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Sexually transmitted infections, benign prostatic hyperplasia and lower urinary tract symptom-related outcomes: results from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

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Objective

To examine whether a history of sexually transmitted infections (STIs) or positive STI serology is associated with prevalent and incident benign prostatic hyperplasia (BPH)/lower urinary tract symptoms (LUTS)-related outcomes in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.

Methods

Self-reported history of STIs (gonorrhoea, syphilis) was ascertained at baseline, and serological evidence of STIs (*Chlamydia trachomatis*, *Trichomonas vaginalis*, human papillomavirus (HPV)-16, HPV-18, herpes simplex virus type 2, human herpesvirus type 8 and cytomegalovirus) was detected in baseline serum specimens. We used data collected on the baseline questionnaire, as well as results from the baseline prostate-specific antigen (PSA) test and digital rectal examination (DRE), to define prevalent BPH/LUTS-related outcomes as evidence of LUTS (self-reported diagnosis of an enlarged prostate/BPH, BPH surgery or nocturia [waking ≥2 times/night to urinate]) and evidence of prostate enlargement (PSA > 1.4 ng/mL or prostate volume ≥30 mL) in men without prostate cancer. We created a similar definition of incident BPH using data from the follow-up questionnaire completed 5–13 years after enrolment (self-reported diagnosis of an enlarged prostate/BPH or nocturia), data on finasteride use during follow-up, and results from the follow-up PSA tests and DREs. We used Poisson regression with robust variance estimation to calculate prevalence ratios (PRs) in our cross-sectional analysis of self-reported (n = 32 900) and serologically detected STIs (n = 1 143) with prevalent BPH/LUTS, and risk ratios in our prospective analysis of self-reported STIs with incident BPH/LUTS (n = 5 226).

Results

Generally null results were observed for associations of a self-reported history of STIs and positive STI serologies with prevalent and incident BPH/LUTS-related outcomes, with the possible exception of *T. vaginalis* infection. This STI was positively associated with prevalent nocturia (PR 1.36, 95% confidence interval (CI) 1.18–1.65), prevalent large prostate volume (PR 1.21 95% CI 1.02–1.43), and any prevalent BPH/LUTS (PR 1.32 95% CI 1.09–1.61); too few men had information on both STI serologies and incident BPH/LUTS to investigate the associations between *T. vaginalis* infection and incident BPH/LUTS-related outcomes.

Conclusions

Our findings do not support associations of several known STIs with BPH/LUTS-related outcomes, although *T. vaginalis* infection may warrant further study.

Keywords

sexually transmitted infection, benign prostatic hyperplasia, nocturia, Prostate lung colorectal and ovarian cancer screening trial

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Introduction

It is estimated that BPH and associated LUTS, such as bothersome night-time urination or urinary urgency, affect half of the male population worldwide to some degree and their prevalence is predicted to rise in the coming decades [1,2]. Billions are spent annually to treat BPH/LUTS [3].

Despite extensive research, the pathophysiology of BPH/LUTS remains incompletely defined. The pathogenesis is probably through multiple independent and inter-related pathways; advanced age, diabetes, metabolic syndrome and depression have all been associated with an increased risk of BPH or LUTS [4–6].

Some authors have suggested that inflammation plays a central role in the pathophysiology of BPH/LUTS, as chronic inflammation is often found in biopsy and surgical specimens of men with BPH/LUTS [7]. One possible source of chronic, prostatic inflammation is sexually transmitted infections (STIs). Several sexually transmitted agents such as *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Trichomonas vaginalis* can elicit chronic inflammation within the prostate gland's parenchyma [8]. In a rat model, *Chlamydia murinarum* produced upregulation of pro-inflammatory cytokines and chemokine genes in the prostate epithelium [9]. STI-related inflammation may cause growth factor secretion and prostate epithelial growth [10]. Many STIs have also been detected in BPH surgical specimens [12–14].

Several observational studies have shown a positive association between STIs and BPH/LUTS [10,11,15–17]. The majority of these studies used cross-sectional data and relied on patient self-report of an antecedent STI, making them susceptible to recall bias [15–17]. The objective of the present analysis was to examine whether a history of STIs or positive STI serology was associated with prevalent and incident BPH/LUTS-related outcomes in the participants of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO).

