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SYSTEMATIC REVIEW

Benign prostate hyperplasia: a further reason to recommend regular physical activity?

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Abstract

Objectives: Benign prostate hyperplasia (BPH) is a major health concern, affecting a large proportion of older men. It reduces their quality of life and causes problems in urination that limit exercise, social involvement and normal sleep. Little is known concerning its etiology or prevention. The primary objective of the present review is to evaluate whether regular physical activity can help to diminish the risk of developing BPH. *Methods*: The Ovid/Medline and Pub-Med data bases were searched systematically from 1996 to May 2106, combining terms for physical activity (exercise, physical activity, sports, athletes, physical fitness and physical education/training) with the terms benign prostate hyperplasia (BPH) and prostatic hyperplasia. *Results*: Combining studies of occupational and leisure activity, 21 studies (4 covering both occupational and leisure activity) have now looked at the association between BPH and physical activity; 16 of these 21 analyses showed a trend to a lower risk of BPH in the more active individuals, with **a** significant advantage in 11 of the 16 evaluations. Most authors pointed to a progressive benefit with a greater frequency, intensity or volume of physical activity, but 2 reports found an adverse effect in highly committed exercisers. The optimum age for undertaking preventive activity remains unclear. Obesity is associated with an increased risk of BPH, and a high level of habitual physical activity may act mainly by reducing the risk of obesity. In studies with more vigorous exercise, a further factor may have been an activity-induced modulation of androgenic hormones. *Conclusions:* Lifelong physical activity is significantly associated with a reduced risk of BPH, and although causality has not been proven, this seems one more reason to encourage participation in regular physical activity. Motivation may not be easy in elderly men, but some data suggest that the risk of BPH is 25% lower in those walking for as little as 2-3 hours per week. **Health & Fitness Journal of Canada 2016;9(2):38-55.**

Keywords: Distance running, Exercise medicine, Leisure activity, Lower urinary tract disorders, Occupational activity, Preventive medicine.

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Introduction

Benign prostatic hyperplasia (BPH) is a major problem in our aging population. Impingement of the enlarged prostate on the urethra causes the affected individual a variety of problems in urination, including a need to urinate frequently, urgency of urination, an involuntary passage of urine, hesitancy (a time lag between trying to urinate and the flow of urine), a weak urinary stream even with straining, incomplete emptying of the bladder and terminal dribbling. Moreover, the condition predisposes to infection of the urinary tract, and it can progress to urinary retention, when the person is totally unable to empty the bladder. These various urinary problems cause a major deterioration in the individual's quality of life, limiting the ability to exercise, engage in social events, and enjoy an uninterrupted night of sleep. Progression of the hyperplasia may eventually require surgical removal of the prostate gland, and unfortunately urinary incontinence is a frequent side effect of this operation.

The pathology is non-cancerous, with a growth in both the glandular epithelial and stromal cells of the prostate leading to a formation of nodules (Cunningham and Kadmon, 2013). BPH is typically a slow process. It can begin as early as 30 yr of age; by the age of 50, about a half of the male population show detectable prostatic enlargement, and 75% are

affected by the age of 80 yr (Verhamme et al., 2002). About a half of cases report significant urinary problems, and a quarter require surgical treatment (Guess et al., 1990). Thus, BPH has become a major source of medical expenditures for older men, with average annual medical and prescription costs in the U.S. of $401 and 371, respectively (Fenter et al., 2006).

Given the personal and economic impact of BPH, there is plainly a need for simple and effective preventive measures, but despite substantial research little is known of etiology, and a consensus recommendation on prevention has yet to emerge. A few investigations have pointed to benefit from a high level of habitual physical activity (Parsons and Kashefi, 2008). The objective of the present review is thus to look at empirical evidence on the prevalence and/or incidence of BPH in relationship to lifelong occupational and/or leisure-time physical activity and obesity (here considered as a surrogate of a sedentary lifestyle), and to evaluate possible mechanisms underlying any observed associations.

Literature search

The Ovid/Medline and Pub-Med databases were searched from 1996 to May 2016, looking for linkages between physical activity and benign prostate hyperplasia. The terms used to define physical activity included exercise, physical activity, sports, athletes, physical fitness, and physical education/training, with a total of 235,307 unique hits. Benign prostate hyperplasia (BPH) and prostatic hyperplasia together yielded 12,649 hits, and a combination of the 2 searches provided 97 titles; these were supplemented by 6 papers drawn from reference lists and personal files. Of these 103 titles, five provided no abstracts. A review of the remaining 98 items identified 69 reports where it was judged useful to obtain the full article. These reports included 17 reviews of varying quality that were focused upon exercise and lifestyle (eight articles), diet and obesity (five articles) and risk factors (four articles). The epidemiological and experimental articles were divided between analyses of specific associations between prostate hyperplasia and occupation (five papers, four covering also leisure) or leisure (18 papers from 16 different laboratories, including the four articles covering also occupation), and other studies examining general risk factors, diet and obesity, and potential mechanisms. Given the relatively small number of investigations looking specifically at associations with physical activity, this entire group of papers has been considered, although they are described in detail to allow careful attention to be paid to various measures of quality of such as study design, subject numbers, measures of BPH and habitual physical activity, and the choice of co-variates.

Results

Articles to be considered include those describing possible associations between BPH and occupation, leisure activity and/or obesity.

Occupational activity

Five reports have examined the risk of BPH in relation to the physical demands of occupation (Table 1); 4 of these used a case-control design, and the remaining study was cross-sectional in type. One investigation found no association between the two variables (Fritschi et al., 2007), and another a favourable trend

Table 1: Association between the physical demands of occupation and the risk of benign prostate hyperplasia.

Author	Sample	Activity	Findings	Comments
Dal Maso et al., 2006	1369 histologically confirmed BPH, 1451 hospital controls	Occupation (heavy vs. light activity)	OR 0.6 (0.4-0.8) age 15-19 & 30-39, 0.7 (0.5-0.9) age 50-59 yr	Data controlled for age, study centre and educational level
Fowke et al. (2013)	Cross-sectional study of 405 men aged 40-93 yr, LUTS severity & sonographic prostate volume	Work classification (none, low, med. high intensity)	Chi^2 values: LUTS p = 0.94 Prostate volume p = 0.04 favouring high intensity activity	Timing of occupational activity assessment unclear
Fritschi et al. (2007)	398 cases of first prostatectomy, 471 controls	7 indices pointing to lifetime of sedentary vs. medium/heavy employment	No association between BPH and occupational activity	Significant effect from heavy consumption of alcohol (>30g/day)
Lacey et al. (2001)	206 men with BPH requiring surgery, 471 age-matched controls	Occupational titles, heavy vs. sedentary work	OR 1.1 age 20-29 (ns), 0.6 (0.4-0.87) age 40-49 yr	Age, marital status, education, BMI, energy intake, waist/hip ratio
Lagiou et al. (2008)	184 surgically treated cases, 246 hospital controls	Blinded classification of occupations (high vs. low activity)	OR 0.59, p = 0.04 for trend	Age and educational level
Abbreviations: BMI = body mass index, BPH = benign prostate hyperplasia. LUTS = lower urinary tract symptoms. OR = odds ratio.				

