APPENDIX

*Model Diagnostics and Sensitivity Analyses*

We conducted several modeling diagnostics to ensure optimal model fit. We assessed normality of residuals and tested model fit by including a quadratic term for phenotypic frailty score, which was statistically significant (*P* <0.001) and, therefore, remained in the final model. We also compared models that used calendar time as the underlying timescale (with adjustment for baseline age). We tested whether AUASI score increases non-linearly with increasing age by including a quadratic term for age. We excluded participants with a studentized residual >|4| one at a time to evaluate the influence of outliers and we separately excluded men with a phenotypic frailty score of 5 at baseline to prevent ceiling effects. Lastly, we performed a lagged analysis to determine if phenotypic frailty was associated with LUTS severity at the subsequent visit and we found that coefficients were similar to our primary models.

**Supplemental Figure 1**. Study flowchart.



LUTS lower urinary tract symptoms; AUASI American Urological Association Symptom Index

**Supplemental Table 1.** Association of longitudinal changes in phenotypic frailty score with concurrent changes in overall, storage, and voiding lower urinary tract symptoms (LUTS).

|  |  |  |
| --- | --- | --- |
|  | **Age/Site-Adjusted** | **Multivariable Adjusted**† |
| **Parameter** | **Regression Coefficient (95%CI)** | **Regression Coefficient (95%CI)** | ***P*-value\*** |
| **Overall LUTS** |  |  |  |
| Phenotypic frailty score (per 1 criterion) |  |  |  |
|  Baseline (between-person) | -0.12 (-0.24, 0.01) | -0.18 (-0.30, -0.06) | 0.003 |
|  Time-updated (within-person) | 0.27 (0.11, 0.43) | 0.22 (0.06, 0.38) | 0.006 |
|  Quadratic time-updated (within-person) | 0.26 (0.19, 0.33) | 0.24 (0.17, 0.31) | <0.0001 |
|  |  |  |  |
| **Storage LUTS** |  |  |  |
| Phenotypic frailty score (per 1 criterion) |  |  |  |
|  Baseline (between-person) | -0.04 (-0.11, 0.03) | -0.07 (-0.14, -0.00) | 0.04 |
|  Time-updated (within-person) | 0.13 (0.04, 0.22) | 0.10 (0.01, 0.19) | 0.02 |
|  Quadratic time-updated (within-person) | 0.14 (0.10, 0.18) | 0.12 (0.08, 0.16) | <0.0001 |
|  |  |  |  |
| **Voiding LUTS** |  |  |  |
| Phenotypic frailty score (per 1 criterion) |  |  |  |
|  Baseline (between-person) | -0.06 (-0.14, 0.01) | -0.10 (-0.17, -0.02) | 0.01 |
|  Time-updated (within-person) | 0.15 (0.05, 0.25) | 0.12 (0.02, 0.22) | 0.02 |
|  Quadratic time-updated (within-person) | 0.14 (0.10, 0.18) | 0.11 (0.07, 0.15) | <0.0001 |
|  |  |  |  |

\* Effect estimates calculated using linear mixed effects models. P-value calculated for change in AUASI per 1 frailty phenotype criterion.

† Adjusted for age, site, diabetes, stroke or Parkinson’s disease, chronic obstructive pulmonary disease, angina, heart failure, and hypertension.

**Supplemental Table 2.** Association of longitudinal changes in phenotypic frailty score with concurrent changes in overall lower urinary tract symptoms (LUTS) after adjusting for potential mediators.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Multivariable Adjusted + Multimorbidity**† | **Multivariable Adjusted + Anxiety/Depression**‡ | **Multivariable Adjusted + Self-Reported General Health Status** | **Multivariable Adjusted +** **# of LUTS Medications** |
| **Parameter** | **Effect Estimate\* (95%CI)** | ***P*-value** | **Effect Estimate\* (95%CI)** | ***P*-value** | **Effect Estimate\* (95%CI)** | ***P*-value** | **Effect Estimate\* (95%CI)** | ***P*-value** |
| Phenotypic frailty score |  |  |  |  |  |  |  |  |
|  Baseline | -0.17 (-0.30, -0.05) | 0.01 | -0.22 (-0.34, -0.9) | 0.001 | -0.26 (-0.39, -0.14) | <0.0001 | -0.17 (-029, -0.05) | 0.01 |
|  Time-updated | 0.22 (0.06, 0.38) | 0.01 | 0.20 (0.04, 0.36) | 0.01 | 0.18 (0.02, 0.34) | 0.03 | 0.21 (0.05, 0.37) | 0.01 |
|  Quadratic time-updated | 0.23 (0.16, 0.30) | <0.0001 | 0.23 (0.16, 0.30) | <0.0001 | 0.23 (0.16, 0.30) | <0.0001 | 0.23 (0.16, 0.29) | <0.0001 |
|  |  |  |  |  |  |  |  |  |

