Risk of erectile dysfunction associated with use of 5-α reductase inhibitors for benign prostatic hyperplasia or alopecia: population based studies using the Clinical Practice Research Datalink

Katrina Wilcox Hagberg,[1] Hozefa A Divan,[2] Rebecca Persson,[1] J Curtis Nickel,[3] Susan S Jick[1]

[1]Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Lexington, MA 02421, USA

[2]New England Research Institute, Watertown, MA, USA

[3]Kingston General Hospital, Queen's University, Kingston, Ontario, Canada

Correspondence to:
K W Hagberg khagberg@bu.edu

ABSTRACT

OBJECTIVE
To estimate the risk of erectile dysfunction in men who used 5-α reductase inhibitors to treat benign prostatic hyperplasia or alopecia.

DESIGN
Cohort studies with nested case-control analyses.

SETTING
UK Clinical Practice Research Datalink.

POPULATION
Two populations of men free of risk factors for erectile dysfunction and other sexual dysfunction or its treatment: men aged 40 or more with benign prostatic hyperplasia who received a prescription for a 5-α reductase inhibitor (finasteride or dutasteride) or α blocker, or both, and men aged 18-59 with alopecia.

EXPOSURES
In the benign prostatic hyperplasia study, exposures were classified as 5-α reductase inhibitors only, 5-α reductase inhibitors+α blockers, or α blockers only. In the alopecia study, exposures were finasteride 1 mg or no treatment.

MAIN OUTCOME MEASURES
Cases were men with a diagnosis of erectile dysfunction or treatment (procedure or prescription for a phosphodiesterase type 5 inhibitor) during follow-up. We calculated incidence rates and adjusted incidence rate ratios with 95% confidence intervals. We also conducted nested case-control analyses to control for major confounders, and calculated adjusted odds ratios with 95% confidence intervals.

RESULTS
In the population with benign prostatic hyperplasia (n=71 849), the risk of erectile dysfunction was not increased with use of 5-α reductase inhibitors only (incidence rate ratio 0.92, 95% confidence interval 0.85 to 0.99; odds ratio 0.94, 95% confidence interval 0.85 to 1.03) or 5-α reductase inhibitors+α blocker (1.09, 0.99 to 1.21, 0.92; 0.80 to 1.06) compared with α blockers only, and remained null regardless of number of prescriptions or timing of use. The risk of erectile dysfunction increased with longer duration of benign prostatic hyperplasia, regardless of exposure. For the alopecia population (n=12 346), the risk of erectile dysfunction was not increased for users of finasteride 1 mg compared with unexposed men with alopecia (1.03, 0.73 to 1.44; 0.95, 0.64 to 1.41).

CONCLUSION
5-α reductase inhibitors do not seem to significantly increase the risk of incident erectile dysfunction, regardless of indication for use. Risk of erectile dysfunction increased with longer duration of benign prostatic hyperplasia.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Erectile dysfunction and other sexual dysfunctions have been reported as adverse effects of 5-α reductase inhibitors in clinical trial settings

Benign prostatic hyperplasia, one of the indications for use of 5-α reductase inhibitors, is a risk factor for erectile dysfunction and other sexual dysfunctions

WHAT THIS STUDY ADDS

Our study results provide evidence that 5-α reductase inhibitors do not increase the risk of clinically meaningful incident erectile dysfunction or non-erectile dysfunction sexual dysfunction in men who are free of sexual dysfunction and major risk factors (eg, prostate, genital, or urinary cancers, surgical procedures), regardless of indication for use (benign prostatic hyperplasia or alopecia)

The risk of erectile dysfunction increased with longer duration of benign prostatic hyperplasia independent of exposure which should be accounted for in the design of future studies evaluating the safety of 5-α reductase inhibitors

Introduction

The 5-α reductase inhibitors finasteride (5 mg) and dutasteride (0.5 mg) are primarily used to treat benign prostatic hyperplasia, with a second indication for finasteride 1 mg to treat alopecia. Though benign prostatic hyperplasia itself is an independent risk factor for erectile dysfunction,[1] evidence suggests that 5-α reductase inhibitors may independently increase the risk of adverse sexual side effects,[2-10] potentially through induction of androgen deficiency by inhibition of 5-α reductase and reduction in available 5-α dihydrotestosterone.[11] Further, these adverse effects may be persistent or irreversible even when treatment is discontinued.[5 9-11] In addition, a recent meta-analysis of sexual adverse events from the few published clinical trials available evaluating the efficacy of finasteride 1 mg for alopecia reported that the data are limited, of poor quality, and insufficient for establishing the safety profile of the drug for alopecia treatment.[12]

Changes to the labeling of finasteride were announced by the Food and Drug Administration in 2011 and 2012 to include a list of reported sexual adverse events.[13] Of particular concern is that many reports of sexual dysfunction were in previously healthy young men using finasteride 1 mg for alopecia.[9] Increasing patient activism, including establishment of a research foundation for "post-finasteride syndrome," is indicative of growing alarm and the need for awareness and research on long term complications of 5-α reductase inhibitor use.[14] Finally, assessment of the safety of 5-α reductase inhibitors for benign prostatic hyperplasia and alopecia is warranted owing to the

large sales volume[15] and prescribing of these drugs for hair loss to otherwise healthy young men. We conducted two cohort studies with nested case-control analyses to evaluate the risk of erectile dysfunction in men who used 5-α reductase inhibitors to treat benign prostatic hyperplasia or alopecia. We also estimated the rate of non-erectile dysfunction sexual dysfunctions (ejaculatory disorder, psychosexual dysfunction, and low libido) in these populations of 5-α reductase inhibitor users.

Methods

Data source

This study was conducted using the UK Clinical Practice Research Datalink (CPRD), a large, longitudinal, population based electronic medical record database that contains data on approximately 10 million people. Participating general practitioners contribute data in an anonymous format, including medical diagnoses, lifestyle details (eg, smoking, body mass index), details of hospital stays and specialist visits, and deaths, as well as details of all drugs prescribed, including formulation and dosing instructions. Data in the CPRD are collected prospectively, and all information on diseases and prescriptions is recorded in the absence of a study hypothesis, so there is no risk of recall bias. Validation studies have indicated that the recorded data are of high accuracy, with more than 90% of information from the manual medical records present in the general practitioner's office recorded on the computer.[16 17]

Patient populations

The study period was 1 January 1992 (the year that finasteride was first available in the UK) through 31 December 2011. We limited the end of the study period to 31 December 2011 owing to changes in the indication for use of phosphodiesterase type 5 inhibitors (drugs indicated for the treatment of erectile dysfunction, which were approved for the treatment of benign prostatic hyperplasia in 2012) and changes in the UK Quality and Outcomes Framework (which prompts all general practitioners to document whether they have asked all men with diabetes about potential erectile dysfunction).

We identified all men in the CPRD who had a prescription for either a 5-α reductase inhibitor (finasteride or dutasteride) or an α blocker (alfuzosin, doxadosin, indoramin, prazosin, tamsulosin, and terazosin), or both, plus a diagnosis of benign prostatic hyperplasia or prostatism recorded at any time prior to the first prescription date through three months after (to allow time for general practitioners to record diagnoses made by specialists). During the study period, α blockers were the only available alternative pharmaceutical treatment for benign prostatic hyperplasia, thus we chose them as an active comparator to ensure that all men included in the study population had benign prostatic hyperplasia severe enough to require treatment. α blockers are also indicated for hypertension; therefore to be included users were required to have a diagnosis of benign prostatic hyperplasia or prostatism. We defined the date of cohort entry as the date of the first prescription for a 5-α

reductase inhibitor or α blocker in the patient's record. The study population was restricted to men who were aged 40 years or older and who had at least three years of history before the cohort entry date. A three year requirement was selected to ensure that men were free from sexual dysfunction before cohort entry and were new users of a study drug. These men (n=71 849) comprised the population with benign prostatic hyperplasia (fig 1).

We then separately identified all men in the CPRD who had a diagnosis of alopecia (male pattern baldness) between 1 January 2002 (the first year finasteride was prescribed for alopecia) and 31 December 2011, were aged 18-59, and had at least one year of history in their record before cohort entry. We defined the date of cohort entry as 1 January 2002 (the start of the study period), the date of the first alopecia diagnosis occurring after 1 January 2002, or the date of the first prescription for finasteride 1 mg where the prescription was recorded before the alopecia diagnosis. We required only one year of history for this analysis because young men have shorter records in the CPRD, and because there is less concern that patients in this age group have a history of sexual dysfunction or finasteride prescriptions prior to cohort entry. These men (n=12 346) comprised the population with alopecia (fig 2).

Men with prostate, genital, or urinary cancer, prostatectomy or orchidectomy, history of erectile dysfunction diagnosis or treatment (eg, procedures or drugs used to treat erectile dysfunction), other sexual dysfunctions (eg, ejaculatory disorder, psychosexual dysfunction, low libido), or Peyronie's disease before cohort entry, or Klinefelter's syndrome recorded at any time were
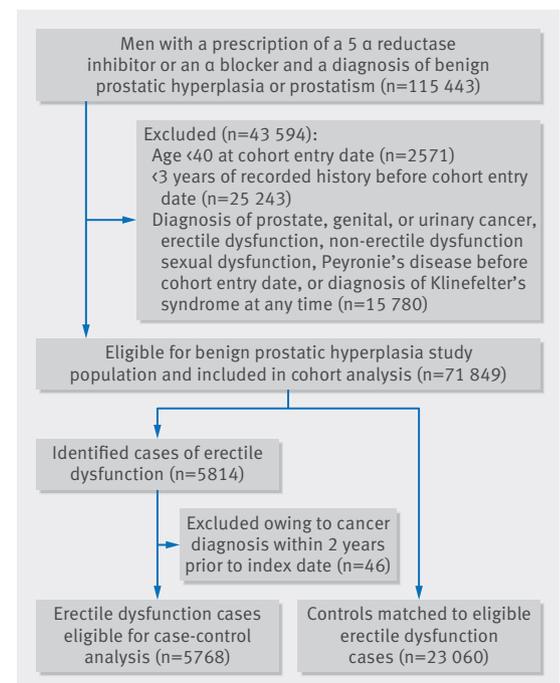

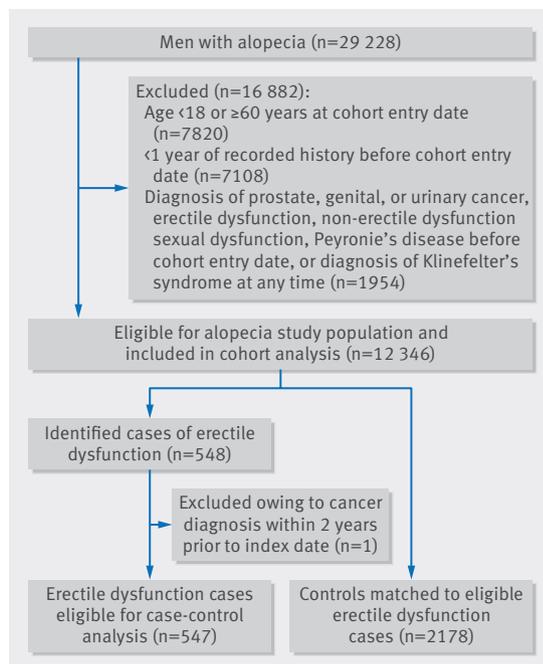Fig 1 | Flowchart for population with benign prostatic hyperplasia

Fig 2 | Flowchart for population with alopecia

excluded from both the benign prostatic hyperplasia and the alopecia study populations.