(Lacey et al., 2001), but the remaining three reports (including by far the largest case/control study) showed a significantly lower risk for men who were currently or had previously been engaged in heavy physical work (Dal Maso et al., 2006; Fowke et al., 2013; Lagiou et al., 2008).

Fritschi et al. (2007) carried out a case-control study on men aged 40-75 yr (398 cases requiring their first prostatectomy, and 471 controls). Nearly two thirds of this sample were aged >65 yr. No association was found between BPH and any indices pointing to previous engagement or the spending of a high proportion of the individual's career in either sedentary or medium to heavy employment. Nor were there any associations of BPH with family history, military engagement, baldness, obesity or smoking; the only risk factor found in this series was a heavy consumption of alcohol (>30 g/d). However, the only co-variate introduced into these analyses was the subject's age.

Fowke et al. (2013) conducted a cross-sectional study of 405 men ranging in age from 40 to 93 yr. They looked at both the severity of lower urinary tract symptoms (LUTS) and sonographic estimates of prostate volume. Work activity was classified as none, low, medium or high intensity, apparently referring to recent employment. Chi^2 evaluations of this data showed no significant relationship between occupational activity and the subjective measure of LUTS (p = 0.94), but there was a significant association with the objective measure of prostatic volume (p = 0.04).

Lacey et al. (2001) compared 206 men with benign prostate hyperplasia who required surgery and 471 age-matched controls. A half of this group were aged >69 yr at interview (Lacey et al., 2001). Participants were classified by occupational titles. After co-varying for age, marital status, education, body mass index, energy intake and waist/hip ratio, there was a significant effect favouring those involved in heavy work at age 40-

49 yr [odds ratio 0.6 (0.4-0.97), p for trend = 0.04], but no association was seen between occupation at age 20-29 yr and BPH (odds ratio 1.1, not statistically significant), and there was again no association relative to the occupation in 1998 (age ~ 79 yr).

Dal Maso et al. (2006) carried out a large case-control study, comparing 1369 histologically confirmed cases of benign prostate hyperplasia in men with a median age of 66 yr, and 1451 hospital controls. After adjusting data for the co-variates of age, study centre and level of education, multivariate odds ratios related the risk of prostate hyperplasia to a 4-level classification of occupation ranging from heavy/strenuous work to jobs that involved mainly sitting (Dal Maso et al., 2006). In terms of the occupation at ages 15-19 and 30-39 yr, the odds ratios favouring active workers (with 95% confidence limits) were both [0.6 (0.4-0.8), p for trend 0.01], and with respect to the occupation at ages 50-59 yr, the odds were [0.7 (0.5-0.9), p for trend 0.01].

Lagiou et al. (2008) conducted a case-control study that compared 184 newly diagnosed and histologically confirmed cases of benign prostate hyperplasia (more than a half of whom were aged > 70 yr) and 246 hospital controls. A blinded assessment of the physical demands of occupation was made, and after allowing for the effects of age and level of education, the odds ratio for those in heavy work was 0.59, with a significant inverse trend of risk (p = 0.04) (Lagiou et al., 2008).

Recreational physical activity

Eighteen investigations from 16 laboratories have related the frequency, intensity, and/or volume of habitual recreational physical activity to the risk of developing benign prostate hypertrophy (BPH)(Table 2). One report found an adverse effect of physical activity (Lacey et al., 2001), 2 studies observed no significant association (Fritschi et al., 2007; Kristal et al., 2007); and a further investigation yielded inconsistent results (Hong et al., 2006). The remaining 12 reports all pointed towards a beneficial outcome, statistically significant in 8 of the 12 trials.

Lacey et al. (2001) found an adverse effect from reported recreational activity. They compared 206 men requiring surgery for BPH with 471 age-matched controls. After controlling statistically for age, marital status, education, body mass index, energy intake and waist/hip ratio, the two groups were compared in terms of either moderate and vigorous energy expenditures, or all physical activity (MET-h/wk), There was a significant *adverse* effect for both of these measures when reporting activity at ages 20-29 yr [odds ratios 1.6 and 1.9 (p for trend = 0.01), and an adverse trend (odds ratio 1.4, 1.3) with respect to reported activity at ages 40-49 yr (Lacey et al., 2001).

Looking next at the studies where no significant association was observed, Fritschi et al. (2007) compared 398 cases of BPH who were receiving surgical treatment with 471 controls selected randomly from the Australian electoral roll (Fritschi et al., 2007). Perceived activity from the age of 12 yr was examined, using a lifetime physical activity questionnaire that examined participation in moderate or vigorous physical activity, but no association with BPH was observed. The only co-variate in this analysis was the subject's age.

Table 2: Associations between leisure activity and risk of developing benign prostate hyperplasia.

Author	Sample	Activity	Findings	Comments
Dal Maso et al. (2006)	1369 histologically confirmed BPH cases, 1451 hospital controls	> 5h/wk vs. <2 h/wk recreational activity	OR 0.5 (0.4-0.7) age 15-19 yr 0.6 (0.5-0.8) age 30-39 yr, 0.7 (0.5-0.8) age 50-59 yr	Data controlled for age, study centre & educational level
Fowke et al. (2013)	LUTS severity & prostate volume	Baecke leisure activity questionnaire (3-level)	chi² tests show benefit from (sport+leisure+work) ($p<0.01$, prostate volume only)	Also positive findings in multivariate model
Fritschi et al. (2007)	398 cases of first prostatectomy, 471 controls	Questionnaire assessment of participation in moderate & vigorous leisure activity since age 12 yr	No association of lesiure activity with BPH	Significant effect from heavy consumption of alcohol (>30g/day)
Gann et al. (1995)	Participants in physicians' health study; 320 developing BPH over 9-yr follow-up, 320 controls	Exercise (> 5 times/wk vs. rarely/never)	OR 0.7 (0.32-1.51)	Co-variates diastolic blood pressure and alcohol consumption
Hong et al. (2006)	Cross-sectional study of 641 men aged 50-79 yr. BPH defined by IPSS, prostate volume & bladder outflow rate	Exercise <2/wk, 3-5/wk, nearly every day	Inconsistent effect of exercise (OR 1.0, 0.48, 1.73 for 3 frequencies)	Co-variates age, chronic bronchitis, PSA, alcohol consumption
Joseph et al. (2003)	708 African-American men, IPSS	Engaging in vigorous physical activity sufficient to work up a sweat	OR 0.61 (0.44-0.85); BUT effect disappears after adjusting for various lifestyle and medical history factors.	Co-variates age, income, smoking, alcohol consumption, heart disease, hypertension & diabetes mellitus
Kristal et al. (2007)	5667 men followed for 7 yr, to treatment or IPSS score >14 on 2 items	Sedentary vs. highly active	No effect of physical activity on risk of total or severe BPH symptom scores	Co-varied for age, ethnicity, smoking, diabetes mellitus, initial IPSS score
Lacey et al. (2001)	206 men with BPH requiring surgery, 471 age-matched controls	Moderate or vigorous energy expenditure (MET-h/wk). All activity, high vs. sedentary	OR 1.6 age 20-29 yr ($p = 0.01$), 1.4 (ns) age 40-49 yr; OR 1.9 age 20-29 yr ($p = 0.01$), 1.3 (ns) age 40-49 yr	Age, marital status, educational level, BMI, energy intake, waist/hip ratio
Meigs et al. (2001	1156 men aged 40-70 followed for 9 yrs, to onset of symptoms or need for surgery	Top vs. bottom quartile of physical activity, kJ/day	>3.6 vs. <0.6 kJ/day, OR 0.5 (0.3-0.9)	Age, marital status, waist/hip ratio, alcohol consumption, hypertension, heart disease, medication use
Platz et al. (1998)	1890 men who underwent surgery, 1853 with symptoms (8 yr follow-up of 30,364 health professionals)	Highest vs. lowest quintile of physical activity (>33.8 vs. < 3.0 MET-h/wk)	OR surgery 0.76 (0.64-0.90), severe symptoms 0.79 (0.62-1.00)	Age, ethnicity, smoking, alcohol consumption