\* Effect estimates 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. P-value calculated for change in American Urological Association Symptom Index (AUASI) per 1 frailty phenotype criterion.

† Multimorbidity defined as the cumulative number of the following chronic medical conditions: stroke, Parkinson’s disease, myocardial infarction, angina, chronic obstructive pulmonary disease, heart failure, diabetes mellitus, osteoporosis, osteoarthritis, hyperthyroidism or hypothyroidism (0, 1, 2, and ≥3).

‡ Short Form-12 Mental Health Component Summary ≤50

**Supplemental Table 3.** Sensitivity analyses of association of longitudinal changes in phenotypic frailty score with concurrent changes in overall lower urinary tract symptoms (LUTS) after adjusting for potential mediators or confounders.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Restricted to Men without Urinary Incontinence** | **Restricted to Men without Cognitive Impairment**† | **Further Adjustment for Diuretic Medication Use**  | **Restricted to Men with Baseline Frailty Score <5** |
| **Parameter** | **Effect Estimate\* (95%CI)** | ***P*-value** | **Effect Estimate\* (95%CI)** | ***P*-value** | **Effect Estimate\* (95%CI)** | ***P*-value** | **Effect Estimate\* (95%CI)** | ***P*-value** |
| Phenotypic frailty score |  |  |  |  |  |  |  |  |
|  Baseline | -0.19 (-0.32, -0.06) | 0.004 | -0.16 (-0.28, -0.03) | 0.01 | -0.17 (-0.30, -0.05) | 0.01 | -0.17 (-0.29, -0.04) | 0.01 |
|  Time-updated | 0.17 (-0.00, 0.34) | 0.05 | 0.22 (0.06, 0.38) | 0.01 | 0.22 (0.06, 0.38) | 0.01 | 0.21 (0.05, 0.37) | 0.01 |
|  Quadratic time-updated | 0.24 (0.16, 0.31) | <0.0001 | 0.24 (0.17, 0.31) | <0.0001 | 0.23 (0.16, 0.30) | <0.0001 | 0.24 (0.17, 0.31) | <0.0001 |
|  |  |  |  |  |  |  |  |  |

 \* Effect estimates 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. P-value calculated for change in American Urological Association Symptom Index (AUASI) per 1 frailty phenotype criterion.

 † Teng Mini-Mental Status (3MS) <80

**Supplemental Table 4.** Association of longitudinal changes in individual frailty phenotype criterion with concurrent changes in overall lower urinary tract symptoms (LUTS).

|  |  |
| --- | --- |
|  | **Multivariable Adjusted\*** |
| **Frailty Phenotype Criterion** | **Regression Coefficient (95%CI)** | ***P*-value** |
| Shrinking/Sarcopenia | -0.56 (-1.27, 0.15) | 0.12 |
| Exhaustion | 1.07 (0.47, 1.66) | <0.0001 |
| Weakness | 1.06 (0.71, 1.41) | <0.0001 |
| Slowness | 1.02 (0.66, 1.38) | <0.0001 |
| Low Physical Activity | 0.51 (0.17, 0.85) | <0.0001 |
|  |  |  |

\* Effect estimates calculated for each binary frailty phenotype criterion using linear mixed effects models adjusted for age, site, diabetes, stroke or Parkinson’s disease, chronic obstructive pulmonary disease, angina, heart failure, and hypertension. P-value calculated for change in American Urological Association Symptom Index (AUASI) different from 0.