Exposure definition

Using the recorded prescribing details, we calculated the duration of each prescription for 5-α reductase inhibitors as the quantity of pills divided by the number of pills prescribed each day. For the benign prostatic hyperplasia population, person days of exposure were accrued in the following categories: 5-α reductase inhibitors only, 5-α reductase inhibitors plus α blockers, and α blockers only, as well as by timing of use, categorized as current (period of filled use plus 30 days), recent (days 31-90 after the end of current use), past (days 91-180 after the end of current use), and distant past use (the number of days after the end of past use). We considered men in the alopecia population to be unexposed until they received a prescription for finasteride 1 mg. Person days of finasteride 1 mg use were accrued and categorized as current (period of filled use plus 30 days), recent (days 31-90 after the end of current use), or past use (all days after the end of recent use). The censor date in both populations was the first of the following: end of record, death, or record of prostate, urinary, genital, pituitary, or adrenal cancers, prostatectomy, orchidectomy, end of study period (31 December 2011), date of being aged 60 years (for those in the alopecia population only), or date of being a case.

Case identification

Cases of erectile dysfunction were men with one or more of the following recorded during follow-up: diagnosis of erectile dysfunction or impotence, prescription for a phosphodiesterase type 5 inhibitor (eg, sildenafil, tadalafil, or vardenafil) where the strength and quantity prescribed was indicated for treatment of erectile dysfunction, or record of procedures for treatment of erectile dysfunction (eg, penile prosthesis, penile injection, or other operations for treatment of erectile dysfunction). We defined the erectile dysfunction index date—the date that the man was identified as a case—as the earliest date of diagnosis, date of prescription for a phosphodiesterase type 5 inhibitor, or date of procedure for erectile dysfunction.

We also identified men with a diagnosis of a non-erectile dysfunction sexual dysfunction (ejaculatory disorder, psychosexual dysfunction, or low libido) recorded during follow-up to assess the rate of these outcomes. In studies on the non-erectile dysfunction sexual dysfunction cohort, the index date was the date that the man was given a diagnosis of ejaculatory disorder, psychosexual dysfunction, or low libido, whichever came first.

Matching criteria for nested case-control analyses

Using the cases of erectile dysfunction identified in the cohort analyses, we conducted nested case-control analyses to control for age, calendar time, and risk factors for erectile dysfunction. We further excluded cases with a diagnosis of cancer (other than non-melanoma skin cancer) within two years before the index date because cancer and its treatment may be associated with the development of erectile dysfunction (n=46 in the population with benign prostatic hyperplasia, n=1 in the alopecia population). For each eligible case, we used risk set sampling to match up to four controls from the population on year of birth (within two years), general practice attended, index date (the same index date as the matched case), and year the patient started in the database (within two years). Controls were required to be present in the study population on the index date (that is, the index date had to fall between the candidate control's cohort entry date and censor date) and must not have had a diagnosis of or treatment for erectile dysfunction before the index date, or have had a diagnosis of any cancer (other than non-melanoma skin cancer) within two years prior to the index date. For the benign prostatic hyperplasia case-control match, 5762 erectile dysfunction cases had four matched controls each, whereas one case was matched to three controls, three cases were matched to two controls, and one case was matched to one control. For the alopecia case-control match, 539 of the cases had four matched controls each, whereas four cases were matched to three controls and three cases were matched to two controls.

Covariates of interest

We assessed the presence of covariates of interest at the cohort entry date (cohort studies) and the index date (case-control analyses). Covariates of interest in this study included known or suspected risk factors for erectile dysfunction and non-erectile dysfunction sexual dysfunctions: age, calendar time, body mass index (<18.5, 18.5-24.9, 25-29.9, ≥30, unknown), smoking status (never, smoker, former smoker, unknown), non-erectile dysfunction sexual dysfunction (eg, ejaculatory disorders, psychosexual dysfunction, low libido), Peyronie's disease, diabetes, hypertension, cardiovascular

disease, atherosclerosis or coronary heart disease, kidney failure or dialysis, cancer, depression, alcohol misuse, and drug misuse. We also identified patients who received prescriptions for β blockers, which have been associated with erectile dysfunction, within six months prior to the cohort entry date and index date. We classified each patient in the benign prostatic hyperplasia population by whether they switched between study drugs (α blockers and 5-α reductase inhibitors) during follow-up. We also evaluated the duration of benign prostatic hyperplasia (<6 months, 6 months-1 year, 1-2 years, 2-5 years, ≥5 years).

Statistical analyses

For the benign prostatic hyperplasia cohort analysis, we calculated incidence rates of erectile dysfunction and incidence rate ratios with 95% confidence intervals for each exposure category, by age, calendar year, and timing of use (current, recent, past, or distant past). In the benign prostatic hyperplasia nested case-control analysis, we used conditional logistic regression to calculate crude odds ratios and 95% confidence intervals, as well as odds ratios adjusted for body mass index, smoking status, non-erectile dysfunction sexual dysfunctions, Peyronie's disease, hypertension, diabetes, hyperlipidemia, depression, orchitis, alcohol misuse, switching status, and duration of benign prostatic hyperplasia, to estimate the risk of erectile dysfunction in users of 5-α reductase inhibitors only and 5-α reductase inhibitors+α blockers compared with use of α blockers only. Odds ratios approximate the incidence rate ratio through the use of risk set sampling.

For the alopecia cohort analysis, we calculated incidence rates of erectile dysfunction and incidence rate ratios with 95% confidence intervals for unexposed men and for users of finasteride 1 mg, by age, calendar year, and timing of finasteride 1 mg use (current, recent, and past). In the alopecia nested case-control analysis, we used conditional logistic regression to calculated crude odds ratios and 95% confidence intervals, as well as odds ratios adjusted for body mass index, smoking status, duration of benign prostatic hyperplasia, non-erectile dysfunction sexual dysfunctions, hypertension, diabetes, hyperlipidemia, cardiovascular disease, liver disease, depression, alcohol misuse, drug misuse, and receipt of a β blocker prescription within six months prior to the index date, to estimate the risk of erectile dysfunction in users of finasteride 1 mg for alopecia compared with unexposed men with alopecia. In both the benign prostatic hyperplasia and the alopecia nested case-control analyses, we stratified the case-control results by age group to assess effect modification. We also assessed the potential for misclassification of cases with erectile dysfunction in sensitivity analyses restricted to the cases with codes that supported the erectile dysfunction diagnosis, including the presence of multiple erectile dysfunction diagnoses or prescriptions for phosphodiesterase type 5 inhibitors, surgical procedures, or referrals to specialty care, and their matched controls. Finally, we calculated incidence rates of non-erectile dysfunction sexual dysfunctions

and incidence rate ratios with 95% confidence intervals for both the benign prostatic hyperplasia population and the alopecia population. We did not conduct a nested case-control study for those outcomes owing to the low number of non-erectile dysfunction sexual dysfunction cases identified. All statistical analyses for this study were conducted using SAS statistical software version 9.3 (SAS Institute, Cary, NC).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

Erectile dysfunction in the benign prostatic hyperplasia population

Overall, 71 849 men with benign prostatic hyperplasia were eligible for inclusion; at cohort entry, 8977 received a prescription for 5-α reductase inhibitors only, 2592 for 5-α reductase inhibitors+α blockers, and 60 280 for α blockers only (table 1). At cohort entry, users of 5-α reductase inhibitors only and 5-α reductase inhibitors+α blockers were older and more likely to switch between study drugs during follow-up compared with users of α blockers only. Users of 5-α reductase inhibitors+α blockers had more comorbidities compared with users of 5-α reductase inhibitors only and α blockers only.

We identified 5814 cases of erectile dysfunction, of whom 5022 (86.4%) had a diagnosis of erectile dysfunction or impotence and 792 (13.6%) were identified based on prescriptions for a phosphodiesterase type 5 inhibitor. The incidence rate of erectile dysfunction was lowest among users of 5-α reductase inhibitors only (15.3 per 1000 person years, 95% confidence interval 14.3 to 16.5), and similar among users of 5-α reductase inhibitors+α blockers (19.2 per 1000 person years, 17.4 to 21.1) and α blockers only (20.1 per 1000 person years, 19.6 to 20.7). Compared with users of α blockers only, the adjusted incidence rate ratios for users of 5-α reductase inhibitors only and 5-α reductase inhibitors+α blockers were 0.92 (95% confidence interval 0.85 to 0.99) and 1.09 (0.99 to 1.21), respectively (table 2).