Table 2 Continued

Author	Sample	Activity	Findings	Comments
Prezioso et al. (2001)	Lower urinary tract symptoms in 1033 men	Reported physical activity	Physical activity associated with lower frequency of incomplete bladder emptying, repeated urination, intermittence and urgency	Age, BMI, smoking, alcohol consumption
Rohrman et al. (2006)	1723 twin pairs with information on moderate/severe urinary tract symptoms	High vs. low physical activity score	OR 0.60 (0.34-1.08)	Age, smoking, alcohol consumption, zygosity
Safarinejad (2008)	Cross-sectional survey of 8466 men aged >40 yr, noting prostate size, urine flow and IPSS	Reported physical activity	OR 0.4 (p = 0.01)	Multivariate adjusted
Smith et al. (2014)	95,089 men free of prostate cancer, presence of severe LUTS	High vs. low physical activity	OR 0.83 (0.76-0.91)	Risks also lower for well-educated, higher for obese, smokers, & those with heart disease
Williams (2008)	28,612 runners followed for 7.7 yr, with 1899 physician-reported cases of BPH	Distance run/week, fastest 10 km time	OR ~ 0.64 in terms of both distance and times	Age, diet, alcohol consumption, BMI (all non-smokers)
Abbreviations: BMI = body mass index, BPH = benign prostate hyperplasia. IPSS = International prostate symptom score. LUTS = lower urinary tract symptoms. MET =- metabolic equivalent. OR = odds ratio, PSA = prostate serum antigen.				

Kristal et al. (2007) followed a cohort of 5667 men for 7 yr, to end-points of surgical treatment of the prostate or attainment of an International Prostate Symptom Score (IPSS) >14 on 2 or more items. After co-varying the data or age, ethnicity, smoking, diabetes mellitus, and the initial IPSS score, a 4-level categorization of leisure physical activity (the method of data collection was not specified) did not show any association with either the total BPH score or with the incidence of severe cases of prostate hyperplasia (Kristal et al., 2007).

Hong et al. (2006) carried out a cross-sectional study of men aged 50-79 yr. Three levels of leisure exercise were identified (less than twice per week, 3-5 times/week, and nearly every day), but after co-varying for age, chronic bronchitis, prostate serum antigen and alcohol consumption, the effect of exercise was inconsistent in terms of reducing the risk of benign prostate hyperplasia, as defined by the IPSS, prostate volume and urinary flow rate; relative to the least active category. In a hierarchical multivariate logistic regression, the odds ratio relative to those exercising less than twice per week was 0.48 (0.23-1.00) for those exercising "3-5 times/week," but in those who reported exercising "nearly every day" (a substantial sample of 73 individuals, 11.8% of the total sample), the odds ratio increased to an adverse value of 1.73 (0.96-3.10) (Hong et al., 2006).

Among the three studies reporting an inconclusive but generally positive trend, Gann et al. (1995) completed a case-control comparison of participants in the on-going physicians' health study. Over a 9-year follow-up, 320 individuals

developed BPH and these were compared with 320 physicians who did not develop prostate symptoms (Gann et al., 1995). The measure of recreational physical activity was the reported frequency of exercise (taken more than 5 times per week versus those who rarely or never exercised). After co-varying for diastolic blood pressure and alcohol consumption, there was a non-significant trend to a lower odds ratio for BPH in the active individuals [odds ratio of 0.7 (0.32-1.51)]; however, the odds ratio became statistically significant in those exercising less than 4 times a week. In this study, hyperplasia was not correlated with blood levels of testosterone, dihydrotestosterone or androstenedione, but there was a trend for an increase of risk with higher oestradiol levels, and a weak inverse trend linking risk to oestrone levels. Rohrman et al. (2006) compared 1723 twin pairs with information on those where one of the pair had developed moderate or severe urinary tract symptoms; after adjusting this data for age, smoking, alcohol consumption, and zygosity, the odds ratio of moderate or severe urinary tract symptoms as measured by the IPPS in those who had a high physical activity score (based on blocks walked and stair climbed) was suggestive (but non-significant) for both monozygotes (0.63, 0.24-1.14) and dizygotes (0.58, 0.24-1.40), the trend to benefit being seen more clearly with severe than with moderate prostate symptoms (Rohrman et al., 2006).

Of the investigations that pointed to statistically significant benefit from physical activity, Dal Maso et al. (2006) conducted a large hospital-based case-control study, comparing Italian men who were taking less than 2 hr/wk of active recreation with those who were taking more than 5 hr/wk (Dal Maso et al., 2006). The odds ratios as determined by multivariate logistic regression analyses that included age, hospital centre and level of education significantly favoured the active individuals, with odds ratios of hospital admissions for diagnostic or therapeutic procedures of 0.5 (0.4-0.7) based on the activity reported for ages 15-19 yr, 0.6 (0.5-0.8) for ages 30-39 yr, and 0.7 (0.5-0.8) for ages 50-59 yr. Joseph et al. (2003) used the IPSS to evaluate 708 African-American men. The crude odds ratio for the development of lower urinary tract symptoms (whether obstruction of urinary flow or irritation) favoured those who engaged in vigorous physical activity that was sufficient to work up a sweat versus those who did not engage in such activity (OR 0.61, 0.44-0.85); however, the authors commented that this advantage disappeared after adjustment of the data for "other lifestyle and medical history risk factors" (Joseph et al., 2003). Fowke et al. (2013) conducted a cross-sectional study on 405 men, measuring the severity of lower urinary tract symptoms (LUTS) and determining prostate size by ultrasonography (Fowke et al., 2013). Work, sport, leisure and household activities were assessed using the Baecke questionnaire, and were expressed in MET-h/week. Application of chi^2 tests to crude data suggested benefit from high intensity work ($p = 0.04$ for both LUTS and prostate volume) and the total of sport, leisure, work and household activity ($p<0.01$ for prostate volume only). Slightly different findings were obtained from multivariate analysis; after controlling for age, race, body mass index, cardiovascular disease, diabetes mellitus and treatment for BPH, higher leisure and

