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Original Research

Longitudinal Associations between Concurrent Changes in Phenotypic Frailty and Lower Urinary Tract Symptoms among Older Men

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Abstract

BACKGROUND: Lower urinary tract symptoms (LUTS) are associated with prevalent frailty and functional impairment, but longitudinal associations remain unexplored.

OBJECTIVES: To assess the association of change in phenotypic frailty with concurrent worsening LUTS severity among older men without clinically significant LUTS at baseline.

DESIGN: Multicenter, prospective cohort study.

SETTING: Population-based.

PARTICIPANTS: Participants included community-dwelling men age ≥65 years at enrollment in the Osteoporotic Fractures in Men study.

MEASUREMENTS: Data were collected at 4 visits over 7 years. Phenotypic frailty score (range: 0-5) was defined at each visit using adapted Fried criterion and men were categorized at baseline as robust (0), pre-frail (1-2), or frail (3-5). Within-person change in frailty was calculated at each visit as the absolute difference in number of criteria met compared to baseline. LUTS severity was defined using the American Urologic Association Symptom Index (AUASI; range: 0-35) and men with AUASI ≥8 at baseline were excluded. Linear mixed effects models were adjusted for demographics, health-behaviors, and comorbidities to quantify the association between within-person change in frailty and AUASI.

RESULTS: Among 3235 men included in analysis, 48% were robust, 45% were pre-frail, and 7% were frail. Whereas baseline frailty status was not associated with change in LUTS severity, within-person increases in frailty were associated with greater LUTS severity (quadratic P<0.001). Among robust men at baseline, mean predicted AUASI during follow-up was 4.2 (95% CI 3.9, 4.5) among those meeting 0 frailty criteria, 4.6 (95% CI 4.3, 4.9) among those meeting 1 criterion increasing non-linearly to 11.2 (95% CI 9.8, 12.6) among those meeting 5 criteria.

CONCLUSIONS: Greater phenotypic frailty was associated with non-linear increases in LUTS severity in older men over time, independent of age and comorbidities. Results suggest LUTS and frailty share an underlying mechanism that is not targeted by existing LUTS interventions.

Key words: Aging, epidemiology, benign prostatic hyperplasia, sarcopenia.

Introduction

Lower urinary tract symptoms (LUTS) increase dramatically with age and almost half of men will be affected after age 70 (1, 2). LUTS is a constellation of frequently overlapping symptoms that occur when urine is generated and stored in the bladder, called storage LUTS (e.g., urgency, frequency, nocturia, and urinary incontinence), during the initiation and process of urination, called voiding LUTS (e.g., weak stream, hesitancy, straining, and incomplete bladder emptying), or immediately after voiding (e.g. post-void dribbling) (3). Older men with LUTS are more likely to be phenotypically frail (4) and functionally impaired (2) and, in some but not all studies, have increased risk of falls, fractures, and death (5-7). The most common male LUTS treatments narrowly target urologic pathology (α-blockers, 5α-reductase inhibitors, and anti-muscarinics) and are independently associated with increased risk of incident falls and fractures (8), depression and suicidal ideation (9), and dementia (10). Despite evidence that both LUTS and existing LUTS treatments are associated with major geriatric conditions, only urinary incontinence, the most bothersome form of LUTS for most adults (11), is considered a geriatric syndrome and some professional societies recommend that older adults with urinary incontinence undergo a comprehensive geriatric assessment and multicomponent intervention (12-14). It remains unknown if older men with other LUTS subtypes may benefit from a more holistic diagnostic and management approach as well.

Male LUTS are frequently attributed to bladder outlet obstruction due to benign prostatic hyperplasia (BPH). However, there are several non-urologic and systemic factors that contribute to LUTS, especially among older men (15). In fact, men with severe LUTS are only 50% more likely to have bladder outlet obstruction confirmed via urodynamics and men with moderate LUTS have the same likelihood of bladder outlet obstruction as those without LUTS (16). The presence of LUTS is similarly a weak predictor of abnormal bladder contractions detected via urodynamics, such as detrusor overactivity (17). These observations have led to the hypothesis that there are alternative, age-related mechanisms of LUTS that are not

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targeted by existing therapies. Novel therapies targeting these mechanisms, such as frailty, sarcopenia, or altered circadian rhythm, may reduce both symptom severity and the risk of co-occurring geriatric syndromes (4). Although LUTS are cross-sectionally associated with phenotypic frailty, it remains unknown if older men develop phenotypic frailty and LUTS concurrently.