In the nested case-control analysis, cases of erectile dysfunction were more likely than matched controls to be overweight or obese (as measured by body mass index) or to have a diagnosis of non-erectile dysfunction sexual dysfunction, hypertension, diabetes, hyperlipidemia, depression, orchitis, or alcohol misuse before the index date. Cases also had longer duration of benign prostatic hyperplasia compared with controls and were more likely to switch between study drugs at some time before the index date (table 3). There was no effect on the risk of erectile dysfunction from use of 5-α reductase inhibitors only (adjusted odds ratio 0.94, 95% confidence interval 0.85 to 1.03) or 5-α reductase inhibitors+α blockers (0.92, 0.80 to 1.06) compared with α

Table 1 | Characteristics of benign prostatic hyperplasia population. Values are numbers (percentages) unless stated otherwise

| Characteristics | Total (n=71849) | Exposure on cohort entry date | | | P value |
		α blockers only (n=60 280)	5-α reductase inhibitors only (n=8977)	5-α reductase inhibitors+α blockers (n=2592)	
Age at cohort entry (years):					
40-49	3588 (5.0)	3400 (5.6)	161 (1.8)	27 (1.0)	
50-59	12 288 (17.1)	11 057 (18.3)	980 (10.9)	251 (9.7)	
60-69	22 228 (30.9)	18 883 (31.3)	2590 (28.8)	755 (29.1)	
70-79	22 125 (30.8)	17 989 (29.8)	3224 (35.9)	912 (35.2)	<0.001
80-89	10 538 (14.7)	8127 (13.5)	1829 (20.4)	582 (22.5)	
≥90	1082 (1.5)	824 (1.4)	193 (2.2)	65 (2.5)	
Year of cohort entry:					
1992-94	3110 (4.3)	1995 (3.3)	1068 (11.9)	47 (1.8)	
1995-99	12 213 (17.0)	9772 (16.2)	2286 (25.5)	155 (6.0)	
2000-04	21 967 (30.6)	19 196 (31.8)	2356 (26.2)	415 (16.0)	<0.001
2005-09	23 979 (33.4)	20 126 (33.4)	2516 (28.0)	1337 (51.6)	
2010-11	10 580 (14.7)	9191 (15.3)	751 (8.4)	638 (24.6)	
Body mass index at cohort entry:					
<18.5	796 (1.1)	639 (1.1)	122 (1.4)	35 (1.4)	
18.5-24.9	22 395 (31.2)	18 571 (30.8)	2985 (33.3)	836 (32.3)	
25-29.9	29 717 (41.4)	24 994 (41.5)	3631 (40.5)	1092 (42.1)	<0.001
≥30	13 689 (19.1)	11 797 (19.6)	1425 (15.9)	467 (18.0)	
Unknown	5255 (7.3)	4279 (7.1)	814 (9.1)	162 (6.3)	
Smoking status at cohort entry:					
Non-smoker	29 757 (41.4)	24 829 (41.2)	3951 (44.0)	977 (37.7)	
Smoker	10 444 (14.5)	8874 (14.7)	1222 (13.6)	348 (13.4)	<0.001
Former smoker	26 631 (37.1)	22 452 (37.3)	3011 (33.5)	1168 (45.1)	
Unknown	5017 (7.0)	4125 (6.8)	793 (8.8)	99 (3.8)	
Comorbidities at cohort entry*:					
Lower urinary tract symptoms	43 948 (61.2)	37 496 (62.2)	4740 (52.8)	1712 (66.1)	<0.001
Hypertension	25 506 (35.5)	21 383 (35.5)	3095 (34.5)	1028 (39.7)	<0.001
Diabetes	7141 (9.9)	5963 (9.9)	869 (9.7)	309 (11.9)	0.002
Hyperlipidemia	11 200 (15.6)	9494 (15.8)	1230 (13.7)	476 (18.4)	<0.001
Cardiovascular disease	21 810 (30.4)	17 544 (29.1)	3356 (37.4)	910 (35.1)	<0.001
Atherosclerosis	1431 (2.0)	1166 (1.9)	207 (2.3)	58 (2.2)	0.04
Metabolic syndrome	13 (0.0)	11 (0.0)	1 (0.0)	1 (0.0)	Not calculated
Kidney failure/dialysis	4242 (5.9)	3399 (5.6)	564 (6.3)	279 (10.8)	<0.001
Cancer	2922 (4.1)	2431 (4.0)	357 (4.0)	134 (5.2)	0.01
Depression	6926 (9.6)	5956 (9.9)	758 (8.4)	212 (8.2)	<0.001
Alcohol misuse	2628 (3.7)	2263 (3.8)	270 (3.0)	95 (3.7)	0.002
Drug misuse	455 (0.6)	389 (0.7)	52 (0.6)	14 (0.5)	0.63
β blocker prescription within 6 months prior to cohort entry date	12 284 (17.1)	10 149 (16.8)	1626 (18.1)	509 (19.6)	<0.001
Switch between or add 5-α reductase inhibitors or α blockers during follow-up†	15 172 (21.1)	11 153 (18.5)	2695 (30.0)	1324 (51.1)	<0.001

*Not mutually exclusive.
†Switching defined as change during follow-up in prescribed study drugs (that is, differed from drug prescribed at cohort entry).

blockers only (table 4). The results remained null regardless of number of prescriptions received or timing of use. To assess effect modification we stratified the estimates by switching status and duration of benign prostatic hyperplasia. The risk of erectile dysfunction was higher for switchers than for non-switchers, independent of exposure. Risk of erectile dysfunction also increased with longer duration of benign prostatic hyperplasia, independent of exposure (table 4). Compared with users of α blockers only with duration of benign prostatic hyperplasia of less than six months, the risk of erectile dysfunction for men with a duration of six months to one year was 1.15 (95% confidence interval 1.01 to 1.32) for users of α blockers only and 1.20 (0.93 to 1.56) for users of 5-α reductase inhibitors only, which increased to 2.80 (2.50 to 3.13) and 2.54 (2.13 to 3.03) for users of α blockers only and 5-α reductase

inhibitors only, respectively, with duration of benign prostatic hyperplasia for five or more years. The pattern was similar for users of 5-α reductase inhibitors+α blockers. Finally, we assessed effect modification by diabetes status by stratifying on the presence or absence of diabetes before the index date. The reference in this analysis was users of α blockers only with no diabetes. The increase in risk of erectile dysfunction was present among men with diabetes, whereas the risk was null for men without diabetes, regardless of exposure to α blockers only, 5-α reductase inhibitors only, or 5-α reductase inhibitors+α blockers (table 4).

When we stratified by age to evaluate effect modification, the risk of erectile dysfunction was similar to that of the main analysis, regardless of age group. Among cases and controls aged 40-69 years, the adjusted odds ratio was 0.94 (95% confidence interval 0.82 to 1.06) for

Table 2 | Incidence rates (IR) and incidence rate ratios (IRR) for erectile dysfunction by exposure in cohort with benign prostatic hyperplasia

Variables	α blockers only				5-α reductase inhibitors only				5-α reductase inhibitors+α blockers			
	Cases (n=4665)	Person years	IR/1000 person years (95% CI)	IRR (95% CI)	Cases (n=727)	Person years	IR/1000 person years (95% CI)	IRR (95% CI)	Cases (n=422)	Person years	IR/1000 person years (95% CI)	IRR (95% CI)
Age group (years):												
40-59	1292	45713	28.3 (26.7 to 29.8)		111	4224	26.3 (21.6 to 31.6)		64	1481	43.2 (22.2 to 55.2)	
60-79	3211	143000	22.5 (21.7 to 23.2)		570	29673	19.2 (17.7 to 20.9)		335	13920	24.1 (21.6 to 26.8)	
>80	162	43012	3.8 (3.2 to 4.4)		46	13472	3.4 (2.5 to 4.6)		23	6606	3.5 (2.2 to 5.2)	
Calendar time:												
1992-95	9	1596	5.6 (2.6 to 10.7)		10	912	11.0 (5.2 to 20.2)		0	50	0.0 (0.0 to 72.7)	
1995-99	299	21940	13.6 (12.1 to 15.3)		90	8396	10.7 (8.6 to 13.2)		10	605	16.5 (7.9 to 30.4)	
2000-04	1590	66291	24.0 (22.8 to 25.2)		214	12402	17.3 (15.0 to 19.7)		63	2702	23.3 (17.9 to 29.8)	
2005-09	1933	97785	19.8 (18.9 to 20.7)		299	17941	16.7 (14.8 to 18.7)		230	11317	20.3 (17.8 to 23.1)	
2010-11	834	44113	18.9 (17.6 to 20.2)		114	7718	14.8 (12.2 to 17.7)		119	7333	16.2 (13.4 to 19.4)	
Timing of use:												
Current	2496	124099	20.1 (19.3 to 20.9)	1.0 (ref)	421	28425	14.8 (13.4 to 16.3)		403	20844	19.3 (17.5 to 21.3)	
Recent	327	13619	24.0 (21.5 to 26.8)		47	2547	18.5 (13.6 to 24.5)		5	278	18.0 (5.8 to 42.0)	
Past	138	5752	24.0 (20.2 to 28.3)		13	999	13.0 (6.9 to 22.3)		3	91	33.1 (6.7 to 96.8)	
Distant past	1704	88255	19.3 (17.5 to 21.3)		246	15398	16.0 (14.0 to 18.1)		11	796	13.8 (6.9 to 24.7)	
Total:												
Crude	4665	231724	20.1 (19.6 to 20.7)	1.0 (ref)	727	47369	15.3 (14.3 to 16.5)	0.76 (0.71 to 0.82)	422	22008	19.2 (17.4 to 21.1)	0.95 (0.86 to 1.05)
Adjusted*				1.0 (ref)				0.92* (0.85 to 0.99)				1.09* (0.99 to 1.21)

*Adjusted for age group, calendar time, and timing of use.

users of 5-α reductase inhibitors only and 0.96 (0.80 to 1.16) for users of 5-α reductase inhibitors+α blockers, whereas among cases and controls aged 70 years or older, the adjusted odds ratio was 0.89 (0.77 to 1.05) for users of 5-α reductase inhibitors only and 0.82 (0.65 to 1.03) for users of 5-α reductase inhibitors+α blockers. The results were also not materially different from the main analysis when we conducted the sensitivity analysis restricted to the erectile dysfunction cases who had additional codes that supported the erectile dysfunction diagnosis (n=4960, 86%) and their matched controls (adjusted odds ratio 0.89 (95% confidence interval 0.80 to 1.00) for 5-α reductase inhibitors only and 0.85 (0.73 to 1.00) for 5-α reductase inhibitors+α blockers, compared with α blockers only).

Erectile dysfunction in the alopecia population

We identified 12 346 men with alopecia who were eligible for inclusion in the alopecia population, of whom 463 received a prescription for finasteride 1 mg at cohort entry (n=868 of the alopecia population who used finasteride 1 mg at some time during follow-up) and 11 883 were unexposed at cohort entry (table 5). At cohort entry, users of finasteride 1 mg for alopecia were younger and more likely to have depression or to have received a prescription for β blockers within the prior six months, whereas unexposed men with alopecia had more diagnoses of lower urinary tract symptoms. We identified 547 cases of erectile dysfunction, of whom 491 (89.8%) had a diagnosis of erectile dysfunction or impotence and 56 (10.2%) were identified based on prescriptions for a phosphodiesterase type 5 inhibitor. The incidence rates of erectile dysfunction were similar for users of finasteride 1 mg (10.1 per 1000 person years (95% confidence interval 7.0 to 13.9) and unexposed men (9.8 per 1000 person years, 8.9 to 10.7) (table 6). The incidence rate ratio, adjusted for age and calendar time, was 1.13 (95% confidence interval 0.80 to 1.58) for users of finasteride 1 mg compared with unexposed men with alopecia (table 6).

