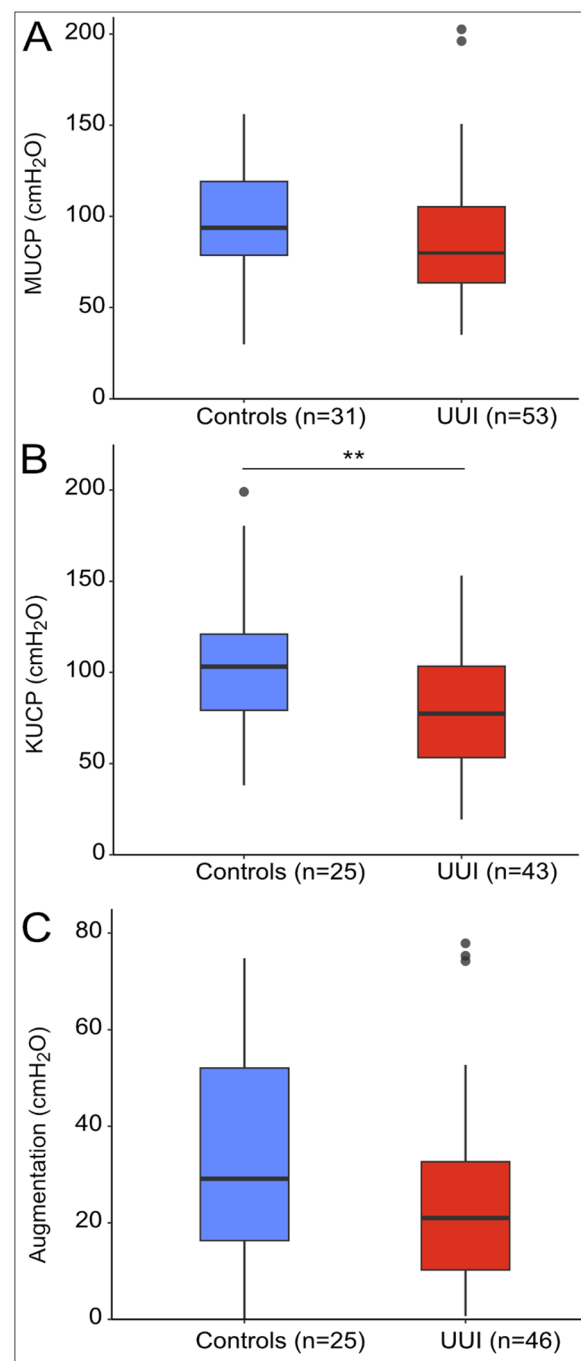


FIGURE 2 | Urethral motor function testing results including, A, resting urethral closure pressure or MUCP, B, active urethral closure pressure or KUCP, and C, increase in closure pressure or augmentation that the participants were able to generate. Despite all three showing the expected trends (lower values for women with UUI on average), only active urethral closure pressure was statistically significant between the two groups. See text for additional details. Numbers of evaluable data points are noted for each group, with some having less due to inability to interpret/absent data. Tests for differences between groups are based on regression models adjusted for age, BMI, and number of vaginal births (details in Table S3). ** $p < 0.01$.

was 34% lower ($p = 0.028$), at strong desire to void (SDV) was 34% lower ($p = 0.0017$), and at maximum cystometric capacity (MCC) was 32% lower ($p = 0.0047$, Figure 3A) in UUI compared to controls. These trends continued after lidocaine with

TABLE 3 | Presence of DO during cystometry (pre-lidocaine fill) (Fisher's Exact test).

Group	+ DO	– DO	Total	% with DO
Control	3	28	31	10%
UII	17	37	54	32%
P-Value	0.019			

reductions of 34% (FDV, $p = 0.0089$), 34% (SDV, $p = 0.0024$), and 26% (MCC, $p = 0.023$, Figure 3B). Both groups demonstrated mean increases in volumes at which each sensation was reported after lidocaine relative to the pre-lidocaine fill (FDV: [93, 53] mL, [controls, UII]; SDV: [95, 63] mL; MCC: [40, 56] mL). Interestingly, we observed a smaller increase in women with UII for FDV (43% less) and SDV (33% less) as compared to controls, although neither was statistically significant (FDV: $p = 0.10$; SDV: $p = 0.26$). In contrast, women with UII had a higher increase in MCC between fills (40% higher), suggesting that MCC may be a different type of sensation than SDV and FDV, although this also was not statistically significant ($p = 0.16$).

