



Benign Prostatic Enlargement

Physical Activity, Benign Prostatic Hyperplasia, and Lower Urinary Tract Symptoms

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Abstract

Background: While some studies have indicated that physical activity may protect against benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS), others have not.

Objective: To evaluate the association of physical activity with BPH and LUTS.

Design, Setting, and Participants: Systematic review and meta-analysis using MEDLINE, the Cochrane Library, EMBASE, and abstracts from the Annual Meeting of the American Urological Association. We selected observational studies that provided empirical data and analyzed abstracted data with random effects models.

Measurements: BPH, LUTS, and physical activity levels.

Results and Limitations: Eleven ($n = 43\ 083$ men) studies met selection criteria. Eight studies observed inverse, 2 studies null, and 1 study equivocal associations of physical activity with BPH or LUTS. Eight studies ($n = 35\ 675$) were eligible for pooled analyses. We stratified physical activity levels into light, moderate, and vigorous categories, with a sedentary category for reference. Compared to the sedentary group, the pooled odds ratios for BPH or LUTS were 0.70 (95% CI 0.44–1.13, $p = 0.14$), 0.74 (95% CI 0.60–0.92, $p = 0.005$), and 0.74 (95% CI 0.59–0.92, $p = 0.006$) for men engaging in light, moderate, and heavy physical activity, respectively.

Conclusions: Physical activity reduces the risks of BPH and LUTS. These findings are consistent with other studies demonstrating that the BPH/LUTS complex is associated with modifiable risk factors of cardiovascular disease and suggest that increased physical activity may prevent or attenuate these conditions.

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1. Introduction

Benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) are highly prevalent conditions among older men. The prevalence of BPH among U.S. men aged 60 to 69 years is estimated to be over 70%, with approximately 6.5 million white men aged 50 to 79 years affected [1]. In 2000, BPH prompted over 4.4 million office visits, 117,000 emergency room visits, and 105,000 hospitalizations in the U.S.A. [1].

The pathophysiology of BPH remains to be elucidated. Traditional causal paradigms have focused on hormones and genetic predisposition. While these factors are important contributors, modifiable risk factors of cardiovascular disease are also linked to BPH and LUTS. Obesity [2,3], elevated fasting plasma glucose [2,4], diabetes [2,5,6], dyslipidemia [7,8], and the metabolic syndrome [7,9] may all significantly increase the risks of BPH and LUTS.

Since cardiovascular risk factors potentially contribute to BPH and LUTS pathogenesis, it is plausible that factors that protect against cardiovascular disease may also protect against BPH and LUTS. Exercise protects against cardiovascular disease and, indeed, increased physical activity has also been associated with decreased risk of BPH surgery [10,11], clinical BPH [12,13], histological BPH [14], and LUTS [9,11].

However, these associations are complex and remain incompletely characterized. The magnitude of the protective effect varies by study population, exercise intensity, and model design. Some studies have noted relatively greater reductions in risk with less exercise [10], others with more exercise [11,12]. Vigorous physical activity was associated with decreased LUTS risk in unadjusted analyses of a cohort of African American men; however, this association disappeared after multivariable adjustment with other lifestyle and disease factors [6]. Moreover, there were no associations of physical activity with BPH in a study of Shanghai men [15].

Further exploration of the relationships between physical activity, BPH, and LUTS may yield new insights into the etiology, treatment, and prevention of these conditions. Systematic reviews constitute a form of clinical evidence that is relatively superior to single cohort or case control studies [16]. Therefore, we performed a systematic review and meta-analysis to examine the associations of physical activity with BPH and LUTS.