In the nested case-control analysis, cases of erectile dysfunction were more likely than matched controls to be overweight or obese, be former smokers, or have non-erectile dysfunction sexual dysfunction, hypertension, diabetes, hyperlipidemia, cardiovascular disease, liver disease, depression, and alcohol and drug misuse before the index date (table 7). The adjusted odds ratio for erectile dysfunction was 0.94 (95% confidence interval 0.64 to 1.40) for users of finasteride 1 mg compared with unexposed men (table 8). The risk of erectile dysfunction increased with increasing number of finasteride 1 mg prescriptions, from 0.69 (95% confidence interval 0.33 to 1.40) for one prescription to 1.43 (0.71 to 2.90) for 10 or more prescriptions, but none of the odds ratios were statistically significant. The risk of erectile dysfunction was null, regardless of timing of use or time since the last prescription (table 8). When we stratified by age to evaluate effect modification, the risk of erectile dysfunction in users of finasteride 1 mg was higher in men aged 40-59 years (adjusted odds ratio 1.45, 95% confidence interval 0.87 to 2.44) than in men aged 18-39

Table 3 | Nested case-control analysis: characteristics of cases with erectile dysfunction and controls in benign prostatic hyperplasia population. Values are numbers (percentages) unless stated otherwise

Characteristics	Cases (n=5768)	Controls (n=23060)	Univariate odds ratio (95% CI)
Age at erectile dysfunction index date (years):			
40-49	221 (3.8)	928 (4.0)	-
50-59	1232 (21.4)	4730 (20.5)	-
60-69	2557 (44.3)	9895 (42.9)	-
70-79	1528 (26.5)	6470 (28.1)	-
80-89	226 (3.9)	1015 (4.4)	-
≥90	4 (0.1)	22 (0.1)	-
Mean (SD)	65.0 (8.5)	65.4 (8.6)	
Erectile dysfunction index year:			
1992-95	19 (0.3)	71 (0.3)	-
1995-99	396 (6.9)	1582 (6.9)	-
2000-04	1854 (32.1)	7413 (32.2)	-
2005-09	2447 (42.2)	9786 (42.4)	-
2010-11	1052 (18.2)	4208 (18.3)	-
Mean (SD) length of record before erectile dysfunction index date (years)	13.2 (4.5)	13.2 (4.5)	-
Body mass index at erectile dysfunction index date:			
<18.5	20 (0.4)	215 (0.9)	0.44 (0.28 to 0.70)
18.5-24.9	1392 (24.1)	6561 (28.5)	1.0 (ref)
25-29.9	2688 (46.6)	9885 (42.9)	1.29 (1.20 to 1.39)
≥30	1481 (25.7)	5163 (22.4)	1.37 (1.26 to 1.49)
Unknown	187 (3.2)	1236 (5.4)	0.71 (0.60 to 0.84)
Mean (SD)	27.9 (4.5)	27.4 (4.6)	
Smoking status at erectile dysfunction index date:			
Non-smoker	2215 (38.4)	9568 (41.5)	1.0 (ref)
Smoker	803 (13.9)	3424 (14.9)	1.01 (0.92 to 1.10)
Former smoker	2582 (44.8)	9191 (39.9)	1.24 (1.16 to 1.32)
Unknown	168 (2.9)	877 (3.8)	0.80 (0.67 to 0.95)
Duration of benign prostatic dysfunction at erectile dysfunction index date:			
<6 months	703 (12.2)	4687 (20.3)	1.0 (ref)
6 months-1 year	549 (9.5)	3269 (14.2)	1.13 (1.00 to 1.28)
1-2 years	870 (15.1)	4233 (18.4)	1.42 (1.27 to 1.58)
2-5 years	1773 (30.7)	5842 (25.3)	2.20 (1.99 to 2.42)
≥5 years	1873 (32.5)	5029 (21.8)	2.87 (2.59 to 3.17)
Mean (SD)	4.2 (4.1)	3.2 (3.8)	
Comorbidities at erectile dysfunction index date:			
Lower urinary tract symptoms	4066 (70.5)	16645 (72.2)	0.92 (0.86 to 0.98)
Non-erectile dysfunction sexual dysfunction*	72 (1.3)	52 (0.2)	5.61 (3.92 to 8.03)
Peyronie's disease	24 (0.4)	34 (0.2)	2.82 (1.67 to 4.76)
Hypertension	2308 (40.0)	8486 (36.8)	1.15 (1.09 to 1.22)
Diabetes	958 (16.6)	2374 (10.3)	1.75 (1.61 to 1.90)
Hyperlipidemia	1232 (21.4)	4474 (19.4)	1.14 (1.06 to 1.22)
Cardiovascular disease	1583 (27.4)	6580 (28.5)	0.94 (0.88 to 1.01)
Atherosclerosis	119 (2.1)	537 (2.3)	0.88 (0.72 to 1.08)
Metabolic syndrome	3 (0.1)	9 (0.0)	1.33 (0.36 to 4.93)
Kidney failure/dialysis	326 (5.7)	1447 (6.3)	0.88 (0.78 to 1.01)
Cancer	201 (3.5)	775 (3.4)	1.04 (0.89 to 1.22)
Depression	869 (15.1)	2854 (12.4)	1.27 (1.16 to 1.38)
Alcohol misuse	296 (5.1)	997 (4.3)	1.20 (1.05 to 1.37)
Drug misuse	50 (0.9)	167 (0.7)	1.20 (0.87 to 1.65)
Orchitis	387 (6.7)	1364 (5.9)	1.15 (1.02 to 1.29)
β blocker prescription within 6 months prior to index date	1043 (18.1)	4209 (18.3)	0.99 (0.92 to 1.07)
Switching between or adding study drug	897 (15.6)	2750 (11.9)	1.38 (1.27 to 1.50)

*Non-erectile dysfunction sexual dysfunction includes ejaculatory disorders, psychosexual dysfunction, and low libido.

years (0.50, 0.26 to 0.98), although the difference in risk by age was not statistically significant.

Since men with alopecia who were prescribed finasteride 1 mg were generally healthier and had fewer risk factors for erectile dysfunction than men with alopecia not taking finasteride 1 mg, we conducted additional analyses to determine whether the null results could be explained by differences in the baseline health status of the two groups. We first restricted the analysis to cases and controls who did not have risk factors for erectile dysfunction (benign prostatic hyperplasia, non-erectile dysfunction sexual dysfunction, Peyronie's disease, or

Table 4 | Nested case-control analysis: risk of erectile dysfunction by exposure in benign prostatic hyperplasia population

Exposure at index date	Cases (n=5768)	Controls (n=23 060)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Exposure				
α blockers only:	4624 (80.2)	18 699 (81.1)	1.0 (ref)	1.0 (ref)
5-α reductase inhibitors only:	723 (12.5)	2844 (12.3)	1.03 (0.94 to 1.13)	0.94 (0.85 to 1.03)
Finasteride	623 (10.8)	2455 (10.7)	1.03 (0.93 to 1.13)	0.93 (0.83 to 1.03)
Dutasteride	100 (1.7)	389 (1.7)	1.05 (0.84 to 1.31)	1.01 (0.80 to 1.28)
5-α reductase inhibitors+α blockers:	421 (7.3)	1517 (6.6)	1.13 (1.01 to 1.27)	0.92 (0.80 to 1.06)
Finasteride	329 (5.7)	1143 (5.0)	1.17 (1.03 to 1.33)	0.94 (0.81 to 1.10)
Dutasteride	92 (1.6)	374 (1.6)	1.00 (0.79 to 1.26)	0.85 (0.67 to 1.10)
No of prescriptions				
α blockers only:				
1 prescription	1005 (17.4)	4688 (20.3)	1.0 (ref)	1.0 (ref)
2-9 prescriptions	1818 (31.5)	8315 (36.1)	1.03 (0.94 to 1.12)	1.00 (0.92 to 1.09)
10-19 prescriptions	747 (13.0)	2683 (11.6)	1.33 (1.20 to 1.48)	1.10 (0.98 to 1.23)
20-29 prescriptions	400 (6.9)	1180 (5.1)	1.64 (1.43 to 1.87)	1.21 (1.05 to 1.39)
≥30 prescriptions	654 (11.3)	1833 (8.0)	1.79 (1.59 to 2.02)	1.09 (0.97 to 1.24)
5-α reductase inhibitors only:				
1 prescription	100 (1.7)	465 (2.0)	1.01 (0.80 to 1.26)	0.96 (0.76 to 1.21)
2-9 prescriptions	348 (6.0)	1283 (5.6)	1.29 (1.13 to 1.48)	1.14 (0.99 to 1.32)
10-19 prescriptions	125 (2.2)	496 (2.2)	1.22 (0.99 to 1.51)	0.89 (0.72 to 1.12)
20-29 prescriptions	63 (1.1)	234 (1.0)	1.34 (1.01 to 1.80)	0.87 (0.65 to 1.18)
≥30 prescriptions	87 (1.5)	366 (1.6)	1.20 (0.94 to 1.54)	0.71 (0.55 to 0.92)
5-α reductase inhibitors+α blockers:				
1 prescription	41 (0.7)	193 (0.8)	1.01 (0.72 to 1.44)	0.96 (0.67 to 1.38)
2-9 prescriptions	167 (2.9)	735 (3.2)	1.10 (0.92 to 1.32)	0.89 (0.72 to 1.09)
10-19 prescriptions	85 (1.5)	289 (1.3)	1.46 (1.13 to 1.88)	0.92 (0.69 to 1.21)
20-29 prescriptions	52 (0.9)	114 (0.5)	2.28 (1.62 to 3.20)	1.27 (0.89 to 1.82)
≥30 prescriptions	76 (1.3)	186 (0.8)	2.11 (1.60 to 2.80)	1.06 (0.79 to 1.43)
Timing of use				
α blockers only:				
Current	2480 (43.0)	11 015 (47.8)	1.0 (ref)	1.0 (ref)
Recent	321 (5.6)	1575 (6.8)	0.91 (0.80 to 1.03)	1.01 (0.89 to 1.15)
Past	134 (2.3)	639 (2.8)	0.94 (0.77 to 1.13)	1.07 (0.88 to 1.30)
Distant past	1689 (7.0)	5470 (23.7)	1.39 (1.29 to 1.49)	1.15 (1.06 to 1.24)
5-α reductase inhibitors only:				
Current	419 (7.3)	1820 (7.9)	1.02 (0.91 to 1.15)	0.93 (0.82 to 1.05)
Recent	47 (0.8)	175 (0.8)	1.20 (0.86 to 1.66)	1.13 (0.81 to 1.58)
Past	13 (0.2)	74 (0.3)	0.78 (0.43 to 1.40)	0.79 (0.43 to 1.45)
Distant past	244 (4.2)	775 (3.4)	1.42 (1.21 to 1.65)	1.07 (0.92 to 1.26)
5-α reductase inhibitors+α blockers:				
Current	402 (7.0)	1446 (6.3)	1.24 (1.10 to 1.40)	0.95 (0.82 to 1.10)
Recent	5 (0.1)	32 (0.1)	0.68 (0.26 to 1.74)	0.61 (0.24 to 1.60)
Past	3 (0.1)	7 (0.0)	1.98 (0.51 to 7.66)	†
Distant past	11 (0.2)	32 (0.1)	1.53 (0.77 to 3.04)	1.08 (0.53 to 2.19)
Stratified by switching status				
α blockers only:				
Non-switcher	4353 (75.5)	17 948 (77.8)	1.0 (ref)	1.0 (ref)
Switcher	271 (4.7)	751 (3.3)	1.51 (1.31 to 1.74)	1.26 (1.09 to 1.46)
5-α reductase inhibitors only:				
Non-switcher	456 (7.9)	1963 (8.5)	0.96 (0.86 to 1.08)	0.96 (0.85 to 1.07)
Switcher	267 (4.6)	881 (3.8)	1.27 (1.10 to 1.46)	1.15 (0.99 to 1.33)
5-α reductase inhibitors+α blockers:				
Non-switcher	62 (1.1)	399 (1.7)	0.65 (0.49 to 0.85)	0.76 (0.57 to 1.00)
Switcher	359 (6.2)	1118 (4.9)	1.34 (1.18 to 1.52)	1.22 (1.07 to 1.39)
Stratified by duration of benign prostatic hyperplasia				
α blockers only:				
<6 months	593 (10.3)	3975 (17.2)	1.0 (ref)	1.0 (ref)
6 months-1 year	457 (7.9)	2669 (11.6)	1.16 (1.01 to 1.32)	1.15 (1.01 to 1.32)
1-2 years	702 (12.2)	3466 (15.0)	1.40 (1.24 to 1.58)	1.39 (1.23 to 1.56)
2-5 years	1426 (24.7)	4706 (20.4)	2.19 (1.97 to 2.44)	2.16 (1.93 to 2.40)
≥5 years	1446 (25.1)	3883 (16.8)	2.88 (2.56 to 3.21)	2.80 (2.50 to 3.13)

