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Research Article

Longitudinal Changes in Adiposity and Lower Urinary Tract Symptoms Among Older Men

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Abstract

Background: Adiposity increases risk for male lower urinary tract symptoms (LUTS), although longitudinal studies have produced conflicting results. No prior studies have evaluated longitudinal associations of changes in adiposity with concurrent LUTS severity among older men.

Methods: We used repeated adiposity measurements from dual-energy x-ray absorptiometry (DXA), body mass index (BMI), and American Urological Association Symptom Index (AUASI) measured at 4 study visits over a 9-year period among 5 949 men enrolled in the Osteoporotic Fractures in Men (MrOS) study. Linear mixed effect models adjusted for age, health-related behaviors, and comorbidities were created to evaluate the association between baseline and change in visceral adipose tissue (VAT) area, total fat mass, and BMI with change in LUTS severity measured by the AUASI.

Results: A nonlinear association was observed between baseline VAT area and change in AUASI: men in baseline VAT tertile (T) 2 had a lower annual increase in AUASI score compared to men in T1 and T3 (T2 vs T1: $\beta = -0.07$; 95% CI −0.12, −0.03; $p = .008$; T3 vs T1: NS) but differences were small. No significant associations were observed between change in VAT area and change in AUASI score. Neither baseline tertiles nor change in total fat mass or BMI were associated with change in AUASI score.

Conclusions: Changes in VAT area, total fat mass, and BMI were not associated with change in LUTS severity in this cohort. Thus, despite other health benefits, interventions targeting adiposity alone are unlikely to be effective for preventing or treating LUTS among older men.

Keywords: Benign prostatic hyperplasia, Overactive bladder, Urological conditions, Weight loss (1–5 MESH)

Publicly available data: https://mrosonline.ucsf.edu

Half of men over age 70 years develop clinically significant and bothersome lower urinary tract symptoms (LUTS) (1,2). LUTS in older men are associated with psychological distress and poor quality of life, as well as increased risk of falls and mortality (3,4). LUTS is a complex syndrome of overlapping symptoms that occur during urine *storage* (urgency, frequency, nocturia, incontinence) or *voiding* (weak stream, hesitancy, straining, incomplete bladder emptying) (5). Particularly among older men, LUTS are heterogenous with multifactorial etiologies (6,7), including both urologic (eg, benign prostatic hyperplasia [BPH] or detrusor overactivity) and nonurologic causes (eg, volume overload states or remobilization of peripheral edema). Although progression of LUTS due to presumed BPH may be delayed or prevented with combination therapy (α-blocker plus

5α-reductase inhibitor) (8), these medications are not safe for all older men (9) and contribute directly to polypharmacy. Therefore, rigorous longitudinal studies of modifiable lifestyle risk factors for LUTS, such as adiposity, among older men are needed (10).

Weight loss is an effective intervention for urinary incontinence among overweight women, but no randomized studies have been conducted among men with urinary incontinence or other LUTS (11). Cross-sectional and prospective studies have consistently demonstrated an association of anthropometric measures of adiposity, including higher body mass index (BMI), waist circumference, and waist:hip ratio, with male LUTS (12–14). However, longitudinal studies examining associations between change in adiposity and LUTS have produced conflicting results, raising the possibility that adiposity is not a modifiable LUTS risk factor (15,16). Multiple changes in body composition occur as men age and may obscure longitudinal relationships between adiposity and LUTS, including increased total body fat mass (17), decreased abdominal muscle area (18), infiltration of adipose tissue into skeletal muscle (19), and a shift from subcutaneous to visceral adipose tissue (VAT) (20). These changes can be measured using dual-energy x-ray absorptiometry (DXA) or computed tomography (CT) (21) and are associated with increased mortality (22) and several age-related diseases in older men (23–25), independent of BMI. To our knowledge, no prior studies have evaluated the association of visceral adiposity and fat mass, or their changes, with changes in LUTS among older men.