Materials and Methods

Study Population and Design

The PLCO was a large, randomized trial designed to determine the effects of prostate, lung, colorectal and ovarian cancer screening on cancer-specific mortality [18]. Men aged 55–74 years with no reported histories of prostate cancer or radical prostatectomy and no reported use of finasteride in the preceding 6 months were eligible for the trial. A total of 76 705 men were recruited between 1993 and 2001 from 10 centres in the USA (Washington, DC; Detroit, MI; Salt Lake City, UT; Denver, CO; Honolulu, HI; Minneapolis, MN; Marshfield, WI; Pittsburgh, PA; St. Louis, MO; and Birmingham, AL). Non-Hispanic white and black people comprised 88 and 5% of the participants, respectively. Of these men, half were randomized to a prostate cancer screening arm, which included undergoing six annual PSA blood tests and four annual prostate DREs, while the control group received standard care. At the start of the study, patients filled out questionnaires that gathered demographic and health-related information. A follow-up questionnaire was administered 5–13 years after enrolment to update risk factor information, including prostate-/BPH-specific questions. A short health survey was sent out annually to inquire about any cancer diagnosis during the past year and the updated status of finasteride use. A small subset of men from PLCO included in a previous prostate cancer nested case–control study had serological STI data [19]. We used control subjects from that study to examine the relationship between serological STI and prevalent or incident BPH/LUTS-related outcomes.

The present analysis includes participants from the intervention arm of the PLCO (n = 38 340). We used the intervention arm because these men had regular systematic prostate cancer screening and, as such, regular periodic PSA results and DREs. We performed both a prevalent and an incident analysis.

For the prevalent analysis, we excluded men who: (i) reported a history of cancer (except basal or squamous-cell skin cancer) at baseline (n = 827); (ii) were diagnosed with prostate cancer on the baseline prostate cancer screen to avoid including men who may have reported BPH/LUTS-related outcomes because of prevalent, possibly advanced stage prostate cancer (n = 609); (iii) did not complete the baseline questionnaire (n = 887); (iv) provided incomplete information on BPH/LUTS-related outcomes (n = 64); (v) missed or had an invalid baseline PSA test or DRE result among those who did not report BPH surgery (n = 3 023); and (vi) did not respond to the question on a history of gonorrhoea or syphilis (n = 30). After these exclusions, 32 900 men remained in the prevalent self-reported STI analysis. Applying these same exclusions to the 1 208 prostate cancer nested case–control study control subjects, 1 072–1 143 subjects had serological results for the various STIs investigated.

For our incident analysis, we further excluded men who (i) had any evidence of BPH/LUTS-related outcomes at baseline (n = 25 521); (ii) were diagnosed with prostate cancer before completion of the follow-up questionnaire, because prostate cancer or its treatment may alter the risk of BPH/LUTS-related outcomes (e.g. PSA elevation, prostate enlargement and nocturia, n = 113); (iii) did not complete the follow-up questionnaire (n = 1 907); (iv) provided incomplete information on BPH/LUTS-related outcomes on the follow-up questionnaire (n = 103); and (v) did not have either a valid baseline PSA test result and at least one valid follow-up

PSA test result, or a valid baseline DRE result and at least one valid follow-up DRE result among those who did not report finasteride use (n = 30). These exclusion criteria resulted in an incident cohort of 5 226 men for the self-reported STI analysis. For the serological incident analysis cohort, 165 men were included.

We examined incidence among men without evidence of *any* previous BPH/LUTS-related outcomes. In addition, to increase the number of incident cases for the analysis of individual outcomes, we also examined incidence among men without previous evidence of the specific BPH-related outcome in question. For example, when examining incident nocturia, we created two separate cohorts, one that excluded all men with *any* history of a BPH/LUTS-related outcome at baseline and another that excluded only men with nocturia at baseline. In both cohorts, we examined the incidence of nocturia over the study period. When reporting our findings, we only considered estimates that were consistent in direction and magnitude (irrespective of statistical significance) across the two alternative incident analyses as suggestive of an association.

Exposure Assessments

We used questions from the baseline questionnaire to determine STI self-report (gonorrhoea, syphilis). At baseline, participants answered the following question: 'Has a doctor ever told you that you had any of the following conditions: syphilis (no or yes) and gonorrhoea (no or yes)?'.

Serological evidence of STIs (*C. trachomatis*, *T. vaginalis*, human papillomavirus-16 [HPV-16], HPV-18, herpes simplex virus-2 [HSV-2], human herpesvirus-8] HHV-8), and cytomegalovirus [CMV]) was determined using baseline serum specimens as described previously [19,20]. IgA and IgG antibodies against *C. trachomatis* major outer membrane proteins were measured using commercially available ELISAs (Medac, Hamburg, Germany), IgG antibodies against the *T. vaginalis* α-actinin protein were measured using an in-house ELISA (≥ scores 3 were considered seropositive), IgG antibodies against HPV-16, and HPV-18 virus-like particles were measured using enzyme immunoassays, anti-HSV-2 IgG antibodies were measured using a solid-phase enzymatic immunodot assay, IgG antibodies against the HHV-8 K8.1 structural glycoprotein were measured using an ELISA, and anti-CMV IgG antibodies were measured using a commercially available microparticle enzyme immunoassay (AxSYM CMV IgG assay; Abbott Laboratories, Abbott Park, IL, USA).