To address this gap in knowledge, we evaluated the association of change in phenotypic frailty with concurrent change in LUTS severity, overall and by storage and voiding subscores, in a large, prospective cohort of older, community-dwelling men without clinically significant LUTS at baseline. We hypothesized that men who become more frail, as manifested by a greater number of phenotypic frailty components, will also have increasing LUTS severity.

Methods

Participants

The Osteoporotic Fractures in Men (MrOS) study is a large, multicenter cohort study of 5,994 community-dwelling men age 65 years or older as previously described (18, 19). Briefly, this cohort was designed to collect comprehensive data to study older men's health, including urologic symptoms, with a particular focus on falls and fractures. Men were recruited from March 2000 to April 2002 from six academic medical centers in Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California. All eligible surviving participants were invited to complete a questionnaire during Year 2 (July 2002 – March 2004) and to return to the clinic during Year 5 (March 2005 – May 2006) and Year 7 (March 2007 – March 2009). The analytic cohort included 3235 men who completed the LUTS questionnaire and at least 3 frailty phenotype components assessed at baseline, and who initially reported none/mild LUTS severity (AUASI<8) (Supplemental Figure 1). All participants gave written informed consent and Institutional Review Boards at each participating institution approved the study.

LUTS Assessment

LUTS were assessed at 4 time points using the validated and widely used 7-item American Urological Association Symptom Index (AUASI) (20), including individual items on urinary frequency, urgency, intermittency, straining, weak urinary stream, incomplete bladder emptying, and nocturia. Responses to each item are on an ordinal scale with values ranging from 0 to 5, with 0 representing no symptoms and 5 representing the highest symptom burden; total scores range from 0 to 35. For example, to evaluate the storage symptom of urgency men were asked "Over the past month, how often have you found it difficult to postpone urination?" and to evaluate the voiding symptom of incomplete emptying men were asked "Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?" Response options included "Not at all", "Less than 1 time in 5", "Less than half the time", "About half the time", "More than half the time", or "Almost always". The AUASI has clinically relevant categories of 0 to 7 (none/mild), 8 to 19 (moderate), and 20 to 35 (severe) (21) and the minimal clinically important difference is 3 points (22). In addition to the total score, we calculated AUASI subscores separately for storage symptoms (urgency, frequency, nocturia) and for voiding symptoms (incomplete emptying, intermittency, weak stream, straining), consistent with the literature (23).

Other Measurements

Age, race/ethnicity and education were assessed via self-administered questionnaires at baseline, and marital status, smoking status, and usual alcohol consumption were updated via self-administered questionnaires at every study visit.18 Participants reported history of myocardial infarction, angina, heart failure, hypertension, diabetes, prostate cancer and prostate cancer treatments (51% treated with surgery, 29% with radiation only, 14% with hormones only, and 6% were not treated), stroke, Parkinson's disease, osteoporosis, osteoarthritis, chronic obstructive pulmonary disease, and thyroid disease. Multimorbidity was defined as the cumulative number of 10 most common chronic diseases listed above (24). All participants completed the Medical Outcomes Study Short Form (SF-12) and the mental health component score ≤50 was used as a measure of psychological distress (25). Cognitive function was assessed using the Modified Mini Mental State Examination (3MS) and cognitive impairment was defined as 3MS<80 (26). Comprehensive prescription medication use was coded from labels on pill packets and canisters brought in by the participant, and medications to treat LUTS (α-antagonist, 5α-reductase, or anti-cholinergic) were identified using the Iowa Drug Information System (IDIS) (27). Men were asked if a doctor had told them they "have or had an enlarged prostate (benign prostatic hyperplasia)" and if so, they were asked if they received "Surgery" for this condition, which was used to define self-reported BPH surgery.