2. Materials and methods

2.1. Literature search

We searched MEDLINE (January 1965 to April 2007) utilizing PubMed, the Cochrane Central Search Library (January 1980 to April 2007), EMBASE (January 1980 to April 2007), and abstracts presented at the Annual Meeting of the American Urological Association (AUA) (2002–2007) accessed through the AUA website (www.auanet.org). We included data from the AUA meeting to maximize the potential for inclusion of the most recent data and minimize the potential for publication bias. We retrieved citations utilizing combinations of the medical subject heading (MeSH) search terms “prostatic hyperplasia” AND “risk factors” and text terms “lower urinary tract symptoms,” “physical activity,” and “exercise.” For MEDLINE, we limited the search to the English language using the *limits* function and expanded the search utilizing the *related articles* function. We also performed hand searches of references identified in electronically abstracted articles.

2.2. Study selection and data abstraction

We included cohort and case control studies that provided empirical outcomes data for both physically active and sedentary groups. The primary outcomes were BPH and LUTS. The primary exposure was physical activity. We excluded studies that did not provide data for unexposed groups or in which the study populations consisted exclusively of cases. If eligibility disagreement occurred, the senior investigator (JKP) made the final decision regarding inclusion or exclusion of the study.

We abstracted the study design, outcomes definitions and adjusted effects estimates, categories of physical activity, and the covariates included in the final adjusted models. We divided physical activity into low, moderate, and vigorous levels corresponding to intensity categories within the individual studies. For studies that included less than 3 categories of physical activity (excluding the reference category), we designated the highest category as vigorous and the second highest as moderate, then performed sensitivity analyses by repeating the algorithms after designating the highest category as moderate and the second highest as low. If a study had more than 4 categories of activity (excluding the reference category), we designated the highest as vigorous, second highest as moderate, third highest as low, and excluded the fourth highest, then repeated the analyses by sequentially excluding each of the categories and comparing the results.

Since two abstracted studies drew upon similar data from the Health Professional’s Follow-up Study cohort, we included only the most recent study [17].

2.3. Statistical analysis

We performed all statistical analyses utilizing Stata version 8.0 commercial software with the most recent updates for meta-analysis commands (Stata Corporation, College Station, TX). We used only adjusted effect estimates. We pooled data utilizing the DerSimonian and Laird random effects

models. Results are summarized as odds ratios (OR). We performed the chi-square test to evaluate the Q statistic for heterogeneity. A two-sided $p < 0.05$ was considered statistically significant.

We performed subgroup analyses based on likely sources of between-study heterogeneity and assessed publication bias using the Egger regression asymmetry test and the Begg adjusted rank correlation test.

We did not use a formal or aggregated score for quality assessment since such instruments may be subjective and interpretation of their findings inconsistent [18].

3. Results

3.1. Study selection

We identified 501 potentially relevant abstracts in our initial search. Of these, 472 were unrelated or were not original research articles. After full review of the 29 original research articles with potential relevance, we excluded 18 that did not meet our study criteria. Table 1 summarizes the characteristics of the 11 studies included in our final analyses. The majority of the studies demonstrated an inverse relationship between physical activity and risk of BPH or LUTS, and none observed an increased risk:

8 studies observed inverse [9–14,19,20], 2 studies null [3,15], and 1 study equivocal [6] associations of physical activity with BPH or LUTS.

3.2. Outcome assessment

Of the 11 studies, 7 used BPH [3,10–15] and 4 used LUTS [6,9,19,20] as the primary outcome. Definitions of BPH varied. Six studies defined BPH as non-cancer prostate surgery: 2 used surgery alone and 4 used surgery in combination with urinary symptoms (Table 1). One study utilized a combination of prostate weight, symptoms, and urinary flow rate [13]. Of the 8 studies that evaluated urinary symptoms as part of the outcome, definitions of LUTS also varied: 5 studies measured the International Prostate Symptom Score (IPSS) [3,6,13,19,20], 2 studies a modified version of the American Urological Association Symptom Index (AUA-SI) [9,11], and 1 study “difficult and/or frequent urination” [12] (Table 1).

Eight studies provided empirical outcomes data based on cross sectional analyses that we incorporated into pooled OR meta-analyses, 6 of which used BPH as an outcome [10–15] and 2 of which used LUTS [9,20].