Outcome Assessment

We used data collected on the questionnaire, and DRE and PSA values at baseline and during follow-up to define prevalent and incident BPH/LUTS-related outcomes. Multiple BPH/LUTS-related outcomes were examined individually and as a composite outcome, as previously [21]. In prevalent analyses, the following individual variables were evaluated: (i) physician diagnosis of an enlarged prostate or benign prostatic hypertrophy; (ii) nocturia (regularly waking ≥2 times/night to urinate); (iii) BPH surgery; (iv) large estimated prostate volume (≥30 mL) on baseline DRE; (v) PSA elevation on baseline PSA test (PSA > 1.4 ng/mL); and (vi) composite outcome: evidence of LUTS (physician diagnosis, nocturia or surgery) and prostate enlargement (large prostate volume or PSA > 1.4 ng/mL). The number of cases, total number of participants and prevalence of each outcome is reported in Table A1.

We created similar definitions of incident BPH/LUTS-related outcomes using data from the follow-up questionnaire completed 5–13 years after enrolment (self-reported diagnosis of an enlarged prostate/BPH or nocturia), data on finasteride use during follow-up, and results from the follow-up PSA tests and DREs. Cumulative incidences of each outcome are reported in Table A1.

Statistical Analysis

We used Poisson regression with robust variance estimation to calculate prevalence ratios (PRs) in our cross-sectional analysis of the association of self-reported and serologically detected STIs with prevalent BPH/LUTS-related outcomes, and to calculate risk ratios (RRs) in our prospective analysis of incident BPH/LUTS-related outcomes. All models were initially adjusted for age. We investigated the potential for confounding (see Table 1 for a list of potential confounders) by adding covariates individually to the regression models and examining their influence on the point estimates for the STI exposures of interest. We retained covariates that shifted any of these estimates by >10%. Furthermore, to account for varying time of enrolment, incident models for physician diagnosis of BPH, nocturia and finasteride use were additionally adjusted for time between completion of the baseline and follow-up questionnaires. Likewise, incident models for enlarged prostate and PSA elevation were further adjusted for number of DREs and time between first and last DRE, and for number of PSA tests and time between first and last PSA test, respectively. Finally, incident models for our composite outcome were adjusted for all of these measures.

We examined each STI individually in relation to prevalent and incident BPH/LUTS. We also created a composite measure of any STI exposure that included all self-reported and serologically detected STIs. As CMV was extremely common in the population and is frequently transmitted by non-sexual means [22], we performed sensitivity analyses excluding this infection; however, no material changes were observed in the PR and RR estimates. A *post hoc* power calculation was

Table 1 Age-adjusted baseline characteristics† of male participants eligible for the prevalent analysis of benign BPH/LUTS-related outcomes in the intervention arm of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.

	Self-reported history of				Serological evidence‡ of												History or evidence of any STIs	
	Gonorrhoea		Syphilis		*Chlamydia trachomatis*		*Trichomonas vaginalis*		HPV-16 or -18		HSV-2		HHV-8		CMV			
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	1 802	31 098	270	32 630	212	931	138	934	300	842	225	918	112	1 031	845	298	978	164
Mean age, years	61.5	62.7**	61.7	62.7**	63.8	64.5	64.4	64.3	63.8	64.5*	64.0	64.4	64.2	64.4	64.7	63.4**	64.5	63.4**
Race/ethnicity, %																		
White	70.0	90.0**	62.7	89.1**	48.7	80.5**	56.5	76.3**	43.7	85.7**	38.8	83.4**	82.9	73.7*	68.9	91.0**	70.7	98.6**
Black	22.4	3.1	26.6	4.0	51.3	19.5	43.5	23.7	56.3	14.3	61.2	16.6	17.1	26.3	31.1	9.0	29.3	1.4
Asian/Pacific Islander	3.8	4.6	7.1	4.6	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Other	3.7	2.2	3.6	2.3	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Body mass index, %																		
<25 kg/m^2	27.2	25.9*	27.8	26.0	24.0	27.1	23.7	27.1	26.0	26.7	24.5	27.0	25.4	26.6	26.1	27.7*	25.9	30.4**
25–29 kg/m^2	46.5	49.7	43.0	49.6	44.8	49.7	45.1	48.6	47.5	49.2	46.1	49.5	52.2	48.5	47.2	53.3	47.5	56.2
≥30 kg/m^2	25.3	23.3	27.4	23.4	29.4	22.1	29.0	23.1	24.5	23.1	26.8	22.6	22.3	23.6	25.3	18.1	25.3	12.8
Smoking history																		
Never smoker	18.0	30.1**	19.2	29.6**	24.3	30.3	31.2	28.9	30.3	28.9*	27.8	29.6	25.0	29.7	30.2	26.6	29.5	27.8*
Current cigarette smoker	17.4	10.7	21.3	11.0	15.5	10.8	10.2	11.7	14.3	10.6	12.9	11.3	11.6	11.6	12.1	10.4	11.8	10.1
Former cigarette smoker	59.1	51.2	53.1	51.6	52.7	50.5	52.2	51.4	50.4	51.2	51.8	50.7	58.1	50.1	50.7	51.6	51.5	48.0
Cigar or pipe smoker only	5.5	8.0	6.4	7.9	7.5	8.4	6.5	8.0	5.0	9.4	7.5	8.4	5.4	8.5	7.1	11.5	7.2	14.1
Current alcohol intake, g/day	20.5	15.7**	21.3	15.9**	14.4	16.2	10.9	16.3	17.2	15.5	14.9	16.1	17.0	15.8	14.1	20.8**	14.8	22.1**
Medical history, %																		
Hypertension	38.3	33.0**	46.4	33.2***	48.8	34.7**	47.0	36.7*	44.3	34.8**	44.6	35.6*	35.8	37.5	39.3	31.9*	38.9	27.8**
Coronary heart disease	13.7	12.8	17.1	12.8*	13.7	14.1	15.1	13.9	13.2	14.2	13.2	14.2	14.4	13.9	13.0	16.7	13.8	14.9
Stroke	3.2	2.4*	4.6	2.4*	2.5	3.2	2.2	3.3	2.5	3.3	3.7	2.9	2.7	3.1	2.8	3.9	2.8	4.5
Diabetes	12.4	8.5**	14.8	8.6**	13.3	9.9	14.5	10.2	15.1	8.9**	15.6	9.3**	7.2	10.9	10.2	11.2	10.9	8.1
Arthritis	34.7	28.9**	30.7	29.2	32.4	31.9	33.2	32.0	33.3	31.7	38.4	30.5*	31.5	32.1	32.4	30.9	32.2	31.4

