

**Supplementary Table 1.** Read codes for the diagnosis of benign prostatic hyperplasia in the CPRD among men with BPH in the UK between 1998 and 2016

Medical codes	Read code	Read Terminologies
2627	K20..16	Prostatism
5906	1AA..00	Prostatism
929	K200.00	Prostatic hyperplasia unspecified
1068	25Q2.11	Prostate enlarged on PR
7555	K20..15	BPH - benign prostatic hypertrophy
3045	K20..00	Benign prostatic hypertrophy
7702	K20..14	Enlarged prostate - benign
16100	14E1.00	H/O: prostatism
16035	K20z.00	Prostatic hyperplasia NOS
15346	K20..11	Benign adenoma of the prostate
25711	K20..12	Benign fibroma of prostate
35676	K202.00	Prostatic hyperplasia of the medial lobe
104567	B7C2000	Adenoma of prostate
71354	K20..13	Benign myoma of prostate
64296	K201.00	Prostatic hyperplasia of the lateral lobe

**Supplementary Table 2.** Prescribing rate ratios of BPH medications among men with BPH in the UK between 1998-2016, modeling age as a continuous variable, a categorical variable, and using a restricted cubic spline to model it non-linearly.

Types of prescription	Years	Crude rate ratio (95% CI)	Adjusted rate ratio (95% CI) (Continuous)	Adjusted rate ratio (95% CI) (Categorical)	Adjusted rate ratio (95% CI)* (Spline)
$\alpha$ -blockers only	1998-2000	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	2001-2003	1.47 (1.46-1.48)	1.45 (1.44-1.46)	1.46 (1.45-1.47)	1.46 (1.45-1.47)
	2004-2006	1.73 (1.72-1.74)	1.69 (1.68-1.70)	1.70 (1.69-1.71)	1.70 (1.69-1.71)
	2007-2009	1.90 (1.88-1.91)	1.84 (1.82-1.85)	1.85 (1.84-1.86)	1.85 (1.83-1.86)
	2010-2012	2.02 (2.01-2.03)	1.94 (1.93-1.96)	1.96 (1.95-1.97)	1.96 (1.94-1.97)
	2013-2016	2.10 (2.09-2.11)	2.00 (1.99-2.02)	2.02 (2.01-2.03)	2.02 (2.01-2.04)
5 $\alpha$ RI only	1998-2000	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	2001-2003	1.18 (1.16-1.19)	1.11 (1.09-1.12)	1.12 (1.11-1.14)	1.11 (1.09-1.12)
	2004-2006	1.65 (1.63-1.67)	1.49 (1.48-1.51)	1.53 (1.51-1.55)	1.50 (1.48-1.52)
	2007-2009	2.04 (2.01-2.06)	1.78 (1.76-1.80)	1.83 (1.81-1.85)	1.79 (1.77-1.81)
	2010-2012	2.19 (2.17-2.22)	1.85 (1.83-1.87)	1.91 (1.89-1.93)	1.87 (1.85-1.89)
	2013-2016	2.24 (2.22-2.27)	1.84 (1.82-1.86)	1.90 (1.88-1.92)	1.86 (1.84-1.88)
$\alpha$ -blocker and 5 $\alpha$ RI combination therapy	1998-2000	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	2001-2003	2.09 (2.02-2.16)	2.01 (1.94-2.08)	2.03 (1.96-2.10)	2.01 (1.95-2.08)
	2004-2006	5.86 (5.69-6.04)	5.49 (5.32-5.66)	5.58 (5.41-5.75)	5.51 (5.34-5.68)
	2007-2009	10.89 (10.57-11.22)	9.94 (9.65-10.24)	10.13 (9.83-10.44)	9.98 (9.69-10.28)
	2010-2012	16.36 (15.88-16.85)	14.60 (14.17-15.04)	14.91 (14.47-15.36)	14.68 (14.25-15.13)
	2013-2016	21.73 (21.10-22.39)	19.00 (18.45-19.58)	19.42 (18.85-20.00)	19.16 (18.60-19.73)
Overall prescription of BPH drugs	1998-2000	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	2001-2003	1.42 (1.42-1.43)	1.39 (1.38-1.40)	1.40 (1.39-1.40)	1.39 (1.38-1.40)
	2004-2006	1.84 (1.83-1.85)	1.76 (1.75-1.77)	1.78 (1.77-1.79)	1.76 (1.75-1.77)
	2007-2009	2.19 (2.18-2.20)	2.07 (2.05-2.08)	2.09 (2.08-2.10)	2.07 (2.06-2.08)
	2010-2012	2.48 (2.47-2.50)	2.30 (2.29-2.32)	2.34 (2.32-2.35)	2.32 (2.31-2.33)
	2013-2016	2.71 (2.70-2.73)	2.48 (2.47-2.50)	2.52 (2.50-2.53)	2.50 (2.49-2.52)

