



European Association of Urology



## Platinum Priority – Editorial and Reply from Authors

Referring to the article published on pp. 1173–1180 of this issue

# Physical Activity, Obesity, and Lower Urinary Tract Symptoms

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The relationship between aging, the development of benign prostatic hyperplasia (BPH), and lower urinary tract symptoms (LUTS) has been well described. Briefly, BPH may lead to increased bladder outlet obstruction and compensatory changes in the bladder. Eventually these changes may manifest as LUTS (eg, frequency, urgency, nocturia) and ultimately lead to a diminished quality of life and an increased risk for depression, falls, and mortality as nicely reviewed by Parsons et al in this issue of the journal [1]. Aside from quality-of-life measures, the medical and surgical management of LUTS creates significant costs to the health system. Due to increasing cost constraints, methods of primary prevention for LUTS are attractive.

Another chronic medical condition that increases medical costs and has become epidemic in both the United States and Europe is obesity. Growing evidence suggests that elderly men with higher body mass index (BMI) are at increased risk for the development of LUTS, although other studies suggest no association between BMI and LUTS. Whereas the Baltimore Longitudinal Aging Study found that men with higher BMI were at higher risk for the development of BPH [2], another study found no association between anthropometric measures at baseline and the subsequent development of LUTS [3]. Data from the Health Professionals Follow-up Study showed that men with higher BMI and men with higher levels of abdominal obesity were more likely to undergo prostatectomy, and among men who did not have a prostatectomy, higher BMI was associated with urinary frequency [4]. Finally, data from a 2008 meta-analysis of 11 previous studies found that increased physical activity was associated with reduced risk of BPH and LUTS [5].

Although most men who live long enough will have BPH, not all men will experience LUTS (ie, symptoms). Further

investigation of the relationships between physical activity level, obesity, and the development of LUTS may help identify men at higher risk for LUTS who may benefit from lifestyle modifications. The current report by Parsons et al describes the risk of developing LUTS over a mean 4.6-yr follow-up in a prospective cohort of 1695 men from the Osteoporotic Fractures in Men Study (MrOS) who were 65–91 yr of age [1]. They found that overweight and obese men had a 29% and 41% higher risk of developing LUTS when compared with men with BMI <25 kg/m<sup>2</sup>. Men with the highest quartile of Physical Activity Scale for the Elderly scores were 29% less likely to develop LUTS during the follow-up than those in the lowest quartile. Additionally, men who reported daily walking were 20% less likely to develop LUTS. These prospective data support previous cross-sectional studies showing an association between increased physical activities and decreased risk of LUTS [5]. They also support previous findings that higher BMI is associated with an increased risk of LUTS [2].

There are a number of potential mechanisms to explain the author's results suggesting a link between increased physical activity and decreased risk of LUTS. Abdominal obesity, which is associated with decreased physical activity, may be associated with increased sympathetic activity [4]. A subanalysis of the Medical Therapy of Prostatic Symptoms study found that increased sympathetic activity was associated not only with the development and progression of BPH [6] but also with the severity of LUTS. In this small study evaluating 38 men, sympathetic activity was assessed by pulse, blood pressure, response to circulatory stress via tilt table, and serum and urinary catecholamine levels. However, some of the measures used in this study may be altered due to aging, and thus the association between elevated sympathetic activity and the

risk of BPH and LUTS may be confounded by aging. Alternatively, men with higher levels of physical activity are less likely to have abnormal blood glucose levels and hyperinsulinemia. In animal models, prolonged periods of increased serum glucose levels have a selective neurotoxic effect on parasympathetic neurons [7]. This may potentially alter the normal physiology of the bladder by increasing bladder outlet obstruction and weakening detrusor contraction. However, in the current study, development of LUTS was not associated with serum glucose levels. Finally, if men with higher BMI are at increased risk of BPH and LUTS, perhaps physically active men are better able to maintain a healthy BMI and thus maintain normal steroid hormone and insulin levels. Altered steroid hormone and insulin levels have both been linked to BPH and LUTS [8,9].