*CMV, cytomegalovirus; HSV-2, herpes simplex virus type 2; HHV-8, human herpesvirus type 8; HPV, human papillomavirus; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; STI, sexually transmitted infection. *0.01 ≤ P < 0.05. **0.001 ≤ P < 0.01. ***P < 0.001. †Additional covariates investigated but not presented in the table were year of entry into the PLCO trial, education, marital status, physical activity, consumption of total energy, carbohydrates, fats, polyunsaturated fats, proteins, fruit, vegetables, red meat, antioxidant nutrients (beta-carotene, selenium, vitamin A, C, and E, and zinc from the diet and supplements, and dietary alpha-carotene, beta-cryptoxanthin, lutein and zeaxanthin and lycopene), multivitamin use and histories of colon polyps and polyp syndromes. ‡Measured in white and black participants only.*

performed and confirmed adequate power to detect associations in the prevalent and self-reported incident analyses (≥80% to detect PRs ranging from 1.08 to 1.52 and RRs ranging from 1.15 to 1.88 for most BPH/LUTS-related outcomes), but much lower power to detect associations in the serological incident analysis (most RRs >1.7).

Results

The demographic characteristics and comorbid disease status of the study population is shown in Table 1. The population with STIs was more likely to be black and to have hypertension.

Generally null results were observed for associations of a self-reported history of STIs and positive STI serologies with prevalent and incident BPH/LUTS-related outcomes. Table 2 shows the PRs and 95% CIs. After adjusting for age, race and year of entry into PLCO, self-reported history of gonorrhoea was positively associated with a prevalent physician diagnosis of an enlarged prostate or BPH (PR 1.18, 95% CI 1.09–1.29) and nocturia (PR 1.09, 95% CI 1.02–1.16), and inversely associated with prevalent large prostate volume (PR 0.93, 95% CI 0.88–0.99) and PSA elevation (PR 0.94, 95% CI 0.88–1.00). Self-report of syphilis increased the prevalence of nocturia by 1.24 times (95% CI 1.09–1.43) and reached near significance for physician diagnosis of enlarged prostate or BPH (PR 1.20, 95% CI 0.97–1.47).

The sample size of the serologically detected STI analysis was substantially smaller than that for self-reported STIs. *T. vaginalis* infection was associated with prevalent nocturia (PR 1.36, 95% CI 1.18–1.65), prevalent large prostate volume (PR 1.21, 95% CI 1.02–1.43) and the composite outcome (PR 1.32, 95% CI 1.09–1.61), while HHV-8 infection was associated with BPH surgery (PR 2.15, 95% CI 1.04–4.47).