To address this gap in knowledge, we evaluated (1) the relationship of baseline VAT area, total body fat mass, and BMI with change in LUTS severity, and (2) the relationship of change in VAT area, total body fat mass, and BMI with change in LUTS severity, during 9 years in a large cohort of older, community-dwelling men. We hypothesized that greater VAT area, total fat mass, and BMI at baseline as well as increasing adiposity measures during follow-up would be positively associated with change in LUTS severity.

Methods

Participants

The Osteoporotic Fractures in Men (MrOS) study is a large, multicenter cohort study of 5 994 community-dwelling men aged 65 years or older as previously described (26). 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 6 academic medical centers. All eligible surviving participants were invited to complete a questionnaire during Year 2 (July 2002–March 2004; n = 5 708) and to return to the clinic during Year 5 (March 2005–May 2006; n = 5 196) and Year 7 (March 2007–March 2009; n = 4 651) (Supplementary 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) (27), 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) (7,28) and the minimal clinically important difference is 3 points (29). In addition to the total score, we calculated AUASI subscores separately for storage symptoms (urgency, frequency, and nocturia) and for voiding symptoms (incomplete emptying, intermittency, weak stream, and straining), consistent with the literature (30).

Other Measurements

Age, race/ethnicity, education, and usual caffeine consumption were assessed via self-administered questionnaires at baseline, and marital status, smoking status, usual alcohol consumption, and physical activity were updated via self-administered questionnaires at every study visit (26). Participants reported history of myocardial infarction, angina, heart failure, hypertension, diabetes, prostate cancer (51% treated with surgery, 29% with radiation only, 14% with hormones only, and 6% were not treated), or neurological disease (stroke or Parkinson's disease). All participants completed the Medical Outcomes Study Short Form (SF-12), and the mental health component score ≤50 was used as a surrogate for psychological distress at each visit (31). 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) as well as diuretics were identified using the Iowa Drug Information System (IDIS) (32). 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," "Prescription medications," or "Other" treatments for this condition, which was used to define self-reported BPH surgery.

Adiposity Measurements

Total fat mass was measured during 3 visits from DXA scans using Hologic QDR 4500 scanners (Hologic, Inc., Bedford, MA) following standardized procedures by certified DXA technicians. Reproducibility was ensured by use of a central quality control laboratory (San Francisco Coordinating Center, San Francisco, CA). A Hologic whole-body phantom was scanned repeatedly at each site to monitor longitudinal changes, which remained within acceptable limits; therefore, cross-calibration correction factors were not required although study site was included in statistical models to adjust for any differences across individual scanners.

VAT area was calculated from the same DXA scans using a standard algorithm (33). The software estimates total adipose tissue within a 5-cm transverse slide with the inferior border placed at the top of the iliac crest (approximately L4 vertebral level) on a 2-dimensional projection of the abdominal-pelvic region. The lateral and medical edges of the abdominal wall musculature are identified. VAT is contained within the visceral cavity inside the medial edge of the abdominal wall musculature, but this area also contains subcutaneous adipose tissue (in addition to areas outside of the lateral edges). The amount of subcutaneous adipose tissue in the medial VAT area can

be estimated from the adipose tissue lateral to the abdominal wall musculature, and the estimated visceral fat area (cm^2) is then calculated as total adipose tissue overlying and within the visceral cavity minus the subcutaneous adipose tissue overlying this area. Although CT scans are considered the gold standard for measuring VAT, DXA-derived VAT is highly correlated with CT-derived VAT and they are similarly associated with metabolic measures in older men (21).

Height and weight measurements were used to calculate a standard BMI. 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.

Statistical Analysis

For this study, the primary independent variables were within-person change in VAT area, total fat mass, and BMI and the primary dependent variable was LUTS severity based on AUASI score (total, storage subscore, and voiding subscore) at each repeated assessment. We excluded men who were missing the AUASI (n = 4) and DXA measures (n = 39) at baseline.