**5 $\alpha$ RI:** Five alpha-reductase inhibitors;  **$\alpha$ -blocker:** Alpha blocker; **BPH:** Benign prostatic hyperplasia; **CI:** Confidence interval; **CPRD:** Clinical Practice Research Datalink; **n:** number; **UK:** United Kingdom; \*The rate ratio was adjusted for age with spline restricted (5%, 27.5%, 50%, 72.5%, 95%).

**Supplementary Table 3.** Temporal trends in the prescription of BPH medications among men with BPH in the UK from 1998-2016, across age categories, with age defined at the time of prescription.

Types of prescription	Age (years)	Number of prescriptions*	Person-year	Prescription rate per 100 per year (95% CI)	Crude rate ratio (95% CI)
$\alpha$ -blockers	40-54	89,511	75,734	118.2 (117.4-119.0)	1.00 (ref)
	55-64	475,980	247,325	192.5 (191.9-193.0)	1.63 (1.62-1.64)
	65-74	963,384	411,298	234.2 (233.8-234.7)	1.98 (1.97-2.00)
	75-84	848,247	343,208	247.2 (246.6-247.7)	2.09 (2.08-2.11)
	$\geq 85$	244,954	98,699	248.9 (247.2-249.2)	2.10 (2.08-2.12)
	<b>Overall</b>	<b>2,622,076</b>	<b>1,176,264</b>	<b>222.9 (222.7-223.2)</b>	---
5 $\alpha$ RIs	40-54	9,382	75,734	12.4 (12.1-12.6)	1.00 (ref)
	55-64	79,816	247,325	32.3 (32.1-32.5)	2.61 (2.55-2.66)
	65-74	247,231	411,298	60.1 (59.9-60.4)	4.85 (4.75-4.95)
	75-84	337,306	343,208	98.3 (98.0-98.6)	7.93 (7.77-8.10)
	$\geq 85$	139,341	98,699	141.2 (140.4-141.9)	11.40 (11.16-11.64)
	<b>Overall</b>	<b>813,076</b>	<b>1,176,264</b>	<b>69.1 (69.0-69.3)</b>	---
$\alpha$ -blocker and 5 $\alpha$ RI combination therapy	40-54	8,427	75,734	11.1 (10.9-11.4)	1.00 (ref)
	55-64	80,479	247,325	32.5 (32.3-32.8)	2.92 (2.86-2.99)
	65-74	218,505	411,298	53.1 (52.9-53.4)	4.77 (4.67-4.88)
	75-84	248,682	343,208	72.5 (72.2-72.7)	6.51 (6.37-6.65)
	$\geq 85$	97,104	98,699	98.4 (97.8-99.0)	8.84 (8.65-9.04)
	<b>Overall</b>	<b>653,197</b>	<b>1,176,264</b>	<b>55.5 (55.4-55.7)</b>	---
Overall prescription of BPH drugs	40-54	107,320	75,734	141.7 (140.9-142.6)	1.00 (ref)
	55-64	636,275	247,325	257.3 (256.6-257.9)	1.82 (1.80-1.83)
	65-74	1,429,120	411,298	347.5 (346.9-348.0)	2.45 (2.44-2.47)
	75-84	1,434,235	343,208	417.9 (417.2-418.6)	2.95 (2.93-2.97)
	$\geq 85$	481,399	98,699	487.7 (486.4-489.1)	3.44 (3.42-3.46)
	<b>Overall</b>	<b>4,088,349</b>	<b>1,176,264</b>	<b>347.6 (347.2-347.9)</b>	---

**$\alpha$ -blocker:** Alpha blocker; **BMI:** Body mass index; **CPRD:** Clinical Practice Research Datalink; **n:** number; **PSA:** Prostate-specific antigen; **SD:** Standard deviation; **UK:** United Kingdom.