Tables 3/A2 shows RRs and 95% CIs for incident BPH/LUTS-related outcomes; no consistent patterns of association were apparent. No associations were observed for self-reported history of gonorrhoea and incidence of any BPH/LUTS-related outcomes, with the exception of an elevated PSA. Gonorrhoea was inversely associated with this outcome (RR 0.86 95% CI 0.76–0.98). For self-reported syphilis, a modest association was seen with the composite BPH/LUTS-related outcome (RR 1.25, 95% CI 1.07–1.46). No associations were observed for serologically detected STIs and BPH-related outcomes, with the possible exception of an inverse association between CMV and PSA elevation (RR 0.74, 95% CI 0.55–1.01); however, the sample size for the incident analysis of serologically detected STIs and BPH-related outcomes was small.

Discussion

In the present large retrospective and prospective analysis of STIs (both self-reported and serological) and BPH/LUTS, null

Table 2 Prevalence ratios and 95% CIs of prevalent BPH/LUTS-related outcomes by baseline history or evidence of sexually transmitted infections; Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial*.

	Self-reported history of		Serologic evidence of					History or evidence of any STIs
	Gonorrhea	Syphilis	*Chlamydia trachomatis*	*Trichomonas vaginalis*	HPV-16 or -18	HSV-2	HHV-8	CMV	
Physician diagnosis of an enlarged prostate/BPH	1.18 (1.09, 1.29)	1.20 (0.97, 1.47)	1.07 (0.81, 1.42)	1.07 (0.79, 1.44)	1.02 (0.79, 1.31)	0.95 (0.71, 1.28)	1.04 (0.73, 1.48)	0.88 (0.70, 1.11)	1.05 (0.77, 1.43)
Nocturia†	1.09 (1.02, 1.16)	1.24 (1.09, 1.43)	1.06 (0.87, 1.29)	1.36 (1.18, 1.65)	0.97 (0.80, 1.18)	1.07 (0.88, 1.30)	0.78 (0.57, 1.06)	1.10 (0.91, 1.33)	0.97 (0.76, 1.23)
BPH surgery	0.89 (0.65, 1.22)	1.44 (0.77, 2.68)	1.63 (0.84, 3.16)	0.47 (0.15, 1.52)	1.23 (0.68, 2.20)	0.63 (0.27, 1.43)	2.15 (1.04, 4.47)	1.47 (0.69, 3.13)	1.54 (0.56, 4.25)
DRE-estimated prostate volume ≥30 mL	0.93 (0.88, 0.99)	0.95 (0.84, 1.09)	1.00 (0.85, 1.17)	1.21 (1.02, 1.43)	0.91 (0.77, 1.06)	0.96 (0.82, 1.13)	0.99 (0.79, 1.25)	0.98 (0.84, 1.14)	1.08 (0.88, 1.32)
PSA > 1.4 ng/mL	0.94 (0.88, 1.00)	0.94 (0.80, 1.10)	0.97 (0.80, 1.18)	0.93 (0.74, 1.17)	0.84 (0.69, 1.02)	0.81 (0.66, 1.00)	1.14 (0.91, 1.44)	0.99 (0.84, 1.16)	0.92 (0.75, 1.12)
Evidence of LUTS and prostate enlargement	1.02 (0.95, 1.09)	1.07 (0.91, 1.26)	1.02 (0.83, 1.25)	1.32 (1.09, 1.61)	0.99 (0.81, 1.20)	0.98 (0.80, 1.21)	1.01 (0.78, 1.31)	1.00 (0.86, 1.20)	0.94 (0.75, 1.20)

*CMV, cytomegalovirus; HSV-2, herpes simplex virus type 2; HHV-8, human herpesvirus type 8; HPV, human papillomavirus; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; STI, sexually transmitted infection. *Calculated by Poisson regression with robust variance estimation and adjusted for age, race, and year of entry into PLCO and also batch or plate dates for serological diagnosis. †Waking ≥2 times/night to urinate.*

Table 3 Risk ratios and 95% CIs of incident BPH/LUTS-related outcomes by baseline history or evidence of sexually transmitted infections; Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial*.