We first compared distributions of established adiposity and LUTS risk factors across tertiles of VAT area and tertiles of total fat mass. To test the hypothesis that greater baseline adiposity measures are associated with greater annual increases in AUASI score, we used linear mixed effect models and modeled tertiles of baseline VAT area, total body fat mass, and BMI. To visualize the trajectory of AUASI scores over time according to baseline adiposity, we created a plot of least square mean AUASI score by age among men aged 66–84 years (excluding men younger than the 10th percentile of age or older than the 90th percentile for the figures only to avoid over-extrapolation), stratified by tertile of VAT area, fat mass, and BMI at baseline. To test the hypothesis that within-person changes in VAT area fat mass, and BMI are positively associated with concurrent changes in AUASI score, we used linear mixed effect models. We separately modeled VAT area, total fat mass, and BMI at baseline and time-varying variables adjusted for baseline (measurement at each visit minus measurement at baseline) to separate between and within-person coefficient estimates (34). All linear mixed models included random intercepts and slopes and used an unstructured variance–covariance matrix.

To identify and control for confounding factors, we applied a change in estimate criteria (35) First, we specified variables to be forced into the model (age, site, and height) and 4 groups of potential confounders: demographics (education, race, and marital status), lifestyle (smoking, alcohol intake, caffeine intake, and physical activity), cardiovascular comorbidities (self-reported history of myocardial infarction, angina, health failure, and hypertension), and other medical comorbidities (SF-12 mental health component score ≤50 (31) and self-reported history of diabetes mellitus, prostate cancer, and neurological disease). Next, we fit a full multivariable model including all forced and grouped variables. 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 at least 10% used to indicate important confounding (all groups met this criteria) (36). Next, we successively removed variables from each group and left variables out if removing them reduced the % change by <1. We repeated this until each remaining group only contained variables that contribute ≥1% of the % change for that group of variables. Lastly, we included age, site, height (for VAT area and total fat mass models), and all remaining potential confounders in each group to the final multivariable model. The final multivariable model included age (continuous in years), study site, height (continuous in cm), usual alcohol consumption (<1, 1-<7, 7-<14, ≥14 drinks/week), smoking (current, former, never), Physical Activity Scale for the Elderly score (continuous), usual caffeine consumption (continuous in mg/day), SF-12 mental health component score ≤50 (yes/no), and self-reported history of angina, heart failure, hypertension, diabetes mellitus, neurological disease, and prostate cancer (yes/no for each).

We assessed effect modification of the main associations by including a cross product term of the combined between and within-person estimates by age, BMI, LUTS treatment (medication or surgery), history of prostate cancer, or diabetes. We also conducted sensitivity analyses adjusting for number of LUTS medications or diuretic medication use, adjusting for self-reported history of BPH surgery, and mutually adjusting for VAT area and total fat mass.

p-value <.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

Baseline demographic and health-related characteristics of the 5 949 community-dwelling men in the analytic sample are reported in Table 1. Men in the highest tertile of VAT area or total fat mass had higher BMI, were more likely to be non-Hispanic White, less physically active, consume more caffeine, report diuretic medication use, and have a history of hypertension or diabetes compared with men in the lowest 2 tertiles. AUASI score at baseline was similar across tertiles of VAT area and total fat mass.

Predicted AUASI scores by age, stratified by baseline VAT area, total fat mass, and BMI are shown in Figure 1. Annual change estimates for AUASI score and associations of baseline VAT area, total fat mass, and BMI with annual change in AUASI are reported in Table 2. Estimated unadjusted annual change in AUASI score was 0.10 (95% CI 0.07, 0.13) for men in Tertile 1 of VAT area, 0.07 (95% CI 0.03, 0.10) in Tertile 2, and 0.08 (95% CI 0.05, 0.11) in Tertile 3. Compared to men in Tertile 1, the estimated adjusted annual change in AUASI among men in Tertile 2 of VAT area at baseline was lower by 0.06 points per year whereas the annual change in AUASI among men in Tertile 3 was not significantly different. Unadjusted annual change in AUASI score ranged from 0.03 to 0.11 per year across tertiles of baseline total fat mass and 0.08 to 0.09 per year across tertiles of baseline BMI, these differences were not statistically significant. The pattern of associations with the AUASI voiding subscore appeared similar for VAT area, total fat mass, and BMI, but the AUASI storage subscore was not associated with any baseline adiposity measure (Supplementary Table 1).