household energy expenditures were significantly associated with a lower risk of LUTS; the association was influenced by body mass index, and was strongest for irritative symptoms, with little association between levels of physical activity and prostate volume. Meigs et al. (2001) also found a significantly lower risk of BPH for those in a cohort of 1709 men initially aged 40-70 yr who reported an active leisure. Participants in this study were followed for 9 yr, looking for the onset of prostate-related symptoms or a need for lower urinary tract surgery. After controlling for age, marital status, waist/hip ratio, alcohol consumption, hypertension, heart disease, and medication use, a comparison between the most active quartile (an energy expenditure >3.6 MJ/day, as estimated by trained interviewers) with the least active quartile (< 0.5 MJ/day) found an odds ratio of 0.5 (0.3-0.9) favouring the active men (Meigs et al., 2001). Platz et al. (1998) followed 30,364 health professionals for 8 yr. During this time, 1890 underwent surgery for benign prostate hyperplasia and 1853 developed severe lower urinary tract symptoms. Comparing the highest versus the lowest quintile of reported physical activity (>33.8 vs. < 3.0 MET-h/wk), after co-varying for age, ethnicity, smoking and alcohol consumption, the OR for those requiring surgery was 0.76 (0.64-0.90) in the active group, and among those who developed severe lower urinary tract symptoms the odds ratio for the active group was 0.79 (0.62-1.00) (Platz et al., 1998). In a cross-sectional study, Prezioso et al. (2001) questioned 1033 men concerning lower urinary tract symptoms. After allowing for their age, body mass index, smoking, and alcohol consumption, a high level of reported physical activity was correlated with lower prostate volumes ($p = 0.04$), and a lower IPSS score ($p = 0.008$); active individuals showed a lower risk of various symptoms including a diminished frequency of incomplete bladder emptying, repeated urination, intermittence and urgency (Prezioso et al., 2001). Safarinejad (2008) also completed a cross-sectional survey of 8466 Iranian men aged >40 yr. Prostate hyperplasia as indicated by a sonographic estimate of prostate size, a poor urine flow and a high prostate symptom score was inversely related to the reported level of physical activity; a multivariate adjusted odds ratio of 0.4 ($p = 0.01$) favoured the more active individuals (Safarinejad, 2008). Smith et al. (2014) made a cross-sectional analysis of data for 95,089 men who were free of prostate cancer. The sample was evaluated for severe LUTS, using the IPSS, and an assessment of physical activity (high or low) was based on findings from the Active Australia Survey (Smith et al., 2014). After adjusting for age, education, income, alcohol consumption and body mass index, the odds ratio favoured the active men (OR 0.83, 0.76-0.91). Risks were also lower for those who were well educated, but were increased for the obese, smokers and those with heart disease.

Williams (2008) obtained a rather different measure of physical activity from a cohort of 28,612 non-smoking male long distance runners. This group was followed for an average of 7.7 yr, and 1899 physician-reported cases of benign prostate hyperplasia were accumulated (Williams, 2008). Physical activity levels were compared in terms of the usual distance that was run per week, and the fastest 10 km times (the latter being essentially a surrogate of the individual's

aerobic fitness). After adjusting for age, diet, alcohol consumption, and body mass index, both criteria showed a significant odds ratio of ~ 0.64 favourlng those men who were more deeply involved in distance running.

Obesity and the metabolic syndrome.

Several investigators have examined associations between the risk of BPH and obesity or the metabolic syndrome, both of the latter possibly serving as markers of a sedentary lifestyle (Mongiu and McVary, 2009; Moul and McVary, 2010; Parsons et al., 2009; Raheem and Parsons, 2014). Three epidemiological investigations found no such association (Table 3), five noted an effect of central obesity as indicated by the waist circumference (but only 1 of the 5 found an effect of body mass index or overall obesity), and one report observed an association of BPH with the metabolic syndrome.

Of the negative reports, Gao et al. (2012) made a cross-sectional examination of 3103 men who were attending a health examination survey. Applying standard guidelines for diagnosis of the metabolic syndrome, the presence of this syndrome showed no assdociation with the risk of mild or severe symptoms on the IPSS. However, no co-variates were used in this analysis (Gao et al., 2012). Gupta et al., (2006) conducted a prospective study of 1206 Air Force veterans who were followed for a total of 15.6 yr. The risk of BPH increased marginally with fasting blood glucose, but was unrelated to body mass, BMI or the metabolic syndrome(Gupta et al., 2006). As a part of a larger trial, Yee et al. (2015) made a cross-sectional comparison of lower urinary tract symptoms in overweigh or obese men aged >50 yr, finding no difference of lower urinary tract symptoms between those with a body mass index in the range 25-30 kg./m^2 and those with values between 30-35 kg/m^2; no co-variates were introduced into this comparison (Yee et al., 2015).

Among the studies with positive findings, Giovannucci et al. (1994) examined 25,892 men recruited to the health professionals follow-up study, 837 having undergone prostate surgery, and 2581 having prostatic symptoms. Waist circumference was used as a measure of abdominal obesity, and after co-varying for age, smoking, and body mass index, there was a strong association of risk with the accumulation of abdominal fat, the odds ratio for a person with an abdominal circumference >1.09 m versus an individual with a circumference <0.89 m was 2.38, with a 95% confidence interval of 1.42-3.99 (Giovannucci et al., 1994). Kristal et al. (2007) reported findings on 5667 men who were initially free of prostate cancer or BPH. These individuals were followed for 7 yr. The risk of developing BPH was strongly associated with waist circumference, each additional 0.05 m of abdominal circumference increasing the risk of both total (p = 0.003) and severe (p =- 0.02) cases of BPH by 10%. The risk of BPH was also significantly associated with the body mass index in this series (Kristal et al., 2007). Laven et al. (2008) examined the influence of abdominal obesity upon LUTS in 27,858 Swedish men who were free of prostatic cancer; 4947 of the group had moderate, and 1120 had severe lower urinary tract symptoms. Men with a low birth weight (<2.5 kg) who were in the top quartile of waist-to-hip ratios had a doubled risk of LUTS (CI 1.29--3.02). In contrast, no associations were seen with

Table 3: Association between obesity, central obesity or metabolic syndrome and the risk of developing benign prostate hyperplasia.