Phenotypic Frailty Component Measurements

For determining frailty status, physical activity was assessed using the Physical Activity Scale for the Elderly (PASE) (28). Tests of physical function included maximum grip strength (measured bilaterally using a hand-held Jamar dynamometer) and walk speed (time in seconds to walk 6 meters at usual pace expressed as m/sec). Study staff measured height at each visit using wall-mounted Harpenden stadiometers. Weight was measured with a digital scale or with a standard regularly calibrated balance beam scale. Height and weight measurements were used to calculate a standard body mass index (BMI). Appendicular skeletal muscle mass, as the measure of lean mass, as well as body fat were determined using dual-energy x-ray absorptiometry (DXA; Hologic QDR4500W scanners, Hologic Inc., Bedford, MA) using standardized scanning procedures.

Assessment of Phenotypic Frailty

We used the framework of phenotypic frailty proposed by Fried et al (29, 30) adapted for the MrOS cohort (31). The following frailty phenotype components were assessed at baseline and 2 subsequent follow-up visits :

1. Shrinking/Sarcopenia, identified by an appendicular lean mass (adjusted for height and total body fat) in the lowest quintile;
2. Weakness, identified by a grip strength in the lowest quintile stratified by BMI (quartiles);
3. Exhaustion, identified at baseline by an answer of "a little or none" to the question "How much of the time during the past four weeks did you have a lot of energy?" from the SF-12 and identified at Visit 2 and 3 by an answer of "no" to the question "Do you feel full of energy?" from the Geriatric Depression Scale;
4. Slowness, identified by a walk speed in the lowest quintile stratified by standing height (median); and
5. Low physical activity, level as identified by a PASE score in the lowest quintile.

Frailty criteria at the follow-up examination were defined using the same cut-points as the baseline examination. Men who met ≥3 criteria were considered frail, those who met 1 or 2 criteria were considered pre-frail, and those who met none of the above criteria were considered robust.

Statistical Analysis

In this analytic cohort, defined in part by the absence of moderate-to-severe LUTS at baseline, the primary independent variable was within-person change in phenotypic frailty score and the primary dependent variable was LUTS severity based on AUASI score (total, storage subscore, and voiding subscore) at each repeated assessment. We first compared distributions of established frailty and LUTS risk factors across categories of frailty phenotype. To test the hypothesis that greater baseline phenotypic frailty is associated with greater annual increases in AUASI score, we used linear mixed effect models and modeled phenotypic frailty categories to represent between-person differences. We then used linear mixed effect models with age as the time variable to test the hypothesis that within-person changes in phenotypic frailty score are associated with concurrent changes in AUASI score because within-person changes are less susceptible to confounding due to characteristics that do not vary over time (32). To represent between-person differences, we included a continuous variable for baseline phenotypic frailty score, and to represent within-person changes, we included a continuous time-varying variable for change in phenotypic frailty score (measurement at each visit minus measurement at baseline) (32). All linear mixed models included random intercepts and slopes and used an unstructured variance-covariance matrix. To visualize the trajectory of AUASI scores over time according to within-person changes in frailty, we created a plot of predicted AUASI scores by within-person change in phenotypic frailty score. For this plot, we set age to the median (73 years), baseline frailty phenotype score to the median (1), and all other covariates to 0.

To identify and control for confounding factors, we applied a change in estimate criteria (33). First, we specified variables to be forced into the model (age and study enrollment site) and four groups of potential confounders: demographics (education, race, and marital status), health-related behaviors (smoking and alcohol intake), cardiovascular comorbidities (self-reported history of myocardial infarction, angina, health failure, and hypertension), and other medical comorbidities (and self-reported history of diabetes mellitus, prostate cancer, chronic obstructive pulmonary disease, and stroke or Parkinson's). Next, we fit a full multivariable model including age, site, and all 4 groups of potential confounders. We then successively removed groups of variables from the full model and each time calculated the % change in the beta coefficient compared to the full model, with a change of ≥10% used to indicate important confounding (all groups met this criteria) (34). Subsequently, we successively removed individual variables from each group until remaining groups only contained variables that contribute ≥1% of the % change for that group of variables. The final multivariable model included age (continuous in years), study site, and self-reported angina, heart failure, hypertension, diabetes mellitus, stroke or Parkinson's disease, and chronic obstructive pulmonary disease.