Table 1 – Studies evaluated

Study	Year	Sample size	Outcome	Definition of outcome	Adjusted variables
Gann et al	1995	640	BPH	Surgery	Age, exercise, alcohol consumption, diastolic blood pressure, estradiol, estrone, and DHT/testosterone ratio
Platz et al	1998	23 635	BPH	Surgery	Age, race/ethnicity, smoking, and alcohol consumption
Lacey et al	2001	677	BPH	Modified AUA Symptom Score Surgery	Age, marital status, education, body mass index, caloric intake, and waist-to-hip ratio
Meigs et al	2001	1019	BPH	Difficult and/or frequent urination with enlarged prostate Surgery	Age, marital status, waist-to-hip ratio, alcohol consumption, and hypertension and heart disease medication use
Prezioso et al	2001	1033	LUTS	I-PSS	Age, BMI, alcohol, and smoking
Joseph et al	2003	708	LUTS	I-PSS	Age, income, smoking, alcohol consumption, hypertension, heart disease, and diabetes
Dal Maso et al	2005	2820	BPH	Surgery with histological confirmation	Age, region, education, BMI, smoking, and alcohol consumption
Hong et al	2006	641	BPH	I-PSS, prostate weight >25 g, and urinary flow rate < 15 ml/s	Age, chronic bronchitis, and PSA
Rohrmann et al	2005	2797	LUTS	Modified AUA Symptom Score	Age, race, waist circumference, cigarette smoking, and alcohol consumption
Rohrmann et al	2006	3446	LUTS	I-PSS	Age, zygosity, smoking, and alcohol consumption
Kristal et al	2007	5667	BPH	Incident treatment (surgical or medical) Incident I-PSS	Age, race/ethnicity, smoking, diabetes, and baseline I-PSS

I-PSS, International Prostate Symptom Score. AUA-SI, American Urological Association Symptom Index.

Three studies presented empirical data that we did not include in the pooled analyses. One study reported an unadjusted OR for moderate to severe LUTS of 0.61 (95% CI 0.44 to 0.85) for those who engaged in vigorous physical activity compared to those who did not; this inverse association disappeared after adjustment for multiple variables (Table 1), but the effect estimates from the final, multivariable adjusted model were not provided [6]. Because we utilized only adjusted estimates, we did not include these data.

A second study reported lower prostate volumes ($p = 0.04$), total IPSS ($p = 0.008$), and IPSS-QoL ($p = 0.007$) among men who engaged in physical activity, and further noted in a multivariable linear regression model (Table 1) a negative association of physical activity with IPSS-QoL ($p = 0.02$) but not with total IPSS ($p = 0.17$) [19].

A third study compared incident BPH cases to physical activity level at study entry in the placebo arm of the Prostate Cancer Prevention Trial [3]. These investigators utilized Cox proportional hazards models to calculate an adjusted hazards ratios (HR) and observed no significant associations of physical activity with incident BPH for light (HR 0.92, 95% CI 0.77 to 1.09), moderate (HR 0.93, 95% CI 0.78 to 1.12), or high (HR 1.01, 95% CI 0.79 to 1.28, p for trend 0.96) physical activity. Because these incident data were different from the cross sectional data provided in other studies, we did not include them in the pooled analyses.

3.3. Exposure assessment

Four studies measured frequency of exercise or recreational activity in times per week [9,10,13] or