(Continued)

Table 4 | Nested case-control analysis: risk of erectile dysfunction by exposure in benign prostatic hyperplasia population

Exposure at index date	Cases (n=5768)	Controls (n=23 060)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
5-α reductase inhibitors only:				
<6 months	78 (1.4)	439 (1.9)	1.20 (0.93 to 1.55)	1.20 (0.93 to 1.56)
6 months-1 year	55 (1.0)	371 (1.6)	1.02 (0.76 to 1.37)	0.96 (0.71 to 1.30)
1-2 years	103 (1.8)	497 (2.2)	1.44 (1.14 to 1.82)	1.33 (1.05 to 1.68)
2-5 years	216 (3.7)	765 (3.3)	2.09 (1.74 to 3.27)	1.95 (1.62 to 2.34)
≥5 years	271 (4.7)	772 (3.4)	2.76 (2.33 to 3.27)	2.54 (2.13 to 3.03)
5-α reductase inhibitors+α blockers:				
<6 months	32 (0.6)	273 (1.2)	0.79 (0.54 to 1.16)	0.71 (0.49 to 1.05)
6 months-1 year	37 (0.6)	229 (1.0)	1.12 (0.78 to 1.61)	0.96 (0.66 to 1.39)
1-2 years	65 (1.1)	270 (1.2)	1.71 (1.29 to 2.28)	1.39 (1.03 to 1.89)
2-5 years	131 (2.3)	371 (1.6)	2.66 (2.13 to 3.32)	2.14 (1.68 to 2.73)
≥5 years	156 (2.7)	374 (1.6)	3.29 (2.66 to 4.06)	2.55 (2.02 to 3.22)
Stratified by diabetes status				
α blockers only:				
No diabetes	3852 (66.8)	16788 (72.8)	1.0 (ref)	1.0 (ref)
Diabetes	772 (13.4)	1911 (8.3)	1.77 (1.62 to 1.94)	1.69 (1.53 to 1.86)
5-α reductase inhibitors only:				
No diabetes	616 (10.7)	2572 (11.2)	1.05 (0.95 to 1.16)	0.95 (0.86 to 1.06)
Diabetes	107 (1.9)	272 (1.2)	1.74 (1.38 to 2.18)	1.42 (1.12 to 1.80)
5-α reductase inhibitors+α blockers				
No diabetes	342 (5.9)	1326 (5.8)	1.14 (1.01 to 1.29)	0.94 (0.81 to 1.09)
Diabetes	79 (1.4)	191 (0.8)	1.85 (1.41 to 2.41)	1.36 (1.02 to 1.81)

*Adjusted for body mass index, smoking status, non-erectile dysfunction sexual dysfunctions, Peyronie's disease, hypertension, diabetes, hyperlipidemia, depression, orchitis, alcohol misuse, switcher, and duration of benign prostatic hyperplasia, conditional on matching factors.
†Too few cases or controls.

orchitis) before the index date. The results were similar to those of the main analysis (adjusted odds ratio 0.97, 95% confidence interval 0.62 to 1.47). We also conducted an analysis restricted to "healthy" cases and controls (those with no diagnoses of hypertension, diabetes, hyperlipidemia, cardiovascular disease, liver disease, or cancer prior to the index date) and found no material differences in the results (0.74, 0.47 to 1.19).

When we conducted a sensitivity analysis restricted to cases of erectile dysfunction who had clinical codes that supported the erectile dysfunction diagnosis (n=332, 61%) and their matched controls, the odds ratio for users of finasteride 1 mg compared with unexposed men were null (adjusted odds ratio 1.49, 95% confidence interval 0.91 to 2.42). When the analysis was further restricted to the "healthy" cases and controls, the odds ratio was similar (0.74, 0.47 to 1.19).

Non-erectile dysfunction sexual dysfunctions
In the benign prostatic hyperplasia population, we identified 232 men with a non-erectile dysfunction sexual dysfunction diagnosis before the censor date (n=27 ejaculatory dysfunction, n=88 psychosexual dysfunction, n=115 low libido, and n=2 with multiple diagnoses recorded on the same date). The rate of non-erectile dysfunction sexual dysfunctions was 0.9 per 1000 person years (95% confidence interval 0.6 to 1.2) for users of 5-α reductase inhibitors only, 0.8 per 1000 person years (0.5 to 1.2) for users of 5-α reductase inhibitors+α blockers, and 0.8 per 1000 person years (0.6 to 0.9) for users of α blockers only. Compared with users of α blockers only, the incidence rate ratio of non-erectile dysfunction sexual dysfunction adjusted for age, calen-

dar time, and timing of exposure was 1.35 (95% confidence interval 0.95 to 1.91) for users of 5-α reductase inhibitors only and 1.62 (0.79 to 2.72) for users of 5-α reductase inhibitors+α blockers. The rates were low and not significantly different by exposure when we considered ejaculatory dysfunction, psychosexual dysfunction, and low libido separately. For ejaculatory dysfunction, the incidence rate was 0.06 per 1000 person years (95% confidence interval 0.01 to 0.17) for users of 5-α reductase inhibitors only, 0.05 per 1000 person years (0.002 to 0.2) for 5-α reductase inhibitors+α blockers, and 0.10 per 1000 person years (0.06 to 0.14) for α blockers only. For psychosexual dysfunction, the incidence rate was 0.3 per 1000 person years (0.2 to 0.5) for users of 5-α reductase inhibitors only, 0.2 per 1000 person years (0.1 to 0.4) for 5-α reductase inhibitors+α blockers, and 0.3 per 1000 person years (0.0 to 0.4) for α blockers only. For low libido, the incidence rate was 0.5 per 1000 person years (0.3 to 0.7) for users of 5-α reductase inhibitors only, 0.65 per 1000 person years (0.3 to 0.9) for 5-α reductase inhibitors+α blockers, and 0.4 per 1000 person years (0.3 to 0.4) for α blockers only.

In the alopecia population, we identified 104 men with a diagnosis of non-erectile dysfunction sexual dysfunction before the censor date (n=40 ejaculatory dysfunction, n=16 psychosexual dysfunction, n=46 low libido, and n=1 with multiple diagnoses recorded on the same date). The rate of non-erectile dysfunction sexual dysfunctions for users of finasteride 1 mg was 2.79 per 1000 person years (95% confidence interval 1.42 to 4.98) and 1.80 per 1000 person years (1.46 to 2.19) for unexposed men with alopecia. The incidence rate ratio of non-erectile dysfunction sexual dysfunction adjusted

Table 5 | Characteristics of population with alopecia. Values are numbers (percentages) unless stated otherwise