We assessed effect modification of the main associations by including a cross product term of the within-person change in phenotypic frailty score by age, LUTS treatment (medication or surgery), neurologic disease (stroke or Parkinson's disease), or diabetes. For missing data, we conducted pattern mixture models to test for informative dropout due to unmeasured variables. Since we observed no evidence of effect modification or bias due to informative censoring, we report all results for the entire study population. We also conducted sensitivity analyses further adjusting for variables that could be confounders or mediators, including anxiety/depression (SF-12 mental health component score ≤5025), multimorbidity, self-reported general health status, and number of LUTS medications. Lastly, we conducted sensitivity analyses excluding men with urinary incontinence (at least weekly), cognitive impairment (3MS <80), or a baseline phenotypic frailty score of 5 (to minimize ceiling effects) and further adjusting for diuretic medication use.

P-value <0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Results

General characteristics of the 3235 community-dwelling older men in the analytic cohort are reported in Table 1. In this analytic cohort, 48% of men at baseline were robust (phenotypic frailty score = 0), 45% were pre-frail (phenotypic frailty score median = 1, range 1-2), and 7% were frail (phenotypic frailty score median = 3, range

Table 1. General characteristics of men enrolled in MrOS with none/mild lower urinary tract symptoms (LUTS) at baseline, by baseline frailty status

Characteristic Variable*	Robust (n=1537)	Pre-Frail (n=1468)	Frail (n=230)
# of frailty phenotype criteria met, median (IQR)	0 (0)	1 (1)	3 (1)
Demographics			
Age, years, mean ± SD	71 ± 5	74 ± 6	78 ± 6
Non-White, n (%)	164 (11)	151 (10)	25 (11)
College education, n (%)	872 (57)	728 (50)	110 (48)
Married, n (%)	1316 (86)	1163 (79)	178 (77)
Biometrics, mean ± SD			
Body Mass Index, kg/m^2	27.4 ± 4	27.3 ± 4	26.9 ± 4
Appendicular lean body mass, kg	25 ± 3	24 ± 3	22 ± 3
Total body fat mass, %	25 ± 5	27 ± 5	28 ± 5
Walking speed, m/s,	1.31 ± 0.2	1.17 ± 0.2	0.94 ± 0.2
Maximum grip strength, kg	46 ± 7	39 ± 8	32 ± 7
Questionnaires			
General Health Status, n (%)			
Excellent	706 (46)	467 (32)	45 (20)
Good	765 (50)	819 (56)	107 (47)
Fair	64 (4)	170 (12)	58 (25)
Poor or Very Poor	2 (0.1)	12 (1.0)	20 (9)
Feeling full of energy†, n (%)	1537 (100)	1382 (94)	156 (68)
PASE score, mean ± SD	179 ± 59	136 ± 67	72 ± 50
Health-related Behaviors, n(%)			
Current Smoking	51 (3)	68 (5)	13 (6)
Alcohol Consumption			
<1 drink/week	661 (43)	724 (49)	144 (63)
1 to <7 drinks/week	397 (26)	290 (20)	36 (16)
7 to <14 drinks/week	296 (19)	269 (18)	24 (10)
≥14 drinks/week	181 (12)	183 (12)	26 (11)
Health Condition, n(%)			
Myocardial Infarction	153 (10)	195 (13)	45 (20)
Angina	149 (10)	183 (12)	55 (24)
Heart Failure	50 (3)	69 (5)	24 (10)
Prostate Cancer	169 (11)	184 (13)	36 (16)
Stroke or Parkinson's Disease	53 (3)	92 (6)	29 (13)
Hypertension	571 (37)	624 (43)	119 (52)
Diabetes	116 (8)	177 (12)	50 (22)
Chronic Obstructive Pulmonary Disease	106 (7)	138 (9)	33 (14)
Cognitive Impairment§	17 (1)	47 (3)	19 (8)
Anxiety/Depression‡	144 (9)	217 (15)	56 (24)
Multimorbidity¶, n(%)			
0 chronic conditions	853 (56)	676 (46)	54 (23)
1 chronic condition	457 (30)	476 (32)	74 (32)
2 chronic conditions	163 (11)	198 (13)	56 (24)
≥3 chronic conditions	64 (4)	118 (8)	46 (20)
Baseline LUTS Severity and Treatments			
AUASI total, mean ± SD	3.6 ± 2	3.7 ± 2	3.8 ± 2
α-Blocker Use, n (%)	127 (8)	135 (9)	25 (11)
5α-Reductase Use, n (%)	28 (2)	27 (2)	5 (2)
Anti-Cholinergic Use, n (%)	4 (<1)	11 (<1)	2 (<1)
Self-reported BPH Surgery, n (%)	553 (36)	569 (39)	99 (43)