A number of potential mechanisms exist to explain the association between LUTS and obesity. Due to the possible association of lower activity levels and higher BMI, there is likely significant crossover in some of these mechanisms. Obese men have lower levels of testosterone compared with normal-weight men. Because testosterone is converted to estradiol in adipose tissue, obese men have a low testosterone, high estrogen hormonal environment compared with normal-weight men. One study found that lower levels of testosterone were associated with the development of BPH and LUTS [10]. A separate study found that increased levels of free estradiol were an independent risk factor for BPH [8]. On a molecular level, the bladder is controlled through acetylcholine activation of M3 muscarinic receptors. The RhoA/ROCK pathway is a major factor responsible for maintaining bladder smooth muscle tone, and estrogens have been shown to upregulate the levels of RhoA/ROCK signaling in vitro [9]. Hyperactivity of the RhoA/ROCK pathway is thought to result in bladder overactivity. Thus the excess estrogen may cause upregulation of RhoA/ROCK signaling, leading to altered bladder smooth muscle tone and overactivity. In addition to changes in steroid hormone levels, obese men are also more likely to have hyperinsulinemia, which has been associated with increased prostate growth and potential development of symptomatic BPH [8]. One potential explanation for these findings is through increased levels of insulin-like growth factor-1, which is mitogenic to prostate tissue. However, the fact that serum glucose levels were not related to the development of LUTS in the study by Parsons et al suggests the mechanisms may not be related to the hyperinsulinemic state but rather to the altered hormonal axis or alternative mechanisms.

The results presented are limited by a few key points. Approximately 72% of the men in the MrOS cohort were excluded because they had LUTS at the onset of the study. As such, it remains unknown whether these results may apply to younger men (ie, <65 yr of age) who have not yet developed LUTS. It also remains unknown whether lifestyle changes may result in a symptomatic improvement in men who already have LUTS. Additionally, the cohort does not reflect the racial diversity of both the United States and Europe. However, the results provide

insight into lifestyle factors associated with development of LUTS for the subset of men studied (ie, predominantly white men without LUTS, >65 yr of age). One question that remains is whether initiating physical activity and/or weight reduction in adulthood could attenuate the risk of LUTS. Perhaps the most physically active quartile in this study had a lifetime history of being physically active and thus years of conditioning *before* the start of the study played a role.

The findings from this prospective study support further investigation including randomized clinical trials evaluating lifestyle changes in men with LUTS and in men at high risk for LUTS. From a public health perspective, it would be ideal to test whether these results apply to asymptomatic men at an earlier age. Testing the effect of lifestyle changes in men who currently have LUTS is also warranted. Perhaps BPH and LUTS could be managed by long-term lifestyle changes to include increased physical activity and maintenance of a healthy BMI.

In summary, the findings presented by Parsons et al support counseling all aging men, specifically those who are inherently at risk for BPH and LUTS, to increase physical activity and maintain a healthy BMI. Aside from the potential of reducing these debilitating disorders, increasing physical activity and maintaining a healthy BMI may also reduce the risk of cardiovascular disease, the number-one cause of death in elderly men, and thus are warranted for that reason alone. The suggestion that increased physical activity and maintaining a healthy BMI may lead to a reduced risk of LUTS provides even more reason for elderly men to eat right and exercise regularly. However, despite the findings presented in the current study, the specific biologic mechanisms linking obesity, physical activity, and LUTS remain unknown, although they are certainly an area for fertile research.

**Conflicts of interest:** The authors have nothing to disclose.

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doi:10.1016/j.eururo.2011.08.012

## Platinum Priority

### Reply from Authors re: Christopher J. Keto, Elizabeth M. Masko, Stephen J. Freedland. Physical Activity, Obesity, and Lower Urinary Tract Symptoms. *Eur Urol* 2011; 60:1181–3

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We appreciate the balanced comments of Keto and colleagues [1]. The complex physiologic mechanisms by which obesity increases and physical activity decreases the risks of lower urinary tract symptoms (LUTS) remain to be elucidated. Nevertheless, accumulating evidence linking modifiable risk factors with LUTS and benign prostatic hyperplasia (BPH) [2,3] demonstrates that lifestyle alterations may substantially alter the natural history of these conditions. We hope that our data—the first prospective analysis of obesity and physical activity with incident urinary symptoms in older men living in the community—will encourage translational studies of lifestyle interventions for LUTS and BPH.

Clinical trials are needed to determine whether behavioral modifications may prevent or delay LUTS onset in asymptomatic men, attenuate LUTS severity in symptomatic men, and obviate the need for medical or surgical

treatment. Obese individuals represent a higher-risk population that may particularly benefit from lifestyle interventions [4]. At least one study has demonstrated the feasibility and efficacy of targeting adiposity to treat urinary symptoms: In a randomized trial, weight loss led to reductions in urinary incontinence in obese women [5]. Still, although weight loss is one potential intervention, the appeal of physical activity is that it is simple and beneficial to overall health and appears to be strongly protective against LUTS and BPH [6].

We look forward to further scientific endeavor in this field. Given their ubiquity among older men, their associated treatment costs, and their considerable morbidity, LUTS and BPH will undoubtedly impose ever-greater burdens on the public health of our aging population.

**Conflicts of interest:** The authors have nothing to disclose.

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doi:10.1016/j.eururo.2011.08.058

DOIs of original articles: 10.1016/j.eururo.2011.07.040, 10.1016/j.eururo.2011.08.012

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