Associations between change in VAT area, total fat mass, or BMI and change in AUASI score are reported in Table 3. Longitudinal within-person changes in VAT area, total fat mass, and BMI were not associated with concurrent changes in total AUASI score (time-updated coefficient $p > .5$ for all). When coefficients for baseline adiposity measures were examined separately, each additional 4 kg/m^2 between-person difference in BMI was associated with a 0.04 points higher AUASI (95% CI 0.00, 0.08, $p = .03$). Similar to total AUASI score, there was no evidence for an association between within-person change in adiposity measures and change in AUASI

Table 1. Summary of Baseline Characteristics of Study Population, by Tertiles of Baseline Visceral Adipose Tissue Area and Total Fat Mass

	Visceral Adipose Tissue (VAT) Area			Total Fat Mass		
Variable	Tertile 1 (n = 1 982)	Tertile 2 (n = 1 983)	Tertile 3 (n = 1 984)	Tertile 1 (n = 1 982)	Tertile 2 (n = 1 983)	Tertile 3 (n = 1 984)
Total Fat Mass, kg						
Mean ± *SD*	16 ± 4	22 ± 4	28 ± 6	15 ± 3	21 ± 2	30 ± 5
Range, min-max	4–41	12–46	16–62	4–18	18–24	24–62
VAT Area, cm^2						
Mean ± *SD*	112 ± 26	176 ± 17	258 ± 44	123 ± 38	180 ± 40	243 ± 57
Range, min-max	12–46	148–207	207–469	28–257	70–320	87–469
Body Mass Index, kg/m^2	24.4 ± 2	27.2 ± 3	30.5 ± 4	24.2 ± 2	26.9 ± 2	31.0 ± 3
Height, cm	174 ± 7	174 ± 7	175 ± 7	172 ± 7	174 ± 7	176 ± 7
Weight, kg	74 ± 9	82 ± 10	93 ± 12	72 ± 8	82 ± 7	96 ± 11
Age, years, mean ± *SD*	74 ± 6	74 ± 6	73 ± 5	75 ± 6	73 ± 6	73 ± 5
Non-Hispanic White, *n* (%)	1 717 (87)	1 770 (89)	1 833 (92)	1 723 (87)	1 788 (90)	1 809 (91)
College education, *n* (%)	1 233 (62)	1 049 (53)	886 (45)	1 171 (59)	1 050 (53)	947 (48)
Married, *n* (%)	1 635 (82)	1 641 (83)	1 616 (81)	1 605 (81)	1 663 (84)	1 624 (82)
Current Smoking, *n* (%)	78 (4)	80 (4)	46 (2)	77 (4)	76 (4)	51 (3)
Alcohol Consumption						