n sample size; IQR interquartile range; SD standard deviation; PASE physical activity scale for the elderly; AUASI American Urological Association Symptom Index; BPH benign prostatic hyperplasia; * Normally distributed continuous variables were reported as mean ± SD, skewed continuous variables were reported as median (IQR), and categorical variables were reported as n (%); † Patients who reported feeling like they "have a lot of energy" at least some of the time; ‡ Short Form-12 Mental Health Component Summary ≤50; § Teng Mini-Mental Status (3MS) <80; ¶ Cumulative number of the following chronic medical conditions: stroke, Parkinson's disease, myocardial infarction, angina, chronic obstructive pulmonary disease, congestive heart failure, diabetes mellitus, osteoporosis, osteoarthritis, hyperthyroidism or hypothyroidism.

Table 2. Association of baseline frailty status with annual changes in overall, storage, and voiding lower urinary tract symptoms (LUTS)

Variable	Unadjusted* Annual Change Estimate (95% CI)	Age/site-Adjusted† Effect Estimate (95%CI)	P-value
Overall LUTS			
Baseline frailty status			
Robust	0.15 (0.13, 0.18)	Ref.	
Pre-frail	0.18 (0.15, 0.20)	-0.16 (-0.39, 0.06)	0.15
Frail	0.12 (0.06, 0.18)	0.20 (-0.35, 0.75)	0.47
Storage LUTS			
Baseline frailty status			
Robust	0.06 (0.05, 0.08)	Ref.	
Pre-frail	0.07 (0.06, 0.09)	-0.08 (-0.21, 0.05)	0.23
Frail	0.06 (0.02, 0.09)	0.12 (-0.20, 0.44)	0.46
Voiding LUTS			
Baseline frailty status			
Robust	0.09 (0.07, 0.10)	Ref.	
Pre-frail	0.10 (0.09, 0.12)	-0.08 (-0.22, 0.06)	0.27
Frail	0.06 (0.02, 0.09)	0.12 (-0.22, 0.46)	0.49

* Annual change estimate calculated using linear mixed effects models; † Effect estimate calculated using linear mixed effects models. P-value calculated for comparison of annual change among pre-frail and frail men compared to the annual change among robust men.

Table 3. Mean predicted AUASI, by cross-classification of baseline and within-person increase in phenotypic frailty score

Baseline frailty status	Baseline phenotypic frailty score	Mean Predicted AUASI* (95% CI)					
		Increase in phenotypic frailty score during follow-up					
		0	1	2	3	4	5
Robust	0	4.2 (3.9, 4.5)	4.6 (4.3, 4.9)	5.6 (5.2, 5.9)	7.0 (6.4, 7.5)	8.8 (8.0, 9.7)	11.2 (9.8, 12.6)
Pre-Frail	1	4.0 (3.7, 4.3)	4.4 (4.1, 4.7)	5.4 (5.0, 5.7)	6.8 (6.2, 7.3)	8.7 (7.8, 9.5)	-
	2	3.8 (3.5, 4.1)	4.3 (3.9, 4.6)	5.2 (4.8, 5.6)	6.6 (6.0, 7.2)	-	-
Frail	3	3.6 (3.2, 4.0)	4.1 (3.6, 4.5)	6.0 (4.5, 5.5)	-	-	-

* Predicted AUASI calculated using linear mixed effects models adjusted for age, site, diabetes, stroke or Parkinson's disease, chronic obstructive pulmonary disease, angina, heart failure, and hypertension with age set to the median (73 years), and all other covariates set to 0.