Characteristics	Total (n=12 346)	Finasteride 1 mg (n=463)	Unexposed (n=11 883)	P value
Age at cohort entry (years):				
18-29	5134 (41.2)	182 (39.3)	4952 (41.7)	
30-39	3692 (29.9)	166 (35.9)	3526 (29.7)	<0.001
40-49	2311 (18.7)	81 (17.5)	2230 (18.8)	
50-59	1209 (9.8)	34 (7.3)	1175 (9.9)	
Year of cohort entry:				
2002-04	5452 (44.2)	145 (31.3)	5307 (44.7)	
2005-09	4793 (38.8)	239 (51.6)	4554 (38.3)	<0.001
2010-11	2101 (17.0)	79 (17.1)	2202 (17.0)	
Body mass index at cohort entry:				
<18.5	288 (2.3)	5 (1.1)	283 (2.4)	
18.5-24.9	4783 (38.7)	207 (44.7)	4576 (38.5)	
25-29.9	3285 (26.6)	128 (27.7)	3157 (26.6)	<0.001
≥30	1262 (10.2)	28 (6.1)	1234 (10.4)	
Unknown	2728 (22.1)	95 (20.5)	2633 (22.2)	
Smoking status at cohort entry:				
Non-smoker	5089 (41.2)	230 (49.7)	4859 (40.9)	
Smoker	3575 (29.0)	99 (21.4)	3476 (29.3)	
Former smoker	1486 (12.0)	80 (17.3)	1406 (11.8)	<0.001
Unknown	2196 (17.8)	54 (11.7)	2142 (18.0)	
Comorbidities at cohort entry:				
Duration of alopecia (years):				Not calculated
<1	9884 (80.1)	463 (100.0)	9421 (79.3)	
1-2	444 (3.6)	0 (0.0)	444 (3.7)	
2-5	937 (7.6)	0 (0.0)	937 (7.9)	
≥5	1081 (8.8)	0 (0.0)	1081 (9.1)	
Benign prostatic hyperplasia	132 (1.1)	5 (1.1)	127 (1.1)	0.93
Lower urinary tract symptoms	1517 (12.3)	3 (8.3)	1514 (12.3)	<0.001
Hypertension	368 (3.0)	13 (2.8)	355 (3.0)	0.85
Diabetes	146 (1.2)	2 (0.4)	144 (1.2)	0.11
Hyperlipidemia	276 (2.2)	13 (2.8)	263 (2.2)	0.39
Cardiovascular disease	276 (2.2)	5 (1.1)	271 (2.3)	0.07
Atherosclerosis	12 (0.1)	0 (0.0)	12 (0.1)	Not calculated
Metabolic syndrome	0 (0.0)	0 (0.0)	0 (0.0)	Not calculated
Kidney failure/dialysis	42 (0.3)	2 (0.4)	40 (0.3)	0.68
Cancer	44 (0.4)	2 (0.4)	42 (0.4)	0.72
Depression	1487 (12.0)	75 (16.2)	1412 (11.9)	0.007
Alcohol misuse	406 (3.3)	9 (1.9)	397 (3.3)	0.09
Drug misuse	245 (2.0)	7 (1.5)	238 (2.0)	0.48
β blocker prescription within 6 months prior to cohort entry date	865 (7.0)	54 (11.7)	811 (6.8)	<0.001

Table 6 | Incidence rates (IRs) and incidence rate ratios (IRRs) for erectile dysfunction by exposure in analysis of alopecia cohort

Variables	Unexposed				Finasteride 1 mg			
	Cases (n=511)	Person years	IR/1000 person years (95% CI)	IRR (95% CI)	Cases (n=36)	Person years	IR/1000 person years (95% CI)	IRR (95% CI)
Age group (years):								
18-29	76	14 518	5.2 (4.1 to 6.6)		7	1016	6.9 (2.8 to 14.2)	
30-39	119	16 767	7.1 (5.9 to 8.5)		6	1386	4.3 (1.6 to 9.4)	
40-49	134	13 286	10.1 (8.5 to 11.9)		11	843	13.0 (6.5 to 23.3)	
50-59	182	7696	23.6 (20.3 to 27.3)		12	334	35.9 (18.5 to 62.7)	
Calendar time:								
2002-04	93	11 433	8.1 (6.6 to 10.0)		7	547	12.8 (5.1 to 26.4)	
2005-09	263	27 625	9.5 (8.4 to 10.7)		19	1960	9.7 (5.8 to 15.1)	
2010-11	155	13 209	11.7 (10.0 to 13.7)		10	1073	9.3 (4.5 to 17.1)	
Timing of finasteride 1 mg use:								
Current	Not applicable	Not applicable	Not applicable		9	1035	6.9 (3.1 to 13.1)	
Recent	Not applicable	Not applicable	Not applicable		2	217	9.2 (1.0 to 33.3)	
Past	Not applicable	Not applicable	Not applicable		25	2057	12.2 (8.0 to 17.0)	
Total:								
Crude	511	52 267	9.8 (8.9 to 10.7)	1.0 (ref)	36	3580	10.1 (7.0 to 13.9)	1.03 (0.73 to 1.44)
Adjusted*				1.0 (ref)				1.13 (0.80 to 1.58)

*Adjusted for age group and calendar year.

Table 7 | Nested case-control analysis: characteristics of cases with erectile dysfunction and controls in alopecia population. Values are numbers (percentages) unless stated otherwise

Characteristics	Cases (n=547)	Controls (n=2178)	Univariate odds ratio (95% CI)
Age at index date (years):			
18-29	83 (15.2)	332 (15.2)	-
30-39	125 (22.9)	501 (23.0)	-
40-49	145 (26.5)	578 (26.5)	-
50-59	194 (35.5)	767 (35.2)	-
Mean (SD)	43.0 (11.0)	42.9 (11.0)	
Index year:			
2002-04	100 (18.3)	396 (18.2)	-
2005-09	282 (51.6)	1123 (51.6)	-
2010-11	165 (30.2)	659 (30.3)	-
Mean (SD) length of record before index date (years)	13.1 (5.0)	13.1 (6.0)	-
Body mass index:			
<18.5	5 (0.9)	43 (2.0)	0.54 (0.21 to 1.39)
18.5-24.9	161 (29.4)	763 (35.0)	1.0 (ref)
25-29.9	194 (35.5)	735 (33.8)	1.27 (1.01 to 1.61)
≥30	116 (21.2)	304 (14.0)	1.83 (1.39 to 2.41)
Unknown	71 (13.0)	333 (15.3)	0.98 (0.72 to 1.33)
Mean (SD)	27.1 (4.9)	26.1 (4.7)	
Smoking status:			
Non-smoker	209 (38.2)	913 (41.9)	1.0 (ref)
Smoker	179 (32.7)	678 (31.1)	1.16 (0.92 to 1.45)
Former smoker	135 (24.7)	424 (19.5)	1.42 (1.11 to 1.81)
Unknown	24 (4.4)	163 (7.5)	0.60 (0.37 to 0.96)
Comorbidities at index date:			
Benign prostatic hyperplasia	21 (3.8)	59 (2.7)	1.47 (0.87 to 2.48)
No benign prostatic hyperplasia	526 (96.2)	2119 (97.3)	1.0 (ref)
Duration of benign prostatic hyperplasia:			
<5 years	9 (1.7)	36 (1.7)	1.03 (0.48 to 2.18)
≥5 years	12 (2.2)	23 (1.1)	2.16 (1.05 to 4.45)
Lower urinary tract symptoms	144 (26.3)	352 (16.6)	1.82 (1.46 to 2.28)
Orchitis	38 (7.0)	109 (5.0)	1.43 (0.97 to 2.11)
Non-erectile dysfunction sexual dysfunction*	19 (3.5)	13 (0.6)	6.17 (2.99 to 12.73)
Peyronie's disease	4 (0.7)	0 (0.0)	†
Hypertension	77 (14.1)	194 (8.9)	1.75 (1.30 to 2.37)
Diabetes	54 (9.9)	48 (2.2)	4.74 (3.18 to 7.06)
Hyperlipidemia	60 (11.0)	146 (6.7)	1.77 (1.28 to 2.46)
Cardiovascular disease	45 (8.2)	113 (5.2)	1.64 (1.14 to 2.36)
Atherosclerosis	5 (0.9)	8 (0.4)	2.57 (0.81 to 8.17)
Metabolic syndrome	0 (0.0)	0 (0.0)	†
Kidney failure/dialysis	8 (1.5)	22 (1.0)	1.49 (0.65 to 3.43)
Cancer	6 (1.1)	12 (0.6)	2.00 (0.75 to 5.33)
Liver disease	7 (1.3)	6 (0.3)	4.66 (1.57 to 13.89)
Depression	182 (33.3)	414 (19.0)	2.18 (1.76 to 2.70)
Alcohol misuse	46 (8.4)	119 (5.5)	1.61 (1.12 to 2.30)
Drug misuse	21 (3.8)	50 (2.3)	1.71 (1.02 to 2.88)
β blocker prescription within 6 months prior to index date	49 (9.0)	84 (3.9)	2.55 (1.75 to 3.73)

*Non-erectile dysfunction sexual dysfunction includes ejaculatory disorders, psychosexual dysfunction, and low libido.
†Too few cases or controls to calculate.

for age, calendar time, and timing of use was 1.55 (95% confidence interval 0.98 to 2.47) for users of finasteride 1 mg compared with unexposed men with alopecia. The rates were low and not significantly different by exposure when we considered ejaculatory disorder, psychosexual dysfunction, and low libido separately. For ejaculatory disorder, the incidence rate was 0.3 per 1000 person years (0.0 to 1.4) for users of finasteride 1 mg and 0.8 per 1000 person years (0.5 to 1.0) for unexposed men. For psychosexual dysfunction, the incidence rate was 0.0 per 1000 person years (0.0 to 0.2) for users of finasteride 1 mg and 0.3 per 1000 person years (0.2 to 0.5) for unexposed men. For low libido, the incidence rate was 0.8 per 1000 person years (0.2 to 2.3) for users of finasteride 1 mg and 0.8 per 1000 person years (0.6 to 1.1) for unexposed men.