3.1.4 | Urethral Sensory Function

Women with UII tended to report loss of urethral vibratory sensation at a lower threshold (median 7) than controls (median 8). This finding was not statistically significant ($p = 0.054$, Figure 4).

3.2 | Multiple Component Comparisons

The following analyses examined multiple physiologic measurements simultaneously, highlighting the complexity of UII.

3.2.1 | Combined Cystometric Variables, DO and MCC, Pre- and Post-Lidocaine

Figure 5 shows MCC and DO status, per participant, for both pre- and post-lidocaine fills, ordered within group by MCC from the pre-lidocaine fill. Patterns seen in the UII group include women with: (1) DO at low MCC volumes; (2) large increases in MCC after lidocaine, and (3) larger MCCs on their first fill, without DO and small changes with lidocaine. As with the single measurement comparisons, these groupings are broad characterizations with exceptions/overlap.

3.2.2 | Multivariable Modeling (Logistic Regression) of Physiological Parameters Versus UII Status

We examined how individual parameters contributed to the group differences between cases and controls using models with increasing complexity. The goal was not to create a model to predict UII, but rather to determine how much weight the physiological measurements contribute to discriminating UII vs controls [9]. The most impactful measurements, KUCP and

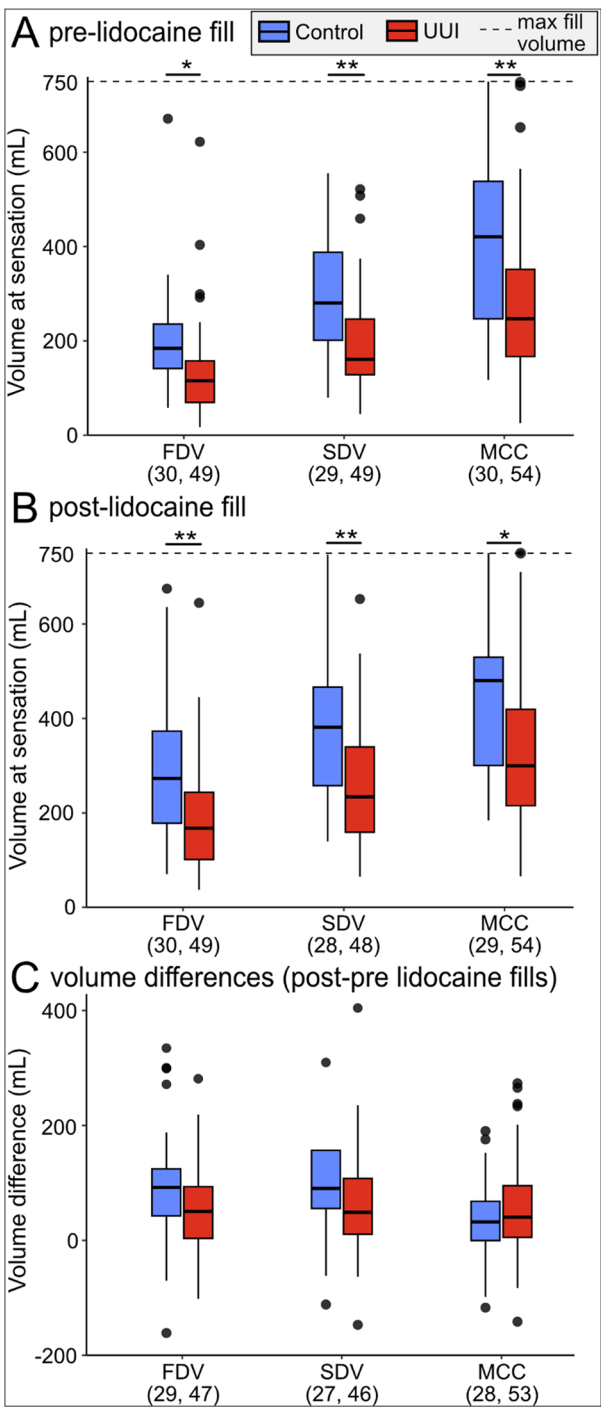


FIGURE 3 | Volumes at which bladder sensations were reported during cystometry and their differences pre- versus post-lidocaine, (A), before lidocaine, (B), after lidocaine instillation. (C), change in sensation volumes between the two fills for each participant. Lower sensation volumes were observed for women with UII, even after lidocaine. Differences in volume for the different sensations were calculated (C). A positive value indicates the participant reported a given sensation at a higher volume after lidocaine. See text for additional details. FDV: first desire to void; SDV: strong desire to void; MCC: maximum cystometric capacity, (#,#): number of control and UII participants respectively. Tests for differences between groups are based on regression models adjusted for age, BMI, and number of vaginal births (details in Table S3). * $p < 0.05$, ** $p < 0.01$.