**Supplementary Table 4.** Temporal trends in the prescription of BPH medications among men with BPH in the UK from 1998-2016, with 5 $\alpha$ RIs sub-classified by molecule.

Types of prescription	Years	Number of prescriptions*	Person-year	Prescription rate per 100 per year (95% CI)	Crude rate ratio (95% CI)
$\alpha$ -blockers only	1998-2000	111,969	90,861	123.2 (122.5-124.0)	1.00 (ref)
	2001-2003	279,933	154,142	181.6 (180.9-182.3)	1.47 (1.46-1.48)
	2004-2006	447,361	209,460	213.6 (213.0-214.2)	1.73 (1.72-1.74)
	2007-2009	563,866	241,425	233.6 (232.9-234.2)	1.90 (1.88-1.91)
	2010-2012	632,366	251,131	249.1 (248.5-249.7)	2.02 (2.01-2.03)
	2013-2016	609,454	229,245	258.8 (258.2-259.5)	2.10 (2.09-2.11)
	<b>1998-2016</b>	<b>2,622,076</b>	<b>1,176,264</b>	<b>222.9 (222.7-223.2)</b>	---
5 $\alpha$ RIs (Dutasteride)	1998-2000	0	90,861	---	---
	2001-2003	626	154,142	0.4 (0.4-0.4)	1.00 (ref)*
	2004-2006	19,709	209,460	9.4 (9.3-9.5)	23.17 (21.40-25.09)
	2007-2009	33,548	241,425	13.9 (13.8-14.0)	34.22 (31.62-37.03)
	2010-2012	37,126	251,131	14.8 (14.6-14.9)	36.40 (33.64-39.39)
	2013-2016	24,998	229,245	10.9 (10.8-11.0)	26.85 (24.80-29.07)
	<b>1998-2016</b>	<b>116,007</b>	<b>1,176,264</b>	<b>9.9 (9.8-9.9)</b>	---
5 $\alpha$ RIs (Finasteride)	1998-2000	34,007	90,861	37.4 (37.0-37.8)	1.00 (ref)
	2001-2003	67,170	154,142	43.6 (43.3-43.9)	1.16 (1.15-1.18)
	2004-2006	109,338	209,460	52.2 (51.9-52.5)	1.39 (1.38-1.41)
	2007-2009	150,482	241,425	62.3 (62.0-62.7)	1.67 (1.65-1.69)
	2010-2012	168,939	251,131	67.3 (67.0-67.6)	1.80 (1.78-1.82)
	2013-2016	167,426	229,245	73.0 (72.6-73.3)	1.95 (1.93-1.97)
	<b>1998-2016</b>	<b>697,251</b>	<b>1,176,264</b>	<b>59.3 (59.1-59.4)</b>	---
$\alpha$ -blocker and 5 $\alpha$ RI combination therapy	1998-2000	4,442	90,861	4.9 (7.8-5.0)	1.00 (ref)
	2001-2003	15,771	154,142	10.2 (10.1-10.4)	2.09 (2.02-2.16)
	2004-2006	60,026	209,460	28.7 (28.4-28.9)	5.86 (5.69-6.04)
	2007-2009	128,545	241,425	53.2 (53.0-53.5)	10.89 (10.57-11.22)
	2010-2012	194,114	251,131	80.0 (79.6-80.3)	16.36 (15.88-16.85)
	2013-2016	227,426	229,245	106.2 (105.8-106.7)	20.29 (16.70-20.90)
	<b>1998-2016</b>	<b>653,197</b>	<b>1,176,264</b>	<b>55.5 (55.4-55.7)</b>	---
Overall prescription of BPH drugs	1998-2000	150,418	90,861	165.6 (164.7-166.4)	1.00 (ref)
	2001-2003	363,500	154,142	235.8 (235.1-236.6)	1.42 (1.42-1.43)
	2004-2006	636,434	209,460	303.9 (303.1-304.6)	1.84 (1.83-1.85)