Discussion

Overall, the results of our study suggest that 5-α reductase inhibitors do not increase the risk of incident erectile dysfunction, regardless of indication for use (benign prostatic hyperplasia or alopecia). In a population of men

Table 8 | Nested case-control analysis: risk of erectile dysfunction by exposure in alopecia population. Values are numbers (percentages) unless stated otherwise

Exposure at index date	Cases (n=547)	Controls (n=2178)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Exposure:				
None	511 (93.4)	2021 (92.8)	1.0 (ref)	1.0 (ref)
Finasteride 1 mg	36 (6.6)	157 (7.2)	0.91 (0.62 to 1.33)	0.94 (0.64 to 1.40)
No of prescriptions:				
None	511 (93.4)	2021 (92.8)	1.0 (ref)	1.0 (ref)
Finasteride 1 mg:				
1 prescription	10 (1.8)	53 (2.4)	0.75 (0.38 to 1.48)	0.69 (0.33 to 1.40)
2-9 prescriptions	15 (2.7)	67 (3.1)	0.89 (0.50 to 1.57)	0.92 (0.51 to 1.67)
≥10 prescriptions	11 (2.0)	37 (1.7)	1.18 (0.60 to 2.35)	1.43 (0.71 to 2.90)
Timing of use:				
None	511 (93.4)	2021 (92.8)	1.0 (ref)	1.0 (ref)
Finasteride 1 mg				
Current	9 (1.7)	51 (2.3)	0.69 (0.34 to 1.43)	0.78 (0.37 to 1.66)
Recent	2 (0.4)	8 (0.4)	†	†
Past	25 (4.6)	98 (4.5)	1.01 (0.64 to 1.60)	0.99 (0.62 to 1.59)
Time since last prescription:				
None	511 (93.4)	2021 (92.8)	1.0 (ref)	1.0 (ref)
Finasteride 1 mg				
<1 year	18 (3.3)	79 (3.6)	0.91 (0.54 to 1.54)	1.01 (0.58 to 1.75)
1-5 years	17 (3.1)	60 (2.8)	1.13 (0.65 to 1.95)	1.05 (0.60 to 1.86)
≥5 years	1 (0.2)	18 (0.8)	†	†

*Adjusted for body mass index, smoking status, duration of benign prostatic hyperplasia, non-erectile dysfunction sexual dysfunctions, hypertension, diabetes, hyperlipidemia, cardiovascular disease, liver disease, depression, alcohol misuse, drug misuse and receipt of a β blocker prescription within six months prior to index date, conditional on matching factors.
†Too few cases or controls to calculate.

age 40 years and older with treated benign prostatic hyperplasia, there was no increase in risk of incident erectile dysfunction with use of 5-α reductase inhibitors (finasteride or dutasteride), alone or in combination with α blockers, compared with use of α blockers only. In addition, among men aged 18-59 with alopecia, there was no material increase in the risk of incident erectile dysfunction in men prescribed finasteride 1 mg compared with unexposed men with alopecia. Finally, the rates of non-erectile dysfunction sexual dysfunctions were low regardless of indication for 5-α reductase inhibitor use. The risk of erectile dysfunction increased with longer duration of benign prostatic hyperplasia, independent of exposure. This finding is noteworthy because UK prescribing guidelines during much of the study period recommended that α blockers be first line treatment for benign prostatic hyperplasia followed by a switch to, or addition of, 5-α reductase inhibitors when treatment with α blockers was not effective or when benign prostatic hyperplasia had progressed. Therefore, users of 5-α reductase inhibitors were likely to have benign prostatic hyperplasia for a longer duration, resulting in a higher risk for erectile dysfunction. The absence of increased risk of erectile dysfunction in users of 5-α reductase inhibitors with benign prostatic hyperplasia, as well as in users with alopecia, provides strong evidence against the hypothesis that 5-α reductase inhibitors independently increase the risk of erectile dysfunction.

Comparison with other studies
Results from clinical trials evaluating the efficacy of 5-α reductase inhibitors for the treatment of benign pros-

tatic hyperplasia or prevention of prostate cancer suggest that these drugs increase the risk of erectile dysfunction, whereas our results were null. The relative risk of erectile dysfunction with use of 5-α reductase inhibitors in clinical trials for prevention of prostate cancer varied from 1.10 to 1.5,[2 3] compared with placebo, and the changes in sexual function associated with 5-α reductase inhibitors were typically noted within the first year of treatment, and became comparable with placebo by study termination. Evidence from clinical trials evaluating the efficacy of finasteride only, α blockers only, and combination treatment for benign prostatic hyperplasia have also suggested that use of 5-α reductase inhibitors, alone or in combination with α blockers, increases the risk of erectile dysfunction compared with placebo. The risks based on published results range from 0.8 to 1.5 for finasteride only compared with α blockers only, whereas the risks of combination treatment range from 1.4 to 1.8 compared with α blockers only.[18-21] Our results yielded no differences in the risk of erectile dysfunction by type of 5-α reductase inhibitor (finasteride or dutasteride), which is consistent with results of a clinical trial that compared the efficacy and safety of finasteride with dutasteride.[22] A post-marketing surveillance study (n=14 772) conducted in the UK in 1992-94, shortly after finasteride was first marketed, found that impotence/ejaculation was reported in 2.1% of patients prescribed finasteride, similar to the rate of erectile dysfunction in our benign prostatic hyperplasia study population.[23]

The results of published studies evaluating the efficacy of finasteride 1 mg to treat alopecia have been inconsistent,[6-9 24-27] whereas our results were null. An increase of sexual side effects has been reported in clinical trials evaluating the efficacy of finasteride 1 mg for treatment of alopecia, with approximately 4% of men treated with finasteride reporting sexual side effects compared with approximately 2% of men treated with placebo.[6-9] A systematic review of six clinical trials that reported on the safety of finasteride 1 mg or 5 mg for treatment of alopecia compared with placebo, found an increased risk of patient reported erectile dysfunction (relative risk 2.22, 95% confidence interval 1.03 to 4.78).[24] In contrast, three small trials conducted in clinical settings with short term follow-up reported no significant difference in erectile dysfunction adverse events.[25-27]

The clinical trials evaluating 5-α reductase inhibitors for the treatment of benign prostatic hyperplasia and alopecia have also identified non-erectile dysfunction sexual dysfunctions as adverse effects of 5-α reductase inhibitor use. A systematic review of available randomized clinical trials reported that ejaculatory dysfunction was more common among users of 5-α reductase inhibitors for treatment of benign prostatic hyperplasia compared with users of placebo (odds ratio 2.73, P<0.001) in trials comparing α blockers and 5-α reductase inhibitors, whereas in trials comparing 5-α reductase inhibitors with α blockers the prevalence of ejaculatory dysfunction was similar for users of both drugs (odds ratio 0.7, P=0.42).[28] Another review of data from clinical

trials found that low libido was reported as an adverse event for 2-5% of patients treated with 5-α reductase inhibitors compared with 1-3% of the placebo group.[10] A small cross sectional study of men attending an outpatient clinic for sexual dysfunction (n=48 patients using 5-α reductase inhibitors) reported a higher prevalence of low libido among users of 5-α reductase inhibitors compared with men who did not use 5-α reductase inhibitors; however, there were no significant differences in the prevalence of premature ejaculation or ejaculatory volume.[29] In comparison, in our study there was no evidence of a substantial increase in risk of non-erectile dysfunction sexual dysfunctions, and the rates were less than three events per 1000 person years regardless of indication for use, lower than those reported in clinical trials. In the UK Clinical Practice Research Datalink (CPRD), codes used to identify non-erectile dysfunction outcomes (ejaculatory disorder, psychosexual dysfunction, and low libido) are neither specific nor used regularly, consistently, or correctly (because of the close relation with diagnosis of erectile dysfunction) by general practitioners. Thus it is likely that we missed cases of non-erectile dysfunction sexual dysfunctions, and therefore the rates reported here are underestimates. Our results for non-erectile dysfunction sexual dysfunctions should be interpreted cautiously in light of the data limitations for these outcomes as well as the small number of exposed cases of non-erectile dysfunction sexual dysfunction identified (n=58 exposed non-erectile dysfunction cases in the benign prostatic hyperplasia population and n=10 exposed non-erectile dysfunction cases in the alopecia population).

Unlike the published clinical trials, men in both our benign prostatic hyperplasia study population and our alopecia study population were free from diagnoses of and treatments for erectile dysfunction prior to cohort entry. In addition, patients with a history of other strong risk factors for erectile dysfunction prior to cohort entry, such as prostate, genital, or urinary cancer, or a history of prostatectomy or orchiectomy, were excluded from the study population or censored on subsequent diagnosis of these major erectile dysfunction and non-erectile dysfunction sexual dysfunction risk factors after cohort entry. Importantly, to be identified as a case of erectile dysfunction in our study men were required either to have a diagnosis or to have received treatment (pharmaceutical or procedural) for erectile dysfunction recorded by the general practitioner in their electronic medical record before the censoring date, whereas all of the clinical trials used questionnaires completed by participants to assess changes in sexual function. Thus, a major strength of our study is that it captured clinically meaningful erectile dysfunction diagnoses that came to the general practitioner's attention. In our study, users of 5-α reductase inhibitors, particularly in combination with α blockers, were generally less healthy than users of α blockers only. Men with benign prostatic hyperplasia who have multiple medical problems may have less sex or may less often bring up concerns about sexual function to their doctor, whereas the doctors may be more concerned with treating the other conditions than about the sexual health of their patients; that is, users of 5-α reductase inhibitors may be less likely to have their erectile dysfunction diagnosed (detection bias). If this were the case, then the true incidence of erectile dysfunction among users of 5-α reductase inhibitors alone or in combination might be higher than we detected in our study.

Alopecia and prostate enlargement/benign prostatic hyperplasia are both related to the conversion of testosterone to dihydrotestosterone, which is stimulated by increased activity of the enzyme 5-α reductase.[10] Owing to underlying biochemistry, men who have benign prostatic hyperplasia or alopecia may be at an increased risk of erectile dysfunction compared with men without either condition, regardless of treatment. Our study was designed to control for confounding by indication. In the benign prostatic hyperplasia study, we used an active comparator (α blockers only) rather than non-exposed, to control for confounding by severity and duration of benign prostatic hyperplasia, whereas men in our alopecia study population were required to have a recorded diagnosis of alopecia. The number of patients in our benign prostatic hyperplasia study population identified as a case of erectile dysfunction (8%) was similar to the proportion of patients who self reported having erectile dysfunction in clinical trials (0% to 16%),[2 3 19-21] whereas the rates of erectile dysfunction among men with alopecia in our study were similar to those reported among men in general.[30 31] Also, erectile dysfunction has not been reported as a common side effect of the α blockers evaluated in our study.[32] Approximately 46% of the patients who used α blockers only in our benign prostatic hyperplasia population were prescribed tamsulosin, followed by alfuzosin (12%) and doxazosin (11%); in our study, the risk of erectile dysfunction did not differ by type of α blocker prescribed (data not shown). We do not believe that the null results found in our study were due to use of comparison groups who had an increased baseline risk for erectile dysfunction.

Strengths and limitations of this study

Strengths of our population based study included the use of CPRD, a large, validated, longitudinal primary care database known for high accuracy of diagnoses and completeness of drug prescribing data. We found known risk factors to be independently associated with risk for erectile dysfunction (eg, increased body mass index, hypertension, hyperlipidemia, diabetes), providing confidence in the quality of the data and its ability to detect associations between benign prostatic hyperplasia treatments and risk of erectile dysfunction. As all information on diseases and drug exposures is recorded in the absence of a study hypothesis, there is no risk of recall bias. The mean length of follow-up was greater than four years. We further controlled our analyses for a range of potential confounders, including non-erectile dysfunction sexual dysfunction, hypertension, diabetes, body mass index, smoking status, depression, and duration of benign prostatic hyperplasia. By excluding

men who had insufficient history in their medical record before cohort entry we reduced the risk of including men who had used the study drugs before cohort entry, as well as reduced the risk of including men with prevalent, rather than incident, erectile dysfunction.