	Self-reported history of			Serological evidence of					History or evidence of any STIs
	Gonorrhoea	Syphilis	*Chlamydia trachomatis*	*Trichomonas vaginalis*	HPV-16 or -18	HSV-2	HHV-8	CMV	
Physician diagnosis of an enlarged prostate/BPH[†]									
Excluding men with any evidence of BPH/LUTS at baseline	0.92 (0.76, 1.13)	0.37 (0.13, 1.07)	1.08 (0.59, 1.99)	0.88 (0.41, 1.90)	1.01 (0.62, 1.66)	1.36 (0.84, 2.21)	0.64 (0.30, 1.37)	0.67 (0.45, 1.00)	0.78 (0.48, 1.29)
Excluding men with the outcome of interest at baseline	1.02 (0.94, 1.11)	0.92 (0.72, 1.17)	0.76 (0.56, 1.03)	0.84 (0.61, 1.18)	0.87 (0.68, 1.12)	0.98 (0.75, 1.30)	0.87 (0.63, 1.21)	1.06 (0.86, 1.30)	1.02 (0.80, 1.30)
Nocturia[†, ‡]									
Excluding men with any evidence of BPH/LUTS at baseline	0.92 (0.75, 1.11)	1.39 (0.93, 2.10)	1.29 (0.73, 2.28)	0.99 (0.48, 2.01)	0.82 (0.45, 1.50)	0.98 (0.53, 1.81)	1.20 (0.60, 2.38)	0.93 (0.60, 1.45)	1.12 (0.63, 1.99)
Excluding men with the outcome of interest at baseline	1.05 (0.94, 1.16)	1.19 (0.91, 1.54)	0.87 (0.61, 1.24)	0.95 (0.64, 1.41)	0.78 (0.54, 1.13)	1.26 (0.92, 1.73)	1.15 (0.81, 1.65)	0.88 (0.69, 1.13)	0.93 (0.68, 1.27)
Finasteride use[†]									
Excluding men with any evidence of BPH/LUTS at baseline	1.28 (0.69, 2.38)	–	–	–	–	–	–	–	–
Excluding men with the outcome of interest at baseline	1.04 (0.79, 1.36)	1.43 (0.78, 2.63)	–	–	–	–	–	–	–
DRE-estimated prostate volume ≥30 mL[§]									
Excluding men with any evidence of BPH/LUTS at baseline	0.95 (0.85, 1.06)	1.00 (0.72, 1.38)	–	–	–	–	–	–	–
Excluding men with the outcome of interest at baseline	0.95 (0.89, 1.03)	1.18 (1.01, 1.37)	1.00 (0.84, 1.18)	0.92 (0.73, 1.15)	0.99 (0.85, 1.16)	0.94 (0.75, 1.17)	1.10 (0.92, 1.31)	0.95 (0.83, 1.08)	0.98 (0.83, 1.15)
PSA > 1.4 ng/mL[§]									
Excluding men with any evidence of BPH/LUTS at baseline	0.79 (0.63, 0.99)	0.51 (0.20, 1.27)	–	–	–	–	–	–	–
Excluding men with the outcome of interest at baseline	0.86 (0.76, 0.98)	0.95 (0.68, 1.34)	1.13 (0.77, 1.65)	1.35 (0.92, 1.99)	0.97 (0.66, 1.42)	0.99 (0.65, 1.50)	0.64 (0.34, 1.21)	0.74 (0.55, 1.01)	0.80 (0.55, 1.16)
Evidence of LUTS and prostate enlargement[†, §, ¶]									
Excluding men with any evidence of BPH/LUTS at baseline	0.86 (0.71, 1.03)	1.14 (0.73, 1.77)	–	–	–	–	–	–	–
Excluding men with the outcome of interest at baseline	0.99 (0.92, 1.07)	1.25 (1.07, 1.46)	0.95 (0.76, 1.19)	1.09 (0.85, 1.40)	0.83 (0.65, 1.05)	1.11 (0.89, 1.39)	0.86 (0.64, 1.16)	1.05 (0.88, 1.24)	1.06 (0.86, 1.31)

*CMV, cytomegalovirus; HSV-2, herpes simplex virus type 2; HHV-8, human herpesvirus type 8; HPV, human papillomavirus; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; STI, sexually transmitted infection. *Calculated by Poisson regression with robust variance estimation and adjusted for age, race, and year of entry into the PLCO trial. [†]Also adjusted for time between the baseline and supplemental questionnaires. [‡]Waking ≥2 times/night to urinate. [§]Also adjusted for number of PSA tests and time between PSA tests. [¶]Also adjusted for number of DREs and time between DREs.*

results were generally observed. The associations that did reach significance were weak and inconsistent across BPH/LUTS outcomes, suggesting that most of the STIs assessed did not contribute to BPH/LUTS development in our study population. The strengths of the present report include its examination of objective STI serological data, the large sample size with ample power to detect associations, and the high-quality prospective nature of the source data.

One novel finding was the modest association of *T. vaginalis* infection with nocturia, a large prostate volume, and the composite outcome in the prevalent analysis. Unfortunately, the incident analysis had too few events to explore this association further. Our prevalent finding for *T. vaginalis* infection is consistent with findings from a recent tissue-based study that reported a high prevalence of *T. vaginalis* DNA in prostate tissue from men who underwent TURP for BPH [12]. It is estimated that 3% of the general young adult population has *T. vaginalis* infection at any given time [23]. Studies have shown that infection can be asymptomatic in 50–75% of infected men [24]. Infection can ascend the urethra and infect the prostate epithelium, eliciting chronic inflammation [25]. *T. vaginalis* infection has been linked to prostate cancer in two recent observational studies [20,26].