Author	Sample	Measure of obesity or metabolic syndrome	Findings	Comment
Gao et al. (2012)	Cross-sectional study of 3103 men attending a health examination survey	Standard guidelines for diagnosis of metabolic syndrome	No association with mild or severe IPSS	No co-variates introduced
Giovannucci et al. (1994)	25,892 men in health professionals follow-up study, 837 with prostate surgery, 2581 with prostatic symptoms	Waist circumference as measure of abdominal obesity	OR for waist circumference >1.09 m vs. <0.89 m 2.38 (1.42-3.99)	Co-variates age, smoking, BMI
Gupta et al. (2006)	Prospective study of 1206 Air Force veterans followed for 15.6 yr	Body mass, BMI, metabolic syndrome criteria	Risk of BPH increased marginally with fasting blood glucose, but not with metabolic syndrome, body mass, or BMI	Men with occupational exposure to herbicides excluded
Kristal et al. (2007)	5667 men initially free of prostate cancer or BPH followed for 7 yr	Waist circumference	Each 0.05 m increase of waist circumference gave 10% increase of total (p = 0.003) and severe (p = 0.02) BPH; also relationship with BMI	Co-varied for age and ethnicity
Laven et al. (2008)	2 7,858 Swedish men, 4947 moderate, 1128 severe LUTS	BMI, waist-to-hip ratio	Men with birth weight <2.5 kg, top quartile of waist-to-hip ratio doubled risk of LUTS (CI 1.29-3.02)	
Lee et al. (2006)	146 men aged >40 yr, no overt obesity disease	BMI, waist circumference	Odds ratio for prostate volume >20 mL = 3.37 (p = 0.037) if waist circumference >0.9 m; no effect of BMI	Co-variates age, blood pressure, fasting glucose, total cholesterol, and nutrition intake
Rohrman et al. (2005)	279 men aged > 60 yr with lower urinary tract symptoms vs. 599 controls	Men with at least 3 components of metabolic syndrome	OR 1.80 (1.11-2.94)	Age, ethnicity, waist circumference, smoking, alcohol consumption
Safarinejad (2008)	Cross-sectional study of 8466 men aged >40 yr	BMI >35 kg /m^2 vs. <25 kg/m^2	OR 2.7(1.72-3.27)	Co-variates age & race
Yee et al. (2015)	Cross-sectional 112 obese men analysis, aged >50 yr	BMI 25-30 kg./m^2 vs. 30-35 kg/m^2	No difference of LUTDS between 2 groups	No co-variates
Abbreviations. BMI =body mass index. CI = confidence interval. LUTS = lower urinary tract symptoms.				

general obesity, as indicated by the body mass index (Laven et al., 2008). Lee et al. (2006) studied 146 men aged >40 yr, with no overt obesity-related disease. After co-

varying for age, blood pressure, fasting glucose, total cholesterol, and nutrition intake, the odds ratio of a prostate volume >20 mL was substantially increased [OR 3.37 (p = 0.037)] in those with central obesity, as shown by an abdominal circumference >0.9 m. However, there was no association with general obesity, as shown by the body mass index (Lee et al., 2006). Rohrman et al. (2005) compared 279 men aged > 60 yr with lower urinary tract symptoms, drawn from the NHANES III survey, with 599 controls taken from the same survey. After controlling for age, ethnicity, waist circumference, smoking, and alcohol consumption, the odds ratio of finding at least 3 components of the metabolic syndrome in those with lower urinary tract symptoms was 1.80 (1.11-2.94) (Rohrman et al., 2005). Safarinejad (2008) conducted a cross-sectional study of 8466 men aged >40 yr. Those with a body mass index >35 kg /m^2 were compared with those where the index was <25 kg/m^2. After co-varying for age and race, those who were obese had a substantially increased risk of BPH as judged from an IPSS >7, a maximal urinary flow <15 mL/s and a prostate mass >30g [OR 2.7(1.72-3.27)] (Safarinejad, 2008).

Discussion

Some 17 yr ago, Hart (1999) reviewed for a respected journal club a prospective study of 30,634 men conducted by Platz et al. (1998). Hart supported the authors' contention that self-reports of a physically active lifestyle seemed a possible deterrent against BPH, and he commented that "*Given the high incidence of this troublesome condition, further exploration of interventions that (**safely)** reduce prostate size are needed, and the role of exercise as part of any overall management strategy deserve4s serious consideration* (Hart, 1999)." The current review appears to support this assertion. More recent publications, including the meta-analysis of Parsons and Kashefi (2008) and the data analyzed here strongly support this assessment of the potential value of regular physical activity, with positive trends now reported in 4 of 5 occupational studies, and 12 of 16 leisure studies, and 11 of the 21 reports showing statistically significant benefits (Parsons and Kashefi, 2008). Nevertheless, there are a number of weaknesses in many of the studies, and there remains a need for larger studies, with clear markers of both BPH and physical activity and a good control of co-variates to provide a categoric answer to this question.

Relative merits of occupational and leisure activity studies

Enlargement of the prostate gland is a relatively slow process, and reliance upon a classification of the physical demands of occupation has the merit that the required effort typically continues for 5 or more hours per day, 5 days a week for many years. On the other hand, because effort is sustained for such long periods, the intensity even of "heavy" work is only moderate (21-31 kJ/min)(Bouchard and Shephard, 1992) and this level of energy expenditure may be insufficient to trigger adaptations that could slow prostatic enlargement. Moreover, for many people, substantial prostatic enlargement does not occur until after retirement, and in all five of the published occupational studies more than a half of subjects were retired, although questionnaires attempted to determine also the occupational demand at various points during the participants'

lifespans. Further, there are differences of personal lifestyle between heavy workers and those in sedentary jobs, including not only leisure activity patterns, but also smoking habits and alcohol consumption; 3 of the 5 occupational reports co-varied for level of education, but this may not have captured all of the differences attributable to social status.

In terms of leisure activity, the big challenge is to obtain from questionnaires accurate information on activity patterns over a large part of the individual's lifespan. Despite these problems, the majority of investigations point to a lower risk of BPH in those reporting a greater frequency, intensity or volume of moderate or vigorous physical activity; of 16 leisure studies, only one suggested a consistent adverse effect of physical activity, and in three other investigations there was no clear effect, but 12 of the 16 reports (including cross-sectional, cohort and case-control studies, typically with good control for other likely risk factors) found a positive trend, and in 8 of these 12 studies the advantage to the more active individuals was statistically significant. In one study reporting an adverse effect from physical activity as a young adult, the data are somewhat puzzlingly co-varied for daily energy intake, and this may have distorted the effects of active leisure. Hong et al. (2006) suggested that the adverse effect of a high level of physical that they observed was also reported by Joseph et al. (2003), although in fact the latter authors merely stated that the beneficial effect of physical activity disappeared after adjusting for "*other lifestyle and medical history risk factors*." One of the reports where no effect was observed used a careful measure of lifetime leisure activity, but included no co-variates other than age when assessing the association of this activity with BPH (Fritschi et al., 2007); the other negative report made a 4-level categorization of leisure activity, but this apparently referred simply to recent activity and did not specify the method of data collection; it is relatively unique in that it looked at the incidence of BPH in relation to the level of physical activity at entry to the study.

Effects of obesity

Studies showing an association between obesity and BPH may be a further pointer to the adverse effects of a sedentary lifestyle. However, this is not necessarily the case, since the adipokines secreted by fat cells can stimulate the sympathetic nervous system and cause insulin resistance (Laven et al., 2008). Moreover, adipose tissue is a synthesis site for oestrogens, and thus obesity could favour hyperplasia by upsetting the balance between oestrogens and androgens. A final possibility is that the obese tissue is predisposing the individual to inflammatioin and oxidative stress.