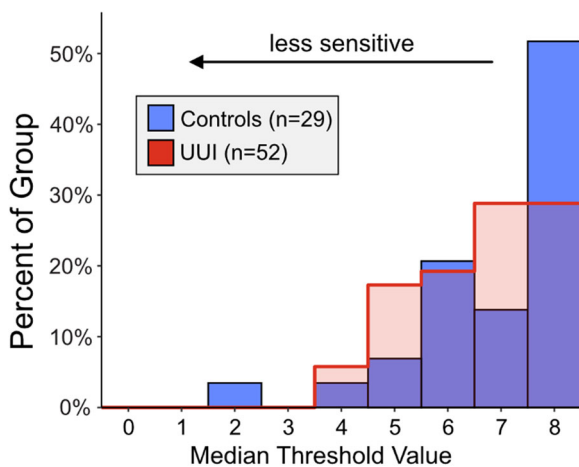


FIGURE 4 | Distribution of vibration sensation responses. No statistically significant difference between the distributions was observed ($p = 0.054$, one-tailed signed-rank test).

MCC, led to notable increases in model performance, whereas addition of other measurements, including DO status, led to minimal model improvement (Table 4). The AUC value of 0.83 suggests unidentified physiological factors, inadequate measurement of current factors, and/or that alternative modeling approaches may be needed (e.g., clustering) to more strongly distinguish between cases and controls. See Table S4 for single-variable performance.

4 | Discussion

4.1 | Main Findings

Using multimodal methodology in a single cohort to evaluate bladder motor and sensory function as well as urethral motor and sensory function, we reject our null-hypothesis that UII dysfunction is predominantly related to abnormal bladder motor function. We found that although bladder motor function (DO) was more often abnormal in women with UII compared to controls, urethral motor function (lower KUCP), and abnormal bladder sensory function (lower sensation volumes) were also abnormal and provided larger discriminability (separation) between cases and controls. Women with UII also showed less urethral sensitivity to vibration, although this difference did not reach a statistically significant threshold. Importantly, although individual functional measures showed differences between women with and without UII, there was overlap showing that no single measurement adequately explains the occurrence of UII. Several different combinations of dysfunction are present in various combinations suggesting that UII has multiple contributing factors, and women with UII are a heterogeneous group of different phenotypes.

4.2 | Extension of the Literature

Our results confirm previous observations and illuminate new ones regarding the four LUT components by performing a full battery of sensory and motor tests in a single well characterized

cohort, including age-matched asymptomatic controls. Consistent with other studies, DO was not observed in all women with UII and it can occur in asymptomatic women [1, 10, 11]. Our lidocaine results are in line with Higson et al. who found that intravesical lidocaine in certain women with idiopathic DO increased bladder capacity [12]. The response magnitude to lidocaine differed noticeably between participants. The mechanisms underlying lidocaine responsiveness is unclear. Interestingly some women demonstrated de-novo DO after lidocaine, an observation noted by others [13]. These results suggest that while some women may have hypersensitive bladders that may benefit from lidocaine (or sensation reduction more generally) to treat their urinary symptoms, others may not achieve symptom relief [14].

The observation that, on average, women with “overactive bladder” report bladder sensations at lower volumes has led to the suggestion that this is due to not only excess detrusor motor activity but also bladder hypersensitivity [15, 16]. Our data support this notion. Therefore, we have avoided the use of the term *overactive bladder*, except when referring to others’ work, because the term implies bladder motor dysfunction, and discounts the possibility of bladder sensory dysfunction (e.g., hypersensitivity or hyposensitivity) and urethral motor dysfunction.

Our urethral function data confirm earlier community-based research that found diminished urethral motor function in a population of White women [17], compared to Black women with UII who had similar values to healthy controls. Even in women that have occasional detrusor contractions during bladder filling a strong urethra may be sufficient to compensate. Thus, for a subset of women with UII and weak urethras, targeting urethral motor function may be beneficial.