Our modest prevalent findings and almost entirely null incident findings contrast with some of the previous literature [10,11,15,16]. Our results may reflect differences in exposure ascertainment, study population characteristics and case ascertainment/outcome measure or other study methodologies. Accurate exposure ascertainment is paramount when considering factors that influence outcomes in observational studies. When examining STI history and relying on patient report, recall bias may affect patient answers. This could be a criticism of older case–control studies of BPH aetiology, particularly when participants were aware that the study topic was BPH [17,27]. Similar concerns could be raised for published cross-sectional studies; however, this would be less of a concern in studies in which multiple exposures and outcomes were obtained [15,16]. We removed or attenuated recall bias by performing an incident analysis and by examining serologies, which might explain our largely null rather than positive findings. Consistent with this possibility, generally null findings were observed in the only available study that did not rely on patient self-report of STI. In that study, Sutcliffe et al. [10] evaluated the prevalence of viral STIs in male participants of the National Health and Nutrition Examination Surveys (NHANES) III using serological data [10] and observed generally null findings between serological evidence of several sexually-acquired viruses and reporting two or more LUTS in men aged ≥60 years. One incidence-based study of self-reported history of STIs and BPH reported positive associations [11], however, which may point towards other possible explanations than recall bias. For example, STI-positive participants in the present study population may differ from those in other study populations that found a positive association. The PLCO population is older and the majority is white [18]. Other research focused on black men [15] and men who have sex with men [16], had a higher prevalence of STIs, and potentially included men with more distinct episodes of each STI, which might translate into a greater risk of BPH/LUTS. Men in older studies [17] were also likely to have been infected before the introduction of antibiotics, when infections lasted for longer periods of time. While these population differences may in part explain the findings of the present study, the cohort with the demographic makeup and STI prevalence most similar to our cohort, the Health Professionals Follow-up Study, found a positive association between STIs and BPH/LUTS outcomes [11], suggesting that differences in STI experiences across study populations may not explain differences in study findings.

Another consideration is our outcome measure. Our BPH/LUTS-related outcomes focus less on LUTS than research that used the AUA Symptoms Index [11,15,16]. Potentially, STI exposure contributes less to BPH and causes LUTS through separate pathways. Similarly to the findings of the present study, serological data from NHANES III in subjects with only four LUTS showed a null STI/LUTS relationship in older ages [10]. While our available outcomes do serve as diverse surrogates for BPH, they lack the gradations found in a validated patient-reported outcome measure, such as the AUA Symptoms Index. This may lead to case misclassification and attenuation of our findings. Finally, our null results and positive associations may be explained by chance alone, particularly given the large number of hypotheses tested in our analysis.

In conclusion, in this large retrospective and prospective analysis of STIs (both self-reported and serological) and BPH/LUTS, null results were generally observed, with the possible exception of *T. vaginalis* infection. Our findings do not support associations of several known STIs with the pathogenesis of BPH/LUTS.

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Conflict of Interest

None declared.

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Abbreviations: STI, sexually transmitted infection; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; CMV, cytomegalovirus; HSV-2, herpes simplex virus type 2; HHV-8, human herpesvirus type 8; HPV, human papillomavirus; PR, prevalence ratio; RR, risk ratio.

Appendix

Table A1 Prevalence and cumulative incidence of BPH/LUTS-related outcomes in the intervention arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

	Analysis of self-reported sexually transmitted infections						Analysis of serologically detected sexually transmitted infections					
	Prevalent analysis			Incident analysis			Prevalent analysis			Incident analysis		
	No. of cases	No. of participants	Prevalence, %	No. of cases	No. of participants	Cumulative incidence, %	No. of cases	No. of participants	Prevalence, %	No. of cases	No. of participants	Cumulative incidence, %
Physician diagnosis of an enlarged prostate/BPH	7 254	32 900	22.1	1 552	5 226	29.7	276	1 144	24.1	62	165	37.6
Nocturia*	10 605	31 859	33.3	1 681	5 065	33.2	410	1 096	37.4	60	158	38.0
BPH surgery	1 041	32 900	3.2	–	–	–	48	1 144	4.2	–	–	–
Finasteride use	–	–	–	161	5 226	3.1	–	–	–	7	165	4.2
DRE-estimated prostate volume ≥30 mL	14 025	29 338	47.8	2 774	4 662	59.5	480	989	48.5	101	148	68.2
PSA > 1.4 ng/mL	12 554	31 838	39.4	1 469	5 206	28.2	451	1 096	41.2	58	165	35.2
Evidence of LUTS and prostate enlargement	10 486	32 794	32.0	1 861	5 221	35.6	414	1 136	36.4	71	165	43.0

Waking ≥2 times/night to urinate.