Potential mechanisms

It is interesting to look at potential causes of prostate hyperplasia, since if these are linked to an individual's level of physical activity, this could be evidence that any observed relationship is causal in type. It may simply be that more active individuals are less likely to become obese as they grew older. Prostatic volume also seems to be correlated with the serum levels of various sex hormones, including free testosterone, androstenedione, delta 5-androstenediol, dehydroepiandronsterone (DHA), dehydroepiandronsterone sulphate (DHA-S), and 17-hydroxypregnenolone

(Partin et al., 1991). An elevated oestradiol/testosterone ratio seems particularly prone to provoke BPH (Barnard and Aronson, 2016). Endurance athletes with low levels of body fat are known to have decreased levels of testosterone (Bennell et al., 1996; Guglielmini et al., 1984; Tanaka et al., 1986), and in some instances exercise could thus slow the growth of prostatic cells by depressing serum levels of sex hormones. This mechanism could certainly be at play in the endurance runners studied by Williams (2008), but it seems an unlikely consequence of the moderate levels of physical activity discussed in many of the investigations cited (Williams, 2008).

BPH has also been linked to increased blood levels of insulin and insulin-like growth factor-1(IGF-1) (Choklingham et al., 2002; Stattin et al., 2001), and there is some evidence of increased activity of IGF receptors in the prostatic stroma of men with BPH (McCarty, 2001; Peehl et al., 1995). Moreover, increased levels of insulin could augment serum levels of free testosterone by suppressing the hepatic production of sex-hormone binding globulin (Barnard and Aronson, 2016). On the other hand, some authors have found increased serum levels of IGF-1 in older individuals in response to endurance training (Poehlman et al., 1994). Finally, a proportion of highly committed and over-zealous exercisers are also involved in the abuse of androgenic steroids, and this could possibly explain the observation of Hong et al. (2006) that the risk of BPH was low in those exercising 3-5 times per week, but was increased in those exercising more than 5 times per week (Hong et al., 2006).

Gann et al. (1995) found no correlation between BPH and blood levels of testosterone, dihydrotestosterone or androstenedione, but there was a trend for the risk to increase with oestradiol levels, and a weak inverse trend linked to oestrone levels (Gann et al., 1995). Barnard et al. (2007) further offered experimental evidence of hormonal involvement, in that serum taken from men who had been involved in a long-term exercise programme inhibited the growth of a culture of prostate epithelial cells (Barnard et al., 2007).

Suggestions for Future Research

Although the studies already available generally support the hypothesis of an inverse association between physical activity and BPH, there remains a need for further large investigations, with clear definitions of BPH and physical activity and a careful control of co-variates to confirm this view. Many current investigations have already included a substantial number of co-variates, but there remains some possibility that apparent inverse associations between BPH and an active lifestyle could have been produced by unmeasured variables. Future research may be helped by use of objective monitors of habitual physical activity (pedometers and accelerometers), or the measurement of attained levels of aerobic fitness. It will also be interesting to focus upon evidence pointing towards a causal relationship, including graded dose-response relationships, evidence of mechanisms, and randomized studies testing the influence of increased physical activity upon the rate of progression of prostate hypertrophy and the development of lower urinary tract symptoms.

Practical implications

The predominance of beneficial trends and the rarity of reports of an adverse response to regular physical activity suggest that habitual physical activity should be recommended as a factor likely to reduce the risk of developing BPH. The extent of such protection remains to be clarified, but several studies have reported odds ratios as low as 0.5-0.6 favouring the most active individuals. In some reports, the odds may have been biased by using as controls individuals who were admitted to hospital for other conditions and thus had a low level of physical activity. On the other hand, in many studies the benefits were probably attenuated by weak assessments of the actual levels of physical activity; for example, Lacey et al. (2001) found a larger reduction of risk when using occupational titles rather than self-reports of the physical intensity of work (Lacey et al., 2001). Neither of these criticisms applies to the observations of Williams (2008), who found a 36% reduction of risk among those who engaged in substantial volumes of distance running (Williams, 2008).

Practitioners would plainly like to know the optimal pattern of physical activity to recommend. Several investigators have attempted to pinpoint the critical age when physical activity should be increased, but their findings have not always agreed. Lagiou et al. (2008) found a trend to a greater reduction in risk in individuals who had an active occupation when they were younger than 65 yr (and presumably still employed) (Lagiou et al., 2008). Dal Maso et al. (2006) found an essentially similar risk reduction with occupational or leisure activity as reported for ages of 15-19, 30-39 and 50-59 yr (Dal Maso et al., 2006). In contrast, Lacey et al. (2001) found a negative association of risk with the reported demands of occupation at an age of 20-29 yr, but positive effects with heavy work at ages of 40-49 yr and ~ 79 yr (Lacey et al., 2001).

Some reports have discussed the optimal frequency and/or the intensity of effort, and most but not all of these investigations have shown a progressive reduction in the risk of BPH through to the highest reported level of physical activity (Dal Maso et al., 2006; Lagiou et al., 2008; Meigs et al., 2001; Platz et al., 1998; Rohrman et al., 2006). Although a meta-analysis by Parson and Kashefi (2008) reported rather similar pooled odds ratios of 0.70. 0.74, 0.74 for light, moderate and heavy activity, even in their analysis, the benefit was statistically significant only for moderate and heavy exercise (Parsons and Kashefi, 2008). As already noted Hong et al. (2006) observed a reduction of risk with exercise 3-5 times/week, but they saw an increase of risk in highly committed exercisers who were active more than 5 times per week (Hong et al., 2006), and the data of Gann et al. (1995) also showed a smaller reduction of risk in those exercising >5 times/week. Given the frequency of steroid abuse among highly enthusiastic amateur athletes, the abuse of androgens may have been a factor increasing risk among highly committed and possibly over-zealous individuals. The endurance exercise practiced by Williams' group of runners (Williams, 2008) is likely to have been particularly appropriate in terms of suppressing serum testosterone levels, and steroid abuse is unlikely to have been a problem amongst distance runners; this particular study is important in demonstrating both a strong dose-response relationship, and a very

favourable odds ratio either for those running a substantial weekly distance, or for those showing a surrogate of aerobic fitness (a low average time taken to run a distance of 10 km).

One problem in recommending a substantial increase in physical activity to a client is poor adherence to such programmes. This is particularly likely to be the case in BPH, given the older age of many patients, and the fact that any resultant slowing of prostate growth is likely to be a slow process. However, practitioners may find encouragement from the fact that at least two investigations saw benefit from quite modest levels of activity. Platz et al. (1998) found a 25% reduction in the risk of either LUTS or a need for prostatic surgery among men who were walking for as little as 2-3 hr/wk, and Wolin et al. (2010) reported a 39% decrease in severe nocturia among men who engaged in more than 1 hr/wk of sweat-provoking activity.

Conclusions

Available data seem to support the idea of benefit from regular physical activity, with positive trends towards the prevention of prostate hyperplasia in 12 studies of recreational activity and three of occupational activity, against only one study showing a consistently adverse effect, and five studies with inconsistent findings. Possibly, beneficial effects are produced by a modulation of growth hormones, although such a response would require a substantial volume of endurance activity. Further research on mechanisms is needed. Moreover, although many authors have included a substantial number of co-variates in their investigations, there remains a need to confirm that apparently beneficial associations were not produced by unmeasured variables. Nevertheless, current evidence suggests that the modulation of BPH is yet one more reason to recommend regular physical activity to an aging population.