We undertook a novel approach for evaluating urethral sensation, using a tuning fork, which is routinely used to assess peripheral neuropathy [7]. More women with UII demonstrated impaired urethral sensation relative to controls, although this result was not statistically significant ($p = 0.054$). A previous study observed impaired urethral sensation in response to electrical stimulation in women with UII [18]. These preliminary data provide a signal that urethral sensation contributes to the occurrence of UII and deserves further investigation.

4.3 | Clinical Implications

Figure 5 suggests several possible phenotypes of UII, elucidated by evaluating multiple variables simultaneously. The findings of this study suggest therapeutic targets not typically considered for patients with UII. For example, the subset of LURN participants with a large lidocaine effect might benefit from bladder anesthetics such as phenazopyridine to reduce bladder sensitivity. Those with low MUCPs might potentially benefit from urethral bulking or suspension procedures or yet to be developed interventions to improve urethral function, rather than antimuscarinic medications. Clinical trials that phenotype women before choosing treatment will be needed to explore these hypotheses. Those with low KUCPs might benefit from

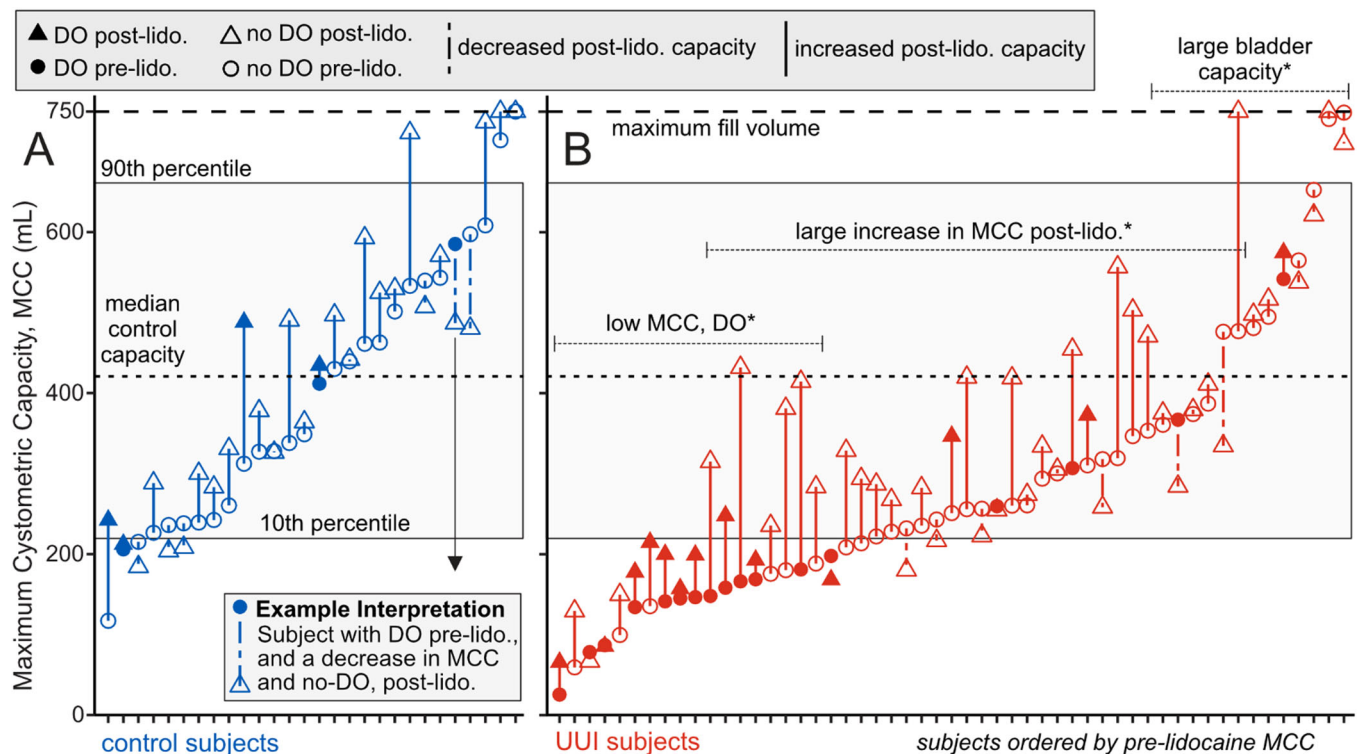


FIGURE 5 | Distribution of individuals based on maximum cystometric capacity (MCC) before and after lidocaine instillation, and the presence/absence of detrusor overactivity (DO) on cystometry for (A), controls and (B), UII participants. See key at top of figure. Gray shaded bar identifies the 10%–90% range of MCC values in the control group, with median control MCC = 420 mL. This type of plot highlights patterns or phenotypes not apparent when examining single measurements. Three potential groupings/phenotypes of women with UII are shown in (B). (*) NB - these are general patterns with both overlap and exceptions.