<1 drink/wk	933 (47)	933 (47)	972 (49)	896 (45)	929 (47)	1 013 (51)
1 to <7 drinks/wk	483 (24)	431 (22)	428 (22)	457 (23)	458 (23)	427 (22)
7 to <14 drinks/wk	375 (19)	366 (19)	329 (17)	391 (20)	361 (19)	318 (16)
14+ drinks/wk	189 (10)	249 (13)	253 (13)	236 (12)	232 (12)	223 (11)
Daily Caffeine Consumption, mg/day, mean ± *SD*	198 ± 230	220 ± 232	226 ± 236	198 ± 226	218 ± 236	226 ± 237
PASE score, mean ± *SD*	151 ± 69	148 ± 67	141 ± 67	151 ± 69	148 ± 67	141 ± 67
History of MI	252 (13)	282 (14)	292 (14)	254 (13)	296 (15)	276 (14)
History of Angina	241 (12)	304 (125)	303 (15)	248 (13)	305 (15)	295 (15)
History of Heart Failure	105 (5)	96 (5)	115 (6)	102 (5)	90 (4)	124 (6)
History of Prostate Cancer	221 (11)	246 (12)	234 (12)	198 (10)	265 (13)	238 (12)
History of Stroke	114 (6)	111 (6)	115 (6)	131 (6)	109 (5)	100 (5)
History of Parkinson's	23 (1)	15 (<1)	13 (<1)	27 (1)	9 (<1)	15 (<1)
History of Hypertension	622 (33)	822 (43)	997 (52)	659 (35)	819 (43)	963 (51)
History of Diabetes Mellitus	135 (7)	201 (10)	312 (16)	150 (8)	207 (10)	291 (15)
Psychological Distress*	335 (17)	312 (16)	316 (16)	325 (16)	320 (16)	318 (16)
Diuretic Medication Use	255 (13)	354 (18)	463 (24)	275 (14)	339 (18)	458 (24)
Surgery for LUTS	280 (14)	266 (13)	291 (15)	287 (14)	302 (15)	248 (12)
Number of LUTS medications						
0	1 567 (83)	1 550 (82)	1 529 (80)	1 558 (81)	1 536 (81)	1 552 (81)
1	300 (16)	327 (17)	343 (18)	322 (17)	327 (17)	321 (17)
2–3	33 (2)	20 (1)	42 (2)	27 (1)	31 (2)	37 (2)
α-Blocker Use	283 (15)	290 (15)	346 (18)	288 (15)	305 (16)	326 (17)
5α-Reductase Use	60 (3)	59 (3)	51 (3)	65 (3)	61 (3)	44 (2)
Anti-Cholinergic Use	24 (1)	19 (1)	30 (2)	24 (1)	24 (1)	25 (1)
Total AUASI score	8.3 ± 6	8.2 ± 6	8.3 ± 6	8.4 ± 6	8.2 ± 6	8.3 ± 6
Storage subscore	4.7 ± 3	4.5 ± 3	4.6 ± 3	4.7 ± 3	4.5 ± 3	4.7 ± 3
Voiding subscore	3.6 ± 4	3.7 ± 4	3.7 ± 4	3.6 ± 4	3.7 ± 4	3.6 ± 4