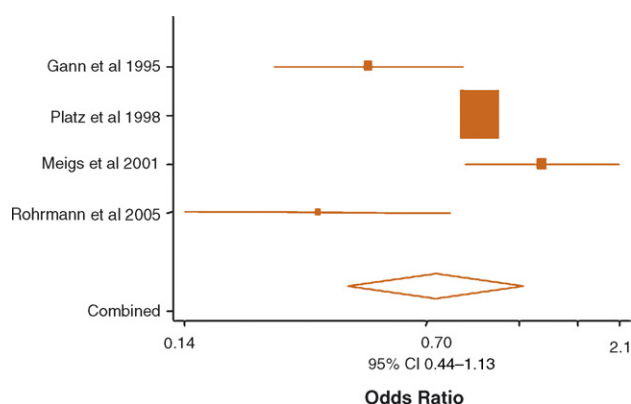


Fig. 1 – Association of low levels of physical activity with odds ratio (OR) of BPH or LUTS. The white diamond represents the pooled OR with 95% confidence limits for all studies, the squares represent individual studies, and the horizontal lines represent 95% confidence limits for individual studies.

hours per week [14]. One study measured MET (metabolic equivalents, which represent the number of kilocalories per hour per kilogram of bodyweight expended in physical activity) hours per week [11], while another study measured MET hours per week and energy equivalents (calculated as the number of hours per week in each activity multiplied by MET and self-reported weight) [15]. One study measured kilocalories expended per day [12] and 1 study calculated a standardized physical activity score based on the daily number of flights of stairs climbed and the daily number of blocks walked [20]. Three studies did not specify how physical activity was assessed [3,6,19]. In the 1 study that reported both recreational and occupational exposures [14], we focused on recreational physical activity.

3.4. Light physical activity

In the pooled analyses, light physical activity was associated with a non-significant trend toward decreased risk of BPH or LUTS (OR 0.70, 95% CI 0.44–1.13, $p = 0.14$) (Fig. 1). The p -value for heterogeneity was 0.007. There was no evidence of publication bias by Begg's test ($p = 0.31$) or Egger's test ($p = 0.50$). Repeating the analysis after excluding the 1 study that used LUTS as the primary outcome [9] yielded similar, non-significant results (OR 0.83, 95% CI 0.53–1.30, $p = 0.41$).

3.5. Moderate physical activity

Moderate physical activity was associated with a significantly decreased risk of BPH or LUTS (OR 0.74, 95% CI 0.60–0.92, $p = 0.005$) (Fig. 2). The p -value for heterogeneity was 0.03. The p -value for publication bias by Begg's test was 0.02 and for Egger's test was 0.15. Repeating the analysis after excluding the 2 studies with LUTS as the outcome [9,20] yielded similar results (OR 0.81, 95% CI 0.68–0.96, $p = 0.01$). Repeating the analysis with LUTS as the primary outcome showed a non-significant trend toward decreased risk (OR 0.43, 95% CI 0.15–1.26, $p = 0.12$).

3.6. Vigorous physical activity

Vigorous physical activity was associated with a significantly decreased risk of BPH or LUTS (0.74, 95% CI 0.59–0.92, $p = 0.006$) (Fig. 3). The p -value for heterogeneity was 0.011. There was no evidence of publication bias by Begg's test ($p = 0.90$) or Egger's test ($p = 0.96$). Repeating the analysis after excluding the 2 studies with LUTS as the outcome [9,20] yielded similar results (albeit with slightly diminished

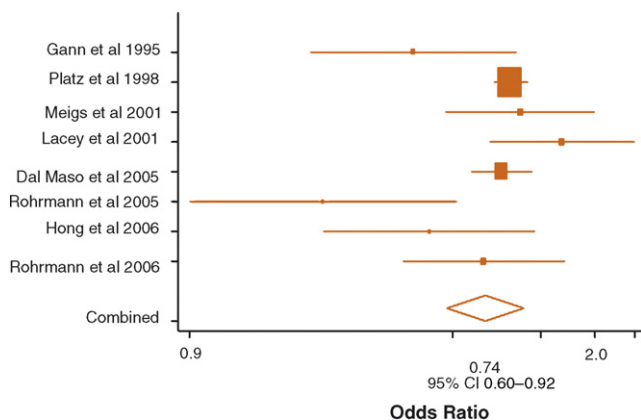


Fig. 2 – Association of moderate levels of physical activity with odds ratio (OR) of BPH or LUTS. The white diamond represents the pooled OR with 95% confidence limits for all studies, the squares represent individual studies, and the horizontal lines represent 95% confidence limits for individual studies.