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Author's qualifications

The author's qualifications are as follows: Roy J. Shephard, C.M.; Ph.D., M.B.B.S., M.D. [Lond.], D.P.E., LL.D., D.Sc., FACSM, FFIMS.

References

Barnard, R.J. , Leung, P.S. , Aronson, W.J., Cohen, P., and Golding, L.A. (2007). A mechanism to explain how regular exercise reduces the risk for prostate cancer. *Eur J Cancer Prev.* 16, 415-421. doi.org/10.1097/01.cej.0000243851.66985.e4.

Barnard, R.J., and Aronson, A.J. . (2016). Benign prostatic hyperplasia: Does lifestyle play a role? *Physician Sportsmed,* 37(4), 141-146. doi.org/10.3810/psm.2009.12.1752.

Bennell, K., Brukner, P.D., and Malcolm, S.A. (1996). Effect of altered reproductive function and lowered testosterone levels on bone density in male endurance athletes. *Br J Sports Med,* 30, 205-208. doi.org/10.1136/bjsm.30.3.205.

Bouchard, C., and Shephard, R.J. (1992). Physical activity, fitness and health. The model and key concepts. In: C. Bouchard, R.J. Shephard and T. Stephens (Eds.), *Physical activity, fitness and health*. Champaign, IL.: Human Kinetics, pp.77-88.

Chokkalingham, A.P., Gao, Y-T., Deng, J., Stanzyk, F.Z., Sesterhenn, I.A., Mostofi, F.K., Fraumeni, J.F., and Hsing, A.W. (2002). Insulin-like growth factors and risk of benign prostatic hypoerplasia. *Prostate 52*, 98-105. doi.org/10.1002/pros.10096.

Cunningham, G.R., and Kadmon, D. . (2013). Epidemiology and pathogenesis of benign prostatc hyperplasia. *http://www.uptodate.com/contents/epide*

miology-and-pathogenesis-of-benign-prostatic-hyperplasia (accessed May 26th, 2016).

Dal Maso, L., Zucchetto, A., Tavani, A., Montella, M., Ramazzotti, V., Polesel, J., Bravi, F., Talamini, R., La Vecchia, C., and Franceschi, S. (2006). Lifetime occupational and recreational physical activity and prostatic hyperplasia. *Int J Cancer,* 118, 2632-2635.

Fenter, T.C., Naslund, M.J., Shah, M.B., Eaddy, M.T., and Black, L. (2006). The cost of treating the 10 most prevalent diseases in men 50 years of age or older. *Am J Manag Care.* 12 (4 Suppl.), S90-S98. doi.org/10.1002/ijc.21668.

Fowke, J.H., Phillips, S., Koyama, T., Byerly, S., Concepcion, R., Motley, S.S., and Clark, P.E. (2013). Association between physical activity, lower urinary tract symptoms (LUTS) and prostate volume. *BJU Int.* 111(1), 122-128. doi.org/10.1111/j.1464-410X.2012.11287.x.

Fritschi, L., Tabrizi, J., Leavy, J., Ambrosini, G., and Timperio, A. (2007). Risk factors for surgically treated benign prostatic hyperplasia in Western Australia. *Public Health.* 121, 781-789. doi.org/10.1016/j.puhe.2007.01.011.

Gann, P.H., Hennekens, C.H., Longcope, C., Verhoek-Oftedahl, W., Grodstein, F., and Stampfer, M.J. (1995). A prospective study of plasma hormone levels, nonhormonal factors, and development of benign prostate hyperplasia. *Prostate.* 26, 40-49. doi.org/10.1002/pros.2990260109.

Gao, Y., Wang, M. , Zhang, H., Tan, A., Yang, X., Qin, X., . . . Mo, Z. (2012). Are metabolic syndromne and its components associated with lower urinary tract symptoms? Results from a Chinese male population survey. *Urology, 79*, 194-201. doi.org/10.1016/j.urology.2011.07.1399.

Giovannucci, E., Rimm, E.B., Chute, C.G., Kawachi, I., Colditz, G.A., Stampfer, M.J., and Willett, W.C. (1994). Obesity and benign prostate hyperplasia. *Am J Epidemiol.* 140, 989-1002. PMID:7527182.

Guess, H.A., Arrighi, H.M., Metter, E.J., and Fozard, J.L. (1990). Cumulative prevalence of prostatism matches the autopsy prevalence of benign prostatic hyperplasia. *Prostate.* 17(3), 241-246. doi.org/10.1002/pros.2990170308.

Guglielmini, C., Paolini, A.R., and Conconi, F. (1984). Variations of serum testosterone concentrations after physical exercise of different duration. *Int J Sports Med.* 5, 246-249. .doi.org/10.1055/s-2008-1025914.

Gupta, A. , Gupta, S., Pavuk, M., and Roehrborn, C.G. (2006). Anthropometric and metabolic factors and risk of benign prostatic hyperplasia: a prospective cohort study of air force veterans. *Urology.* 68, 1198-1205. doi.org/10.1016/j.urology.2006.09.034.

Hart, L.E. (1999). Physical activity and benign prostate hyperplasia. *Clin J Sports Med.* 9(2), 106. doi: org/10.1097/00042752-199904000-00018.

Hong, J., Kwon, DS., Yoon, H. , Lee, H., Kim, H.H., Jeong, E.K., and Park, H. (2006). Risk factors for benign prostatic hyperplasia in South Korean men. *Urol Int,* 76, 11-19.doi.org/10.1159/000089729.

Joseph, M.A. , Harlow, S.D., Wei, J.T., Sarma, A.V., Dunn, R.L., Taylor, J.M., James, S.A., Cooney, K.A., Doerr, K.M., Montie, J.E., and Schottenfeld, D. (2003). Risk factors for lower urinary tract symptoms in a population-based sample of African American men. *Am J Epidemiol.* 157, 906-914. doi.org/10.1093/aje/kwg051.

Kristal, A.R., Arnold, K.B., Schenk, J.M., Neuhouser, M.L., Weiss, N., Goodman, P., Antvelink, C.M., Penson, D.F., and Thompson, I.M. (2007). Race/ethnicity, obesity, health-related behaviors and the risk of symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. *J Urol.*177, 1395-1400. doi.org/10.1016/j.juro.2006.11.065.

Lacey, J.V., Deng, J., Dosemeci, M., Gao, Y.T., Mostofi, F.K., Sesterhenn, I.A., Xie, T., and Hsing, A.W. (2001). Prostate cancer, benign prostate hyperplasia and physical activity in Shanghai, China. *Int J Epidemiol.* 30, 341-349. doi.org/10.1093/ije/30.2.341.

Lagiou, A. , Samoli, E. , Georgila, C. , Minaki, P., Barbouni, A., Tzonou, A., Trichopolos, D., and Lagiou, P. (2008). Occupational physical activity in relation with prostate cancer and benign prostate hyperplasia.

Eur J Cancer Prev. 17, 336-339. doi.org/10.1097/CEJ.0b013e3282f5221e.