Notes: AUASI = American Urological Association Symptom Index; LUTS = lower urinary tract symptoms; MI = myocardial infarction; *n* = sample size; PASE = Physical Activity Scale for the Elderly.

*Medical Outcomes Study Short Form (MOS SF-12) mental health component score ≤50.

storage or voiding subscores, although baseline BMI was associated with higher AUASI storage subscores (Supplementary Table 2). Results were materially unchanged after combining the between and within-person coefficient estimates for VAT area and total fat mass (Supplementary Table 3).

We did not observe evidence of effect modification by age, LUTS treatment (time-updated LUTS medication use or surgery), history of prostate cancer, diabetes, or baseline BMI (tested for VAT area and total fat mass models only). Differences in baseline characteristics between men with complete data, those who were missing at least one AUASI score during follow-up, and those who died during follow-up were observed only among variables included in the full multivariable model and we did not observe evidence of effect modification by pattern of missing data. Results were materially unchanged after adjustment for number of LUTS medications, self-reported history of BPH history, or diuretic medication use and after mutual adjustment for VAT area and total fat mass in planned sensitivity analyses (data available upon request).

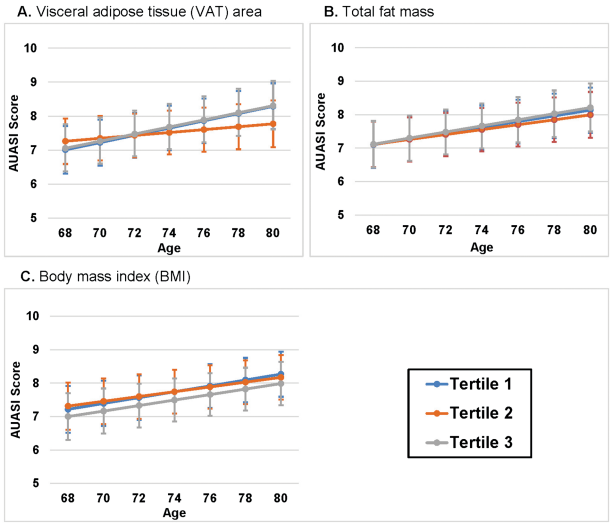

Figure 1. Line plot showing predicted American Urological Association Symptom Index (AUASI) score by age, stratified by tertiles of baseline **A**) visceral adipose tissue area, **B**) total fat mass, and **C**) body mass index. Full color version is available within the online issue.

Discussion

In this prospective cohort study of older, community-dwelling men, we found that tertile of baseline VAT area, but not total fat mass or BMI, was independently associated with a small but statistically significant difference in annual change in AUASI. Specifically, annual increase in AUASI, overall and voiding subscore, was smallest among men in the middle tertile of VAT area compared to greater annual increases among men in the lowest tertile. However, we did not observe evidence for an association of within-person change in any adiposity measure with concurrent change in AUASI.

Cross-sectional studies have consistently demonstrated an association of greater adiposity with both voiding and storage LUTS (37), and these associations have now been confirmed in multiple prospective cohort studies. Using the same MrOS cohort data as our study, Parsons et al. (38) demonstrated that men with BMI ≥25 kg/m^2 were more likely to develop incident LUTS, and Marshall et al. (13) demonstrated that men with BMI ≥25 kg/m^2 were more likely to have a progressive LUTS trajectory compared to men with BMI <25 kg/m^2. In a secondary analysis of the Prostate Cancer Prevention Trial, men with higher BMI or waist:hip ratio at baseline randomized to the placebo arm had an increased risk of incident LUTS due to presumed BPH (39). In the Health Professionals Follow-up Study, higher BMI, greater waist circumference, and waist:hip ratio, as well as greater weight gain since age 21 years were all associated with increased risk of overall LUTS incidence and progression (12). Our study provides contrary evidence that baseline adiposity, including both BMI and DXA-derived measures which are more proximal surrogates of regional adiposity that could affect the lower urinary tract, is not associated with a meaningful annual change in LUTS severity among older men.

Table 2. Association of Baseline VAT Area, Total Fat Mass, and BMI Tertiles With Annual Change in LUTS Severity Among MrOS Participants

Variable	Unadjusted* Annual Change Estimate (95% CI)	Minimally-Adjusted† Estimated Difference in Annual Change (95% CI)	Multivariable Adjusted‡ Estimated Difference in Annual Change (95% CI)	*p*-value
Baseline VAT area, cm^2				
Tertile 1	0.10 (0.07, 0.13)	Ref.	Ref.	
Tertile 2	0.07 (0.03, 0.10)	−0.07 (−0.12, −0.03)	−0.06 (−0.11, −0.02)	.008
Tertile 3	0.08 (0.05, 0.11)	−0.01 (−0.06, 0.03)	−0.00 (−0.04, 0.05)	.93
Baseline total fat mass, kg				
Tertile 1	0.11 (0.08, 0.14)	Ref.	Ref.	
Tertile 2	0.03 (0.00, 0.06)	−0.03 (−0.07, 0.01)	−0.02 (−0.06, −0.03)	.44
Tertile 3	0.10 (0.07, 0.13)	−0.02 (−0.06, 0.02)	−0.01 (−0.05, 0.04)	.82
Baseline BMI, kg/m^2				
Tertile 1	0.09 (0.06, 0.12)	Ref.	Ref.	
Tertile 2	0.08 (0.04, 0.11)	−0.02 (−0.06, 0.03)	−0.01 (−0.05, 0.04)	.74
Tertile 3	0.09 (0.06, 0.12)	−0.00 (−0.05, 0.04)	0.01 (−0.04, 0.06)	.67

Notes: BMI = body mass index; LUTS = lower urinary tract symptoms; VAT = visceral adipose tissue.