Table A2 Age-adjusted baseline characteristics[†] of male participants eligible for the incident analysis of BPH/LUTS-related outcomes in the intervention arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

	Self-reported history of				Serological evidence[‡] of												History or evidence of any STIs	
	Gonorrhoea		Syphilis		*Chlamydia trachomatis*		*Trichomonas vaginalis*		HPV-16 or -18		HSV-2		HHV-8		CMV			
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	270	4 956	28	5 198	21	144	14	144	40	125	22	143	19	146	112	53	134	31
Mean age, years	59.2	60.7***	59.1	60.6	62.4	62.7	61.2	62.7	63.8	62.3	63.2	62.6	62.8	62.7	63.2	61.7	62.9	61.6
Race/ethnicity, %																		
White	79.9	91.2***	93.2	90.6	73.2	87.2	57.3	87.5**	65.3	91.9***	68.8	88.0*	93.4	84.4	80.0	97.0**	82.3	99.1*
Black	11.8	1.6	0.0	2.1	26.8	12.8	42.7	12.5	34.7	8.1	31.2	12.0	6.6	15.6	20.0	3.0	17.7	0.9
Asian/Pacific Islander	7.0	5.7	7.0	5.7	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Other	1.4	1.6	0.0	1.6	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Body mass index, %																		
<25 kg/m^2	28.3	25.7	21.7	25.9	10.1	27.0	22.1	24.2	21.8	25.8	34.2	23.4	29.4	24.3	22.1	30.7*	22.1	36.6*
25–29 kg/m^2	50.0	50.3	58.2	50.3	66.0	51.5	58.0	53.4	64.5	49.8	56.1	52.9	44.5	54.5	50.5	59.3	52.1	58.7
≥30 kg/m^2	21.3	23.0	20.1	23.0	24.0	21.5	19.9	22.4	13.7	24.4	9.7	23.7	26.2	21.3	27.4	10.1	25.8	4.7
Smoking history, %																		
Never smoker	20.5	30.1***	21.1	29.7	30.1	33.8	58.9	32.5	32.1	33.7	22.8	35.0	25.2	34.4	34.3	31.2	32.8	35.5
Current cigarette smoker	16.6	10.4	20.4	10.6	8.0	9.3	12.6	8.5	13.1	7.8	9.1	9.1	1.0	10.1	11.3	4.3	9.7	6.3
Former cigarette smoker	57.6	51.3	51.4	51.7	48.7	49.1	21.5	51.4	50.1	48.8	54.8	48.2	62.5	47.3	47.9	51.5	50.1	44.7
Cigar or pipe smoker only	5.3	8.1	7.1	8.0	13.2	7.8	6.9	7.7	4.7	9.7	13.4	7.7	11.4	8.1	6.4	12.9	7.3	13.5
Current alcohol intake, g/day	22.5	17.0**	27.3	17.2	11.0	19.9	6.8	18.8	29.0	16.0	35.4	16.4*	31.1	17.1	16.5	23.3	19.2	17.0
Medical history, %																		
Hypertension	24.9	26.5	44.0	26.3*	30.2	28.9	15.2	31.2	27.5	29.6	32.1	28.6	30.5	28.9	28.2	31.1	29.2	28.6
Coronary heart disease	8.3	9.1	1.0	9.1	5.0	6.2	13.8	5.6	8.2	5.4	9.5	5.5	5.0	6.2	6.4	5.3	6.1	5.7
Stroke	1.0	1.2	0.4	1.2	0.1	1.4	0.3	1.4	0.0	1.7	0.0	1.4	0.0	1.4	1.7	0.2	1.5	0.2
Diabetes	5.5	5.4	11.1	5.3	4.0	5.7	7.4	5.5	4.3	5.8	8.7	5.0	16.4	4.0*	5.3	5.8	5.8	4.0
Arthritis	28.4	23.3	19.8	23.5	39.7	31.0	39.0	30.9	30.3	32.7	40.1	30.9	36.0	31.6	31.0	34.5	30.9	37.3

*CMV, cytomegalovirus; HSV-2, herpes simplex virus type 2; HHV-8, human herpesvirus type 8; HPV, human papillomavirus; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; STI, sexually transmitted infection. *0.01 ≤ P < 0.05. **0.001 ≤ P < 0.01. ***P < 0.001. [†]Additional covariates investigated but not presented in the table were years of entry into the PLCO trial, education, marital status, physical activity, consumption of total energy, carbohydrates, fats, polyunsaturated fats, proteins, fruit, vegetables, red meat, antioxidant nutrients (beta-carotene, selenium, vitamin A, C, and E, and zinc from the diet and supplements, and dietary alpha-carotene, beta-cryptoxanthin, lutein and zeaxanthin, and lycopene), multivitamin use, and histories of colon polyps and polyp syndromes. [‡]Measured in white and black participants only.*