Laven, B.A., Orsini, N., Andersson, S-O., Johansson, J.E., Gerber, G.S., and Wolk, A. (2008). Birth weight, abdominal obesity and the risk of lower urinary tract. symptoms in a population-based study of Swedish men. *J Urol.* 179, 1891-1896. doi.org/10.1016/j.juro.2008.01.029.

Lee, S., Min, H.G., Choi, S.H. , Kim, Y.J., Oh, S.W. , Kim, Y.J., Park, Y., and Kim, S.S. (2006). Central obesity as a risk factor for prostatic hyperplasia. *Obesity.* 14, 172-179. doi.org/10.1038/oby.2006.21.

McCarty, M.F. (2001). Upregulation of hepatic IGFBP-1 production as a strategy for preventing benign prostatic hyperplasia. *Med Hypoth.* 56 (1), 1-4. doi.org/10.1054/mehy.1999.1013.

Meigs, J.B., Mohr, B., Barry, M.J., Collins, M.M., and McKinlay, J.B. (2001). Risk factors for clinical benign prostatic hyperplasia in a community-based population of aging men. *J Clin Epidemiol.* 54, 935-944. doi.org/10.1016/S0895-4356(01)00351-1.

Mongiu, A.K., and McVary, K.T. (2009). Lower urinary tract symptoms, benign prostatic hyperplasia, and obesity. *Curr Urol Rep.* 10(4), 247-253. doi.org/10.1007/s11934-009-0041-8.

Moul, S., and McVary, K.T. (2010). Lower urinary tract symptoms, obesity and the metabolic syndrome. *Curr Opin Urol.* 20(1), 7-12. doi.org/10.1097/MOU.0b013e3283336f3f.

Parsons, J.K., and Kashefi, C. (2008). Physical activity, benign prostatic hypertrophy and lower urinary tract symptoms. *Eur Urol.* 53, 1228-1235. doi.org/10.1016/j.eururo.2008.02.019.

Parsons, J.K., Sarma, A.V. , McVary, K. , & Wei, J.T. (2009). Obesity and benign prostatic hyperplasia: Clinical connections, emerging etiological paradigns and future directions. *J Urol 182(6 Suppl)*, S27-S31. doi.org/10.1016/j.juro.2009.07.086.

Partin, A.W., Oesterling, J.E., Epstein, J.I., Horton, R., and Walsh, P.C. (1991). Influence of age and endocrine factors on the volume of benign prostatic hyperplasia. *J Urol,* 145(2), 405-409. PMID: 1703242.

Peehl, D.M., Cohen, P., and Rosenfeld, P.G. (1995). The insulin-like growth factor system in the prostate. *World J Urol.* 1, 306-311. doi.org/10.1007/bf00185974.

Platz, E., Kawachi, I. , Rimm, E.B. , Colditz, G.A., Stampfer, M.J., Willett, W.C., and Giuovannucci, E. (1998). Physical activity and benign prostatic hyperplasia. *Arch Intern Me.,* 158, 2349-2356. doi.org/10.1001/archinte.158.21.2349.

Poehlman, E., Rosen, C.J., and Copeland, K.C. (1994). The influence of endurance training on insulin-like growth factor-1 in older individuals. *Metabolism.* 43(11), 1401-1405. doi.org/10.1016/0026-0495(94)90035-3.

Prezioso, D., Catuogno, C., Galassi, P., D'Andrea, G., Castello, G., and Pirritano, D. (2001). LIfestyle in patients with LUTS suggestive of BPH. *Eur Urol.* 40(Suppl 1), 9-12. doi.org/10.1159/000049871.

Raheem, O.A., and Parsons, J.K. (2014). Associations of obesity, physical activity and diet with benign prostatic hyperplasia and lower urinary tract symptoms. *Urology.* 24(1), 10-14. doi.org/10.1097/mou.0000000000000004.

Rohrman, S., Fallin, M.D., Page, W.F., Reed, T., Partin, A.W., Walsh, P.C., and Platz, E.A. (2006). Concordance rates and modifiable risk factors for lower urinary tract symptoms in twins. *Epidemiology.* 17, 419-427. doi.org/10.1097/01.ede.0000219723.14476.28.

Rohrman, S., Smit, E., Giovannucci, E., and Platz, E.A. (2005). Association between markers of the metabolic syndrome and lower urinary tract symptoms in the Third National Health and Nutrition Examination Survey (NHANES III). *Int J Obesity.* 29, 310-316. doi.org/10.1038/sj.ijo.0802881.

Safarinejad, M.R. (2008). Prevalence of benign prostatic hyperplasia in a population-based study in Iranian men 40 years old or older. *Int Urol Nephrol.* 40, 921-931. doi.org/10.1007/s11255-008-9338-7.

Smith, D.P., Weber, M.F., Soga, K. , Korda, R.J., Tikellis, G., Patel, M.I., Clements, M.S., Dwyer, T., Latz, I.K., and Banks, E. (2014). Relationship between lifestyle and health factors and severe lower urinary tract

symptoms (LUTS) in 106,435 middle-aged and older Australian men: Population-based study. *PLoS-One.* 9(10)e109278. doi.org/10.1371/journal.pone.0109278.

Stattin, P., Kaaks, R., Riboli, E., Ferrari, P., Dechaud, H., and Hallmans, G. (2001). Circulating insulin-like growth factor-1 and benign prostatic hyperplasia. A prospective study. *Scand J Urol Nephrol.* 35, 122-126. doi.org/10.1080/003655901750170506.

Tanaka, H., Cléroux, J., de Champlain, J., Ducharme, J.R., and Collu, R. (1986). Persistent effects of a marathon run on the pituitary-testicular axis. *J Endocrinol Invest.* 9, 97-101. doi.org/10.1007/BF03348075.

Verhamme, K., Dieleman, J.P., Bleumink, G.S., van der Lei, G., Sturkenboom, M.C., Artibani, W., . . . Triumph Pan European Expert Panel. (2002). Incidence and prevention of lower urinary tract symptoms suggestive of benign prostatic hyperplasia in primary care- the Triumph project. *Eur Urol.* 42(4), 323-328. doi.org/10.1016/S0302-2838(02)00354-8.

Williams, P.T. (2008). Effects of running distance and performance on incident benign prostatic hyperplasia. *Med Sci Sports Exerc.* 40(10), 1733-1739. doi.org/10.1249/MSS.0b013e31817b8eba.

Wolin, K.Y., Luly, J., Sutcliffe, S., Andriole, G.L., and Kibel, A.S. (2010). Risk of urinary incontinence following prostatectomy: The role of physical activity and obesity. *J Urol.* 183(2), 629-633. doi.org/10.1016/j.juro.2009.09.082.

Yee, C-H., Soi, W-Y., Yip, S.K.H., Wu, E., Yau, P., and Ng, C-F. (2015). Effect of weight reduction on the severity of lower urinary tract symptoms in obese male patients with benign prostate hyperplasia: A randomized controlled trial. *Korean J Urol.* 56, 240-247. doi.org/10.4111/kju.2015.56.3.240.