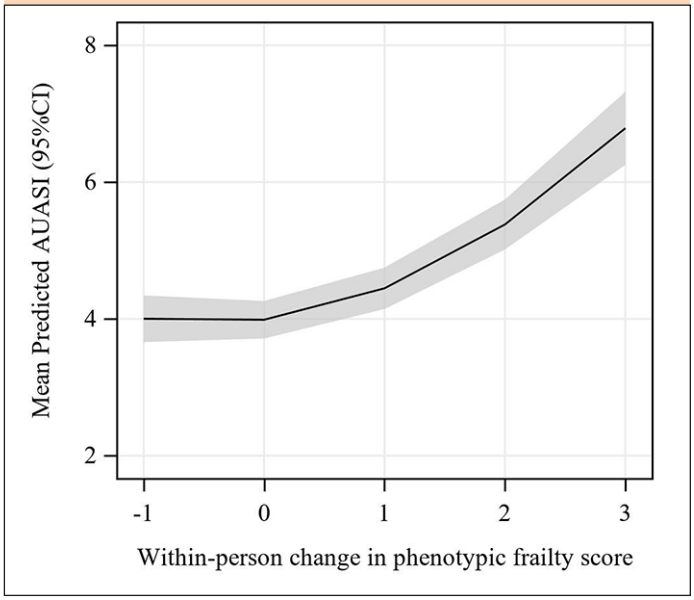
3-5). Men categorized as frail were older, less likely to be college educated or married, had lower appendicular lean body mass, walking speed, and maximum grip strength, were less likely to report "Excellent" general health status or feeling full of energy, were more sedentary, and had greater burden of comorbidities. Frail men were also more likely to report a history of BPH surgery.

Annual change estimates for AUASI score and age/site-adjusted associations between baseline frailty status and annual change in AUASI are reported in Table 2. Estimated unadjusted annual change in AUASI score was 0.15 (95% 0.13, 0.18) among robust men, 0.18 (95% CI 0.15, 0.20) among pre-frail men, and 0.12 (95% CI 0.06, 0.18) among frail men. In age/site-adjusted models, baseline frailty status was not significantly associated with annual change in AUASI. Baseline frailty status was similarly not associated with change in storage or voiding LUTS subscores.

Predicted AUASI scores by within-person change in phenotypic frailty score during follow-up are reported in Table 3. Among robust men who did not meet any frailty criterion at baseline or during follow-up, mean predicted AUASI was 4.2 (95% CI 3.9, 4.5). Among robust men who developed new pre-frailty during follow-up (meeting an additional 1 or 2 frailty criteria), mean predicted AUASI was 4.6 (95% CI 4.3, 4.9) and 5.6 (95% CI 5.2, 5.9), respectively. Among robust men who developed new frailty (meeting an additional 3 or more frailty criteria) during follow-up, mean predicted AUASI was 7.0 (95% CI 6.4, 7.5) among those with 3 criteria, 8.8 (95% CI 8.0, 9.7) among those with 4 criteria, and 11.2 (95% CI 9.8, 12.6) among those with 5 criteria. Among men who met 1 frailty criterion at baseline and during follow-up, mean predicted AUASI was 4.0 (95% CI 3.7, 4.3) and increased to 8.7 (95% CI 7.8, 9.5) for those who met 4 additional criteria during follow-up. We visualized this concurrent and non-linear increase in AUASI score with increasing frailty scores among men who met 1 frailty phenotype criterion at baseline in Figure

1. Among men with 2 or more frailty criteria at baseline, similar increases in mean predicted AUASI were observed. Regression coefficients for these non-linear associations are reported in Supplemental Table 1.

Figure 1. Line plot showing predicted AUASI score by within-person change in phenotypic frailty score



Predicted AUASI calculated using linear mixed effects models adjusted for age, site, diabetes, stroke or Parkinson's disease, chronic obstructive pulmonary disease, angina, heart failure, and hypertension with age set to the median, baseline frailty phenotype score set to 1, and all other covariates set to 0.

In sensitivity analyses, results were materially unchanged after further adjustment for anxiety/depression, multimorbidity, self-reported general health status, and number of LUTS medications (Supplemental Table 2). Results were also materially unchanged after further adjustment for diuretic medication use and after excluding men with at least weekly urinary incontinence, cognitive impairment, or a baseline phenotypic frailty score of 5 (Supplemental Table 3). When individual frailty phenotype components were examined separately, newly developing each of 4 components (all but shrinking/sarcopenia) was independently associated with worsening LUTS severity (Supplemental Table 4).