2007-2009	876,441	241,425	363.0 (362.3-363.8)	2.19 (2.18-2.20)
2010-2012	1,032,545	251,131	411.2 (410.4-412.0)	2.48 (2.47-2.50)
2013-2016	1,029,193	229,245	449.0 (448.1-449.8)	2.71 (2.70-2.73)
<b>1998-2016</b>	<b>4,088,531</b>	<b>1,176,264</b>	<b>347.6 (347.3-347.9)</b>	---

**5 $\alpha$ RI:** Five alpha-reductase inhibitors;  **$\alpha$ -blocker:** Alpha blocker; **BPH:** Benign prostatic hyperplasia; **CI:** Confidence interval; **CPRD:** Clinical Practice Research Datalink; **n:** number; **UK:** United Kingdom

\*The reference period for the dutasteride analysis was 2001-2003.

**Supplementary Table 5.** Temporal trends in the prescription of BPH medications among men with BPH in the UK from 1998-2016, with  $\alpha$ -blockers subclassified by molecule.

Types of $\alpha$ -blockers prescription	Years	Number of prescriptions*	Person-year	Prescription rate per 100 per year (95% CI)	Crude rate ratio (95% CI)
Alfuzosin	1998-2000	16,248	90,861	17.9 (17.6-18.2)	1 (ref)
	2001-2003	41,286	154,142	26.8 (26.5-26.4)	1.50 (1.47-1.53)
	2004-2006	65,801	209,460	31.4 (31.2-31.7)	1.76 (1.73-1.79)
	2007-2009	77,313	241,425	32.0 (31.8-32.3)	1.79 (1.76-1.82)
	2010-2012	67,470	251,131	26.9 (26.7-27.1)	1.50 (1.48-1.53)
	2013-2016	49,015	229,245	21.4 (21.2-21.6)	1.20 (1.17-1.22)
	<b>1998-2016</b>	<b>317,133</b>	<b>1,176,264</b>	<b>27.0 (26.9-27.1)</b>	---
Doxazosin	1998-2000	15,742	90,861	17.3 (17.1-17.6)	1 (ref)
	2001-2003	56,683	154,142	36.8 (36.5-37.1)	2.12 (2.09-2.16)
	2004-200	99,482	209,460	47.5 (47.2-47.8)	2.74 (2.70-2.79)
	2007-2009	117,306	241,425	48.6 (48.3-48.9)	2.80 (2.76-2.85)
	2010-2012	112,575	251,131	44.8 (44.6-45.1)	2.59 (2.54-2.63)
	2013-2016	91,622	229,245	40.0 (39.7-40.2)	2.31 (2.27-2.35)
	<b>1998-2016</b>	<b>493,410</b>	<b>1,176,264</b>	<b>42.0 (41.8-42.1)</b>	---
Indoramin	1998-2000	25,855	90,861	28.5 (28.1-28.8)	1 (ref)
	2001-2003	31,398	154,142	20.4 (20.2-20.6)	0.72 (0.70-0.73)
	2004-2006	27,584	209,460	13.2 (13.0-13.3)	0.46 (0.46-0.47)
	2007-2009	21,158	241,425	8.8 (8.7-8.9)	0.31 (0.30-0.31)
	2010-2012	13,283	251,131	5.3 (5.2-5.4)	0.19 (0.18-0.19)
	2013-2016	8,776	229,245	3.8 (3.7-3.9)	0.13 (0.13-0.14)
	<b>1998-2016</b>	<b>128,054</b>	<b>1,176,264</b>	<b>10.9 (10.8-11.0)</b>	---
Phenoxybenzamine	1998-2000	78	90,861	0.09 (0.07-0.11)	1 (ref)
	2001-2003	60	154,142	0.04 (0.03-0.05)	0.45 (0.32-0.63)
	2004-2006	88	209,460	0.04 (0.03-0.05)	0.49 (0.36-0.66)
	2007-2009	51	241,425	0.02 (0.02-0.03)	0.25 (0.17-0.35)
	2010-2012	3	251,131	0.00 (0.00-0.00)	0.01 (0.00-0.04)
	2013-2016	7	229,245	0.00 (0.00-0.01)	0.04 (0.02-0.08)
	<b>1998-2016</b>	<b>287</b>	<b>1,176,264</b>	<b>0.02 (0.02-0.03)</b>	---
Phentolamine	1998-2000	S	S	0.01 (0.01-0.02)	1 (ref)
	2001-2003	S	S	0.00 (0.00-0.01)	0.18 (0.06-0.56)
	2004-2006	0	209,460	---	---
	2007-2009	0	241,425	---	---