TABLE 4 | Logistic regression model performance (AUC) from using the best 1 to 5 physiological measurements.

Variables	AUC	AIC ^a
Controlled Variables (CV) Only: age, BMI, vaginal parity	0.70	110.0
Best 1: CVs, MCC	0.78	103.2
Best 2: CVs, MCC, KUCP	0.82	97.7
Best 3: CVs, MCC, KUCP, Tuning Fork	0.83	98.8
Best 4: CVs, MCC, KUCP, Tuning Fork, DO Status	0.83	100.6
Best 5: CVs, MCC, KUCP, Tuning Fork, DO Status, Difference in SDV	0.83	101.1

Note: Each row after the first, was chosen by adding the physiological measurement that increased the AUC the most relative to the model considered in the previous row. MCC and KUCP were the physiological measurements that led to the largest increase in AUC taking into account the controlled variables; other variables, including DO, led to minimal increases in model performance, and increasing/worsening AIC. The AUC metric ranges from 0.5 to 1, whereas these models reach only 0.83, despite training on all data (i.e., no validation/testing data were withheld). Together with the relatively small sample size this means the AUC value of 0.83 is likely overoptimistic.

^aSmaller values for AIC indicate better model fit.

pelvic floor strengthening with a pelvic floor physical therapist. By rejecting the notion that UII is due to a single pathophysiology (e.g., DO), a precision medicine approach to determine specific dysfunctions and address them in individual patients could improve UII treatment outcomes. We are not

suggesting that this expanded urodynamic testing be performed on all patients with clinical UII, but that physiologically guided treatment may be warranted.

4.4 | Research Implications

We have shown that UII pathology is multifactorial, and as the multivariable analysis demonstrates, there are likely organ-based factors other than the ones examined here that contribute to UII. We expect that through improved physiological testing, combined with new data analysis techniques (e.g., sub-typing, clustering) we will improve our ability to explain UII for a given individual. Notable areas for future improved testing include urethral smooth muscle function, vascular integrity, reflexes, and brain function [19, 20], as well as general efforts to simplify testing, reduce cost and time burdens, and ensure reliable measurements.

4.5 | Strengths and Limitations

There are several strengths to this study. We recruited and tested a well-defined group of care-seeking women with UII, along with a similar asymptomatic control group. In addition, we conducted tests that would assess not just one aspect of dysfunction, such as DO, but studied both sensory and motor function for the urethra and the bladder. To our knowledge, this

is one of the largest multi-component lower urinary tract physiology studies done to date.

The study had limitations. Our sample size was modest, impacting the statistical power to detect differences. Detrusor overactivity is not reliably captured during clinical cystometry [21], and its absence during a cystometrogram is not a reliable reflection of actual bladder function. The order of lidocaine administration could not be randomized due to its lasting effect so the order effect of the two fills must be considered. Current urethral manometry only measures pressure at one location at any given time. Urethral sensation testing is in its infancy and needs further development. Our findings do not rule out the possibility that urethral sensory dysfunction may contribute to UUI symptoms.

5 | Conclusion

UUI is not a single entity. In addition to bladder motor dysfunction, bladder sensory dysfunction and urethral motor dysfunction were also observed. Women with UUI are heterogeneous in their physiologies. Future work should clarify what additional factors are needed to discriminate between those with and without symptoms, and how physiological parameters impact treatment response.

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Dr. Helfand, Dr. Glaser, Dr. Antoniuk, and Ms. Talaty are at Endeavor Health. Dr. Bretschneider, Dr. Cella, Dr. Geynisman-Tan, Mr. Boehm, Ms. Marquez, and Ms. John are at Northwestern Medicine.

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Ethics Statement

The study was approved by Salus IRB (Study Number 20112-04).

Consent

All study participants provided written informed consent.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study will be openly available in the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) Central Repository at <https://repository.niddk.nih.gov/>; please reference the acronym "LURN".

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.