Discussion

In this multicenter, prospective cohort study with 7 years of follow-up, we found that older men without clinically meaningful LUTS at baseline who developed increasing phenotypic frailty were also more likely to report greater LUTS severity during follow-up. These non-linear associations were modest in size but consistent across both storage and voiding LUTS, and independent of age, comorbidities, and LUTS treatments. Conversely, baseline frailty status alone was not associated with change in LUTS severity. Importantly, observed associations persisted among men without urinary incontinence or cognitive impairment. Our findings support further investigations into the mechanisms of why frailty and LUTS develop concurrently in order to identify novel frailty-related LUTS phenotypes and treatment targets.

Phenotypic frailty or surrogates of frailty are consistently associated with more severe LUTS in cross-sectional studies. Using data from the same MrOS cohort, our group previously demonstrated that the prevalence of moderate LUTS among men with phenotypic frailty was 46% versus 37% among robust men (adjusted OR= 1.4, 95% CI 1.1, 1.7) and the prevalence of severe LUTS was 13% among men with phenotypic frailty versus 5% among robust men (adjusted OR= 2.5, 95% 1.8, 3.6) (4). Consistent with the current study, these associations were independent of age, comorbidities, or LUTS treatments and persisted among men without urinary incontinence. Similar associations were observed among in small studies among older Korean and Japanese men (35, 36). Our group also previously reported that older men seeking subspecialty treatment for LUTS were more likely to have slow Timed-Up-And-Go-Test times compared to those with other urologic conditions (37) and that slow Timed-Up-And-Go-Test times are associated with detrusor overactivity (38), which can contribute to storage LUTS. This study adds to the cross-sectional literature and is the first study, to our knowledge, to examine the association of baseline phenotypic frailty and change in phenotypic frailty with change in LUTS severity.

Taken together with the cross-sectional studies mentioned above, our study suggests that men with phenotypic frailty and those who develop phenotypic frailty both have greater LUTS severity, but frail men without LUTS at baseline do not have a higher risk of developing worsening LUTS in the future. The conflicting results of models using baseline frailty status versus within-person changes in phenotypic frailty are thought-provoking and highlight several strengths of our approach. First, to determine if worsening phenotypic frailty is an independent risk factor for developing new and progressively worsening LUTS we selected an analytic cohort of older men without moderate-to-severe LUTS, therefore pre-frail and frail men who met our inclusion criteria may be less susceptible to frailty-associated LUTS. Second, coefficient estimates for the association of baseline frailty status with change in a LUTS severity are susceptible to unmeasured confounding. Men who are frail at baseline are almost certainly different than men who are robust at baseline, some but not all of which are captured in the comprehensive questionnaires, interview questions, and functional testing that men agree to complete as MrOS participants. When within-person change in phenotypic frailty is modeled separately from baseline frailty, it is less likely to be biased due to measured or unmeasured baseline characteristics that do not change over time. Adjustment for time-varying confounders, as we have done in this study, further supports the hypothesis that within-person increases in phenotypic frailty are independently associated with worsening LUTS severity. Third, men who have already developed frailty prior to the baseline visit are much more likely to be lost to follow-up due to illness or death, which could bias results towards the null if they developed worsening LUTS prior to being lost to follow-up. Thus, although the effect sizes were modest, these findings suggest that, among men without LUTS at baseline, increasing number of phenotypic frailty components over time

is independently associated with concurrent worsening LUTS severity. This study represents an important first step toward understanding whether interventions to prevent or treat frailty could similarly help mitigate age-related LUTS in older men.