A major strength of our study is that it relied on doctor recorded diagnoses, rather than patient reported changes in sexual function, to identify cases. Finally, the population of men prescribed 5-α reductase inhibitors and α blockers for benign prostatic hyperplasia (n=71 849) and the population of men with alopecia (n=12 346, of which 868 received prescriptions for finasteride 1 mg during follow-up) described in our study are robust and are the largest populations of "real world" users of these drugs evaluated to date. This allowed us to study the effects of these drugs as prescribed in routine clinical practice. This is not possible in clinical trials given their smaller size and highly selected study populations.

There are some limitations to consider. Drug information in the CPRD covers written, not dispensed prescriptions; therefore we cannot be sure that patients used all prescribed drugs. However, the relative risks did not change among those with repeat (≥2) prescriptions, suggesting that this did not affect the results. During our study period, phosphodiesterase type 5 inhibitors were available in the UK for prescriptions through private sources; therefore, we may have missed some cases of erectile dysfunction where these drugs were prescribed outside of the general practitioner's office. This is unlikely to be differential by exposure category, and thus may have biased the true estimates toward the null. Objective measures of the severity of benign prostatic hyperplasia are not captured in the CPRD data, thus we were unable to assess the impact of severity on the results. We were able to identify codes relating to lower urinary tract symptoms; however, these codes are symptom based, are not specific to benign prostatic hyperplasia, and might be related to other urological and medical conditions. Severe lower urinary tract symptoms are known to be associated with erectile dysfunction, but in our study such symptoms did not confound the relation between exposure and outcome in either the benign prostatic hyperplasia population or the alopecia population. Although the populations of men evaluated in these studies were robust, in some of the analyses the numbers of exposed cases were small, particularly for non-erectile dysfunction sexual dysfunctions (n=36 exposed erectile dysfunction cases in the alopecia population, n=58 exposed non-erectile dysfunction sexual dysfunction cases in the benign prostatic hyperplasia population, and n=10 exposed in the alopecia population); thus the results for these analyses should be interpreted with caution. However, it is important to note that the CPRD is one of the few observational data sources in the world where these numbers of erectile dysfunction and non-erectile dysfunction sexual dysfunction cases could be identified and evaluated. Our study results suggest that the duration of benign prostatic hyperplasia is a strong independent risk factor for erectile dysfunction; therefore,

studies evaluating the incidence of erectile dysfunction after use of 5-α reductase inhibitors or α blockers should be interpreted cautiously and with consideration to the duration of benign prostatic hyperplasia.

Conclusions and policy implications

The results of our study provide evidence that 5-α reductase inhibitors do not increase the risk of clinically meaningful incident erectile dysfunction in men who are free of sexual dysfunction and major risk factors (eg, prostate, genital, or urinary cancers, surgical procedures), regardless of indication for use (benign prostatic hyperplasia or alopecia). The risk of erectile dysfunction increases with longer duration of benign prostatic hyperplasia, which should be accounted for in the design of future studies evaluating the safety of 5-α reductase inhibitors. Since benign prostatic hyperplasia and alopecia are common conditions in men and 5-α reductase inhibitors are primary drug treatments for these conditions, the results of this study provide reassurance that these drugs are not associated with a materially important increased risk of clinically meaningful erectile dysfunction in every day clinical practice.

1 Glina S, Glina FPA. Pathogenic mechanisms linking benign prostatic hyperplasia, lower urinary tract symptoms and erectile dysfunction. *Ther Adv Urol* 2013;5:211-8. doi:10.1177/1756287213488236.

2 Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003;349:215-24. doi:10.1056/NEJMoa030660.

3 Andriole GL, Bostwick DG, Brawley OW, et al. REDUCE Study Group. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med* 2010;362:1192-202. doi:10.1056/NEJMoa0908127.

4 Rittmaster RS, Fleshner NE, Thompson IM. Pharmacological approaches to reducing the risk of prostate cancer. *Eur Urol* 2009;55:1064-73. doi:10.1016/j.eururo.2009.01.037.

5 Thompson IM, Tangen CM, Goodman PJ, Lucia MS, Klein EA. Chemoprevention of prostate cancer. *J Urol* 2009;182:499-507, discussion 508. doi:10.1016/j.juro.2009.04.015.

6 Kaufman KD, Olsen EA, Whiting D, et al. Finasteride Male Pattern Hair Loss Study Group. Finasteride in the treatment of men with androgenetic alopecia. *J Am Acad Dermatol* 1998;39:578-89. doi:10.1016/S0190-9622(98)70007-6.

7 Leyden J, Dunlap F, Miller B, et al. Finasteride in the treatment of men with frontal male pattern hair loss. *J Am Acad Dermatol* 1999;40:930-7. doi:10.1016/S0190-9622(99)70081-2.

8 Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997;49:822-30. doi:10.1016/S0090-4295(97)00238-0.

9 Irwig MS, Kolukula S. Persistent sexual side effects of finasteride for male pattern hair loss. *J Sex Med* 2011;8:1747-53. doi:10.1111/j.1743-6109.2011.02255.x.

10 Traish AM, Hassani J, Guay AT, Zitzmann M, Hansen ML. Adverse side effects of 5α-reductase inhibitors therapy: persistent diminished libido and erectile dysfunction and depression in a subset of patients. *J Sex Med* 2011;8:872-84. doi:10.1111/j.1743-6109.2010.02157.x.

11 Irwig MS. Persistent sexual side effects of finasteride: could they be permanent? *J Sex Med* 2012;9:2927-32. doi:10.1111/j.1743-6109.2012.02846.x.

12 Belknap SM, Aslam I, Kiguradze T, et al. Adverse event reporting in clinical trials of finasteride for androgenic alopecia. *JAMA Dermatol* 2015;151:600-6. doi:10.1001/jamadermatol.2015.36.

13 US Food and Drug Administration. Questions and answers: finasteride label changes. Silver Spring, MD: US Food and Drug Administration [cited 2012 December 3]. www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm299754.htm

14 The Post-Finasteride Syndrome Foundation. Welcome to the Post-Finasteride Syndrome Foundation [Internet]. Somerset, NJ: the Post-Finasteride Syndrome Foundation [cited 2012 December 3]. www.pfsfoundation.org/

15 MM&M Online. Pharma Report 2011. http://media.mmm-online.com/documents/23/pharma_report_5720.pdf [cited 2012 Dec 3].

16 Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the general practice research database. *Pharmacotherapy* 2003;23:686-9. doi:10.1592/phco.23.5.686.32205.

17 Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010;69:4-14. doi:10.1111/j.1365-2125.2009.03537.x.

18 Wu XJ, Zhi Y, Zheng J, et al. Dutasteride on benign prostatic hyperplasia: a meta-analysis on randomized clinical trials in 6460 patients. *Urology* 2014;83:539-43. doi:10.1016/j.urology.2013.10.007.

19 Lepor H, Williford WO, Barry MJ, et al. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. *N Engl J Med* 1996;335:533-40. doi:10.1056/NEJM199608223350801.

20 Kirby RS, Roehrborn C, Boyle P, et al. Prospective European Doxazosin and Combination Therapy Study Investigators. Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. *Urology* 2003;61:119-26. doi:10.1016/S0090-4295(02)02114-3.

21 McConnell JD, Roehrborn CG, Bautista OM, et al. Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003;349:2387-98. doi:10.1056/NEJMoa030656.

22 Nickel JC, Gilling P, Tammela TL, Morrill B, Wilson TH, Rittmaster RS. Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS). *BJU Int* 2011;108:388-94. doi:10.1111/j.1464-410X.2011.10195.x.

23 Wilton L, Pearce G, Edet E, Freemantle S, Stephens MDB, Mann RD. The safety of finasteride used in benign prostatic hypertrophy: a non-interventional observational cohort study in 14,772 patients. *Br J Urol* 1996;78:379-84. doi:10.1046/j.1464-410X.1996.00091.x.

24 Mella JM, Perret MC, Manzotti M, Catalano HN, Guyatt G. Efficacy and safety of finasteride therapy for androgenetic alopecia: a systematic review. *Arch Dermatol* 2010;146:1141-50. doi:10.1001/archdermatol.2010.256.

25 Tosti A, Pazzaglia M, Soli M, et al. Evaluation of sexual function with an international index of erectile function in subjects taking finasteride for androgenetic alopecia. *Arch Dermatol* 2004;140:857-8. doi:10.1001/archderm.140.7.857.

26 Tosti A, Piraccini BM, Soli M. Evaluation of sexual function in subjects taking finasteride for the treatment of androgenetic alopecia. *J Eur Acad Dermatol Venereol* 2001;15:418-21. doi:10.1046/j.1468-3083.2001.00315.x.

27 Narasimhalu CRV. Randomized questionnaire based case-control research study on evaluation of sexual function in Indian patients taking oral finasteride for androgenetic alopecia. *Dermatol Ther (Heidelb)* 2015;5:231-4. doi:10.1007/s13555-015-0084-3.

28 Gacci M, Ficarra V, Sebastianelli A, et al. Impact of medical treatments for male lower urinary tract symptoms due to benign prostatic hyperplasia on ejaculatory function: a systematic review and meta-analysis. *J Sex Med* 2014;11:1554-66. doi:10.1111/jsm.12525.

29 Corona G, Rastrelli G, Maseroli E, et al. Inhibitors of 5α-reductase-related side effects in patients seeking medical care for sexual dysfunction. *J Endocrinol Invest* 2012;35:915-20.

30 Kubin M, Wagner G, Fugl-Meyer AR. Epidemiology of erectile dysfunction. *Int J Impot Res* 2003;15:63-71. doi:10.1038/sj.ijir.3900949.

31 Medical Surveillance Monthly Report (MSMR). Erectile dysfunction among male active component service members, U.S. Armed Forces, 2004-2013. Sept 2014;21:13-16. www.ncbi.nlm.nih.gov/pubmed/25267600.

32 Van Asseldonk B, Barkin J, Elterman DS. Medical therapy for benign prostatic hyperplasia: a review. *Can J Urol* 2015;22(Suppl 1):7-17.