*Annual change estimate for American Urological Association Symptom Index total score calculated using linear mixed effects models.

†Estimated difference in annual change calculated using linear mixed effects models adjusted for age, site, and height (for VAT area and total fat mass but not BMI models). *p*-value calculated for comparison of the annual change in each tertile versus the annual change in the lowest tertile of adiposity measure.

‡Adjusted for covariates in minimally adjusted model plus caffeine intake, smoking, alcohol consumption, physical activity, psychological distress, and history of angina, heart failure, hypertension, diabetes, neurological disease, or prostate cancer.

Table 3. Association of Longitudinal Changes in VAT Area, Total Fat Mass, and BMI With Concurrent Changes in Overall, Storage, and Voiding LUTS Among MrOS participants

	Minimally-Adjusted*	**Multivariable Adjusted†**	
Parameter	Effect Estimate (95% CI)	Effect Estimate (95% CI)	p-value
VAT area, per 70 cm^2			
Baseline (between-person differences)	0.16 (0.01, 0.30)	0.03 (−0.12, 0.18)	.73
Time-updated (within-person change)	−0.00 (−0.00, 0.00)	−0.00 (−0.00, 0.00)	.82
Total fat mass, per 7 kg			
Baseline (between-person differences)	0.22 (0.07, 0.37)	0.09 (−0.06, 0.24)	.26
Time-updated (within-person change)	0.01 (−0.03, 0.04)	0.01 (−0.03, 0.04)	.75
BMI, per 4 kg/m^2			
Baseline (between-person differences)	0.08 (−0.04, 0.11)	0.04 (0.00, 0.08)	.03
Time-updated (within-person change)	0.01 (−0.06, 0.08)	0.02 (−0.05, 0.09)	.64

Notes: BMI = body mass index; LUTS = lower urinary tract symptoms; VAT = visceral adipose tissue.

*Effect estimates calculated using linear mixed effects models adjusted for age, site, and height (for VAT area and total fat mass but not BMI models). *p*-value calculated for change in AUASI per approximate 1 *SD* of each adiposity measure.

†Adjusted for covariates in minimally adjusted model plus race/ethnicity, smoking, alcohol consumption, physical activity, psychological distress, and history of angina, heart failure, hypertension, diabetes, neurological disease, or prostate cancer.

Contrary to our hypothesis, we observed a lower annual increase in AUASI score among men in the middle tertile of VAT area compared to men in the lowest or highest tertiles. If confirmed, this nonlinear association would suggest that moderate amounts of visceral adiposity in older men is associated with smaller annual increases in LUTS severity, independent of total fat mass, but that above a certain threshold higher VAT area is no longer associated with lower LUTS severity. The estimated annual increases in AUASI were small and of questionable clinical significance, but they are similar to differences in annual change in AUASI between men with different sized prostates or urinary flow rates (40)—objective measures of bladder outlet obstruction due to BPH, the most commonly attributed cause of LUTS in older men (41). In addition to potential causal interpretations, the observed association of baseline VAT and AUASI change could be due to unresolved confounding from several factors that we are unable to test using the available data but may inform future studies. For example, men with the lowest baseline VAT area may have subclinical chronic disease or other unmeasured confounders that cause both lower VAT area and worsening LUTS severity. Additional studies are needed to verify this unexpected finding.

The majority of existing studies do not evaluate whether change in adiposity is associated with change in LUTS severity, which has only been assessed in 2 prospective studies with conflicting results. Among men enrolled in the EPIC-Heidelberg cohort, >2 kg/m^2 increase in BMI over 4 years was associated with higher risk of incident LUTS compared to stable or decreased BMI (15). Conversely, using combined data from 2 population-based cohorts, the Olmsted County Study and Flint Men's Health Study, ≥5% weight loss or weight gain was not associated with change in LUTS after 4 years (16). Our study contributes additional evidence that changes in multiple adiposity measures, including VAT area, total fat mass, and BMI, are not associated with change in LUTS severity over almost a decade of follow-up.