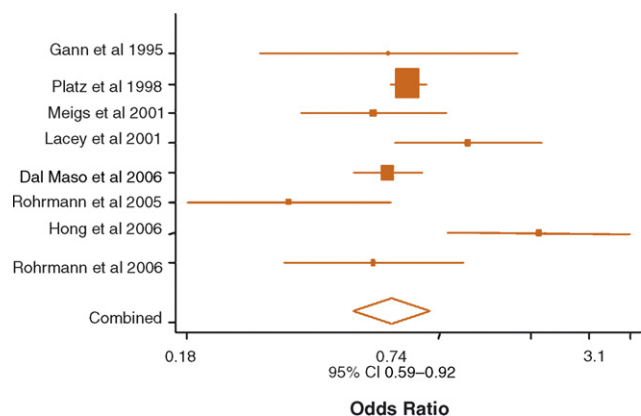


Fig. 3 – Association of vigorous levels of physical activity with odds ratio (OR) of BPH or LUTS. The white diamond represents the pooled OR with 95% confidence limits for all studies, the squares represent individual studies, and the horizontal lines represent 95% confidence limits for individual studies.

statistical significance) (OR 0.80, 95% CI 0.68–1.00, $p = 0.05$), as did repeating the analysis with LUTS as the primary outcome (OR 0.47, 95% CI 0.28–0.79, $p = 0.005$).

3.7. Sensitivity analysis for physical activity intensity and age at exposure

Systematically repeating the analyses after sequentially substituting all reported results for the studies with > 3 [10,11] and < 3 [13–15] physical activity intensity categories produced similar effect estimates for all levels of physical activity (data not shown).

For the 1 study reporting multiple age-associated exposures [14], repeating the analyses after substituting all reported age categories at the time of exposure also produced similar results for all physical activity categories (data not shown).

4. Discussion

Our results suggest that moderate to vigorous physical activity may reduce the risk of BPH or LUTS by as much as 25% relative to a sedentary lifestyle. Although the strength of the association appears to be greater with higher levels of activity, there was a non-significant trend toward a protective effect with even light physical activity. Adjustment for multiple confounders in the studies included in this analysis underscores the independence of the protective effect of physical activity on the BPH/LUTS complex.

The notion that physical activity and other modifiable lifestyle factors may alter the risks and severity of BPH and LUTS challenges traditional etiological paradigms and intimates the need for the development of new pathogenic models for the BPH/LUTS disease complex. The assumption that BPH and LUTS are relatively immutable consequences of aging—driven by a combination of genetic predisposition, androgens, and estrogens—underpins prior models. While genotype [20] and hormones are important components, the relationship of physical activity with BPH/LUTS demands consideration of additional modulators of these processes.

It is possible that physical activity influences prostate growth pathways through alterations in hormone levels [10,14]. However, we believe a more likely explanation is that physical activity exerts beneficial effects through improved cardiovascular health. Pre-clinical and observational data indicate that cardiovascular disease might promote BPH and LUTS. In one study, rats fed high-fat diets subsequently developed hyperlipidemia (i.e. high serum concentrations of LDL-cholesterol), prostate smooth muscle hypertrophy, and bladder overactivity [21]. In another study, arterial insufficiency resulted in bladder overactivity, fibrosis, neuropathy, and decreased bladder compliance in a rabbit model [22].

Similarly, men who suffer from components of the metabolic syndrome, a clinical constellation of abnormalities (obesity, glucose intolerance, dyslipidemia, and hypertension) that increases the risk of cardiovascular disease, are more likely to have BPH and LUTS [7,9], as are men with heart disease [6,12]. The metabolic syndrome is associated with systemic inflammation and oxidative stress [7], and

inflammation potentially drives BPH [23,24]. Thus, exercise—which promotes weight loss, enhances vascular flow, normalizes serum lipid and lipoprotein concentrations, and prevents heart disease—might mitigate the lower urinary tract manifestations of systemic cardiovascular disease.