Due to an absence of well-validated preclinical models for age-related LUTS beyond traditional models of bladder outlet obstruction, the mechanisms of phenotypic frailty contributing to or developing concurrently with male LUTS remain unknown. Men who develop phenotypic frailty may report that it is "difficult to postpone urination" (urgency) because it takes them longer to travel to the bathroom after they first detect the sensation of a full bladder. Alternatively, men who are developing frailty may be less able to suppress the sensation of urgency via pelvic floor muscle or skeletal abdominal muscle contractions (39). The sensations of "not emptying your bladder completely", having to "push or strain to begin urination," or weak urinary stream may be caused by obstruction due to BPH or, alternatively, men with worsening frailty may be unable to generate the same force of urinary expulsion as robust men due to smooth and/or skeletal muscle weakness. Although the role of skeletal muscle in LUTS has been minimally explored, the external urethral sphincter (40), pelvic floor (41), and abdominal musculature (39) are all skeletal muscles suspected to play a role in both micturition control and regulation of bladder sensations. Frail older men produce excess urine at night (42), potentially due to changes in the circadian rhythm of water excretion (43, 44). Lastly, changes within the lower urinary tract that occur with increasing age, such as decreased functional bladder capacity and increased detrusor instability, may be more exaggerated among frail older men (44). Additional work is needed to identify which of these mechanisms contribute to the association between concurrently worsening frailty phenotype and LUTS among older men observed in this study.

The link between phenotypic frailty and LUTS may also be due to a common underlying cause. Although there are several biological mechanisms that contribute to multiple geriatric syndromes, such as white matter intensities (45), our team is particularly interested in the possibility that phenotypic frailty and LUTS are both caused by fundamental biological processes of aging that drive aging-related pathophysiology locally and/or systemically (e.g., the "geroscience hypothesis"). Increasing chronological age is one of the strongest risk factors for LUTS in both men and women (46). In addition to the geriatric syndromes mentioned above that are associated with LUTS, several chronic diseases of aging (47, 48), age-related metabolic (49, 50) and immune (51) derangements, and health-related behaviors that accelerate biological aging (52, 53) are associated with both phenotypic frailty and LUTS. Instead of each chronic disease, phenotype, or syndrome of aging representing a unique LUTS risk factor, perhaps these conditions are all caused by a shared biological mechanism of aging. Although it is impossible to directly measure perceived bladder sensations in animals, evidence from mouse models further supports the aging bladder phenotype as a consequence of centrally mediated adaptive failure (e.g., reduced resilience) due to systemic biologic aging rather than local urogenital tissue changes (54). Future human and animal studies of geroscience mechanisms and interventions should consider including assessments of LUTS and bladder function.

We recognize several limitations to our study. First, MrOS is a cohort of predominantly healthy, older men (to be eligible for the study, men must have been able to walk without assistance and must have lived in the community), most of whom are White. Thus, the results may not be generalizable to younger men or to institutionalized, less-healthy, or more racially diverse men. Second, this is an observational study so men were not randomized to interventions that change their frailty or LUTS status and therefore residual time-varying confounding may explain the observed associations. Third, men with frailty but none/mild LUTS at baseline may have had more severe LUTS in the past and received treatment, which would bias our estimates towards the null when examining the association between frailty status at baseline and change in LUTS. Fourth, the MrOS cohort was initiated more than two decades ago when older generation LUTS treatments that may theoretically contribute to greater risk of frailty, such as non-selective α-blockers, were more commonly prescribed (55). However, we did not observe any evidence of effect modification by LUTS treatment (including medications) and evidence from pooled analyses of randomized clinical trials suggest that older and newer generation α-blockers have similar efficacy. Thus, treatments for LUTS are unlikely to explain observed differences in LUTS severity (56). Lastly, we only tested associations with phenotypic frailty, which is one of multiple valid definitions and conceptual models of frailty (30). It is unknown if other methods to define frailty, such as deficit accumulation, would yield similar results. Similarly, we defined LUTS severity using AUASI total score and subscores, which are commonly used in clinical and urologic research settings, but we did not consider global urinary bother or alternative definitions of LUTS severity, such as number of individual LUTS.

In conclusion, within-person increases in components of phenotypic frailty are associated with concurrent non-linear increases in LUTS severity among older men without clinically meaningful LUTS at baseline. Although observed associations were modest in magnitude, they were independent of age, comorbidities, and LUTS medications and persisted among men without urinary incontinence or cognitive impairment. Further studies are needed to investigate the mechanistic basis of this association and to determine whether frailty interventions could prevent or treat LUTS in older men.

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