In addition to conflicting evidence regarding the relationship between adiposity and male LUTS, the mechanisms of this association remain poorly understood (10). Previously proposed mechanisms include adiponectin deficiency (42), bladder and prostate inflammatory infiltration and fibrosis (43,44), increased prostate growth (10), metabolic (45) or hormonal derangements (46), and cellular senescence (47). However, each of these potential mechanisms is variably associated with adiposity depending on how it measured (eg, location—central, regional, or total; anatomic area—subcutaneous or visceral; measurement modality—anthropometric, DXA, computerized tomography [CT], or magnetic resonance imaging [MRI]) and whether measurements are repeated over time. For example, although visceral fat contains inflammatory cells and is consistently associated with inflammatory markers, metabolic syndrome, and insulin resistance (21), associations between VAT area and clinical disease have been less consistent (48). Our study represents one of a few conflicting longitudinal epidemiologic studies with repeated measures of adiposity, LUTS severity, and potential confounders that are essential to identify which lifestyle risk factors for LUTS are truly modifiable. However, contrary to our hypothesis, the findings of our study do not support mechanistic pathways in which increasing VAT area, total fat mass, or BMI lead to concurrent increases in male LUTS severity, or vice versa.

We recognize several limitations to our study. MrOS is a cohort of relatively healthy older men, 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. This is an observational study so men were not randomized to interventions that change their adiposity and therefore residual confounding of the observed associations remains possible. For example, malnutrition could be associated with both lower adiposity and worse LUTS. Likewise, greater vitality could be associated with greater adiposity and fewer LUTS. If these conditions occurred in our study, such residual confounding would bias our results toward the null. However, we suspect confounding by nutritional status or vitality would be explained by demographic or clinical variables, including history of comorbidities that we adjusted for in our multivariable model. Changes in adiposity during the follow-up period were modest and it is possible that larger intentional changes, such as those that occur during an intensive weight loss intervention, are needed to observe changes in LUTS severity. However, the changes in adiposity observed in this cohort are likely realistic among community-dwelling older men receiving the standard of care in terms of healthy weight recommendations. Some modern LUTS treatments, such as

β3-adrenergic receptor agonists, were not widely used at the time of this study, but we do not expect that to influence observed associations. Lastly, CT or MRI-derived measures of regional adiposity may be more sensitive to small changes not detected via DXA; however, DXA-derived VAT area is highly correlated with both CT and MRI measures (21,49).

In conclusion, a nonlinear association was observed between baseline VAT area, but not total fat mass or BMI, and change in LUTS severity, although effect sizes were small. Within-person changes in VAT area, total fat mass, and BMI were not associated with change in LUTS severity in this cohort of older, community-dwelling men. Therefore, change in adiposity is unlikely to be a clinically meaningful modifiable risk factor for LUTS among older men.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Author Contributions

S.R.B.: conception and design, acquisition of data, analysis and interpretation of data, drafting and revising the article, final approval of the version to be published. S.L.H.: analysis and interpretation of data, revising the article for important intellectual content, final approval of the version to be published. P.M.C.: conception and design, acquisition of data, analysis and interpretation of data, revising the article for important intellectual content, final approval of the version to be published. A.S.: analysis and interpretation of data, revising the article for important intellectual content, final approval of the version to be published. S.A.K.: analysis and interpretation of data, revising the article for important intellectual content, final approval of the version to be published. A.M.S.: analysis and interpretation of data, revising the article for important intellectual content, final approval of the version to be published. C.E.M.: conception and design, acquisition of data, analysis and interpretation of data, revising the article for important intellectual content, final approval of the version to be published. K.C.: analysis and interpretation of data, revising the article for important intellectual content, final approval of the version to be published. L.M.M.: conception and design, acquisition of data, analysis and interpretation of data, revising the article for important intellectual content, final approval of the version to be published. Sponsor's Role: The study sponsors had no role in the design, methods, subject recruitment, data collections, analysis or preparation of this paper.

Conflict of Interest

None declared.

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