In fact, the BPH/LUTS complex often occurs in association with erectile dysfunction (ED) [25], which is strongly associated with cardiovascular disease [26]. It is thus possible that the BPH/LUTS complex and ED share a common etiology related to cardiovascular disease. Pre-clinical and clinical data substantiate this concept: in the hyperlipidemic rat model, erectile dysfunction developed concomitant with prostate hypertrophy and bladder dysfunction [21], while a recent trial demonstrated simultaneous improvements in erectile function and LUTS with sildenafil [27].

A shared cardiovascular etiology for the BPH/LUTS complex and ED would also explain why the 2 conditions are associated with the same modifiable lifestyle factors, including obesity, diabetes, and hyperlipidemia. Moreover, increased physical activity has been associated with a lower risk of erectile dysfunction [28]. At least 1 study has indicated that sedentary men may improve their erectile function by exercising [29]—which would intimate that implementing a physical activity regimen may also improve clinical manifestations of the BPH/LUTS complex.

There are several limitations of our analysis that bear mention. First, we did not include the MeSH term “prostatism” in our search because we focused on more common, recent terms for the BPH/LUTS complex. Since these terms are similar to “prostatism,” it is likely that its addition to the search would not have yielded additional papers. However, since “prostatism” is an older term, we may have potentially not identified older studies.

Second, there was a significant amount of heterogeneity between studies, likely reflecting differences between study populations, model selection (i.e. covariates and consideration of different confounders), analytic methodology, exposure assessment, and operational definitions of BPH and LUTS. Our results should thus be considered within this context, particularly with respect to outcomes definitions. Variations in outcome assessment are acknowledged limitations of observational BPH research [30], reflecting the lack of uniform diagnostic criteria.

Heterogeneity in outcome assessment between studies may have introduced observational biases. However, these biases would likely have been non-informative and thus biased associations of physical activity with BPH and LUTS toward the null. More-

over, these outcomes represent the most common measures of the BPH/LUTS complex in both the scientific literature and current clinical practice; as such, acknowledgement of heterogeneity in BPH/LUTS outcomes assessment does not preclude a meaningful interpretation of these data. Nevertheless, the presence of heterogeneity points to the need for consensus definitions for BPH and LUTS in future observational and population-based studies.

Third, these studies were predominantly cross sectional analyses; the only study to utilize incident BPH discerned no associations of baseline physical activity with subsequent BPH diagnosis [3]. The argument may thus be made that current physical activity does not protect against future BPH diagnosis. However, since the dynamics of these interactions over time are not well understood, and since current behaviors do not necessarily predict future ones, it is possible that cross sectional studies represent a more relevant measure of concomitant BPH/LUTS risk. Moreover, Dal Maso et al observed strong inverse associations of physical activity with subsequent development of BPH several decades prior to BPH diagnosis [14].

Finally, publication bias (defined as the increased likelihood for studies with statistically significant results to be submitted and published compared to those with null or non-significant results) may have potentially influenced our results. For the most part, though, we did not uncover much evidence of publication bias, although one test suggested bias in those publications reporting moderate physical activity.

5. Conclusion

Physical activity reduces the risks of BPH and LUTS. These findings are consistent with other studies demonstrating that the BPH/LUTS complex is associated with modifiable risk factors of cardiovascular disease. Further studies are needed to determine whether alterations in physical activity may alter the natural history of BPH/LUTS.

Author contributions: J. Kellogg Parsons had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Parsons.

Acquisition of data: Parsons, Kashefi.

Analysis and interpretation of data: Parsons.

Drafting of the manuscript: Parsons, Kashefi.

Critical revision of the manuscript for important intellectual content: Parsons, Kashefi.

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