	2010-2012	0	251,131	---	---
	2013-2016	0	229,245	---	---
	<b>1998-2016</b>	<b>17</b>	<b>1,176,264</b>	<b>0 (0-0)</b>	---
Prazosin	1998-2000	7,312	90,861	8.1 (7.9-8.2)	1 (ref)
	2001-2003	9,886	154,142	6.4 (6.3-6.5)	0.80 (0.77-0.82)
	2004-2006	9,101	209,460	4.3 (4.3-4.4)	0.54 (0.52-0.56)
	2007-2009	5,770	241,425	2.4 (2.3-2.5)	0.30 (0.29-0.31)
	2010-2012	4,246	251,131	1.7 (1.6-1.7)	0.21 (0.20-0.22)
	2013-2016	3,144	229,245	1.4 (1.3-1.4)	0.17 (0.16-0.18)
	<b>1998-2016</b>	<b>39,459</b>	<b>1,176,264</b>	<b>3.4 (3.3-3.4)</b>	---
Tamsulosin	1998-2000	35,684	90,861	39.3 (38.9-40.0)	1 (ref)
	2001-2003	123,544	154,142	80.2 (79.7-80.6)	2.04 (2.02-2.07)
	2004-2006	229,457	209,460	109.6 (109.1-110.0)	2.79 (2.76-2.82)
	2007-2009	331,128	241,425	137.2 (136.7-137.6)	3.49 (3.45-3.53)
	2010-2012	423,125	251,131	168.5 (168.0-169.0)	4.29 (4.24-4.34)
	2013-2016	440,892	229,245	192.3 (191.8-192.9)	4.90 (4.84-4.95)
	<b>1998-2016</b>	<b>1,583,830</b>	<b>1,176,264</b>	<b>134.7 (134.4-134.9)</b>	---
Terazosin	1998-2000	11,412	90,861	12.6 (12.3-12.8)	1 (ref)
	2001-2003	19,077	154,142	12.4 (12.2-12.6)	0.99 (0.96-1.01)
	2004-2006	20,263	209,460	9.7 (9.5-9.8)	0.77 (0.75-0.79)
	2007-2009	17,309	241,425	7.2 (7.1-7.3)	0.57 (0.56-0.58)
	2010-2012	12,974	251,131	5.2 (5.1-5.3)	0.41 (0.40-0.42)
	2013-2016	9,054	229,245	4.0 (3.9-4.0)	0.31 (0.31-0.32)
	<b>1998-2016</b>	<b>90,089</b>	<b>1,176,264</b>	<b>7.7 (7.6-7.7)</b>	---

**$\alpha$ -blocker:** Alpha blocker; **BPH:** Benign prostatic hyperplasia; **CI:** Confidence interval; **CPRD:** Clinical Practice Research Datalink; **n:** number; **ref:** Reference Category; **S:** Denotes small cells that were suppressed due to CPRD privacy protection policies. **UK:** United Kingdom.

**Supplementary Table 6.** The association between baseline characteristics and adherence\* to BPH medications at one year among men with BPH in the UK between 1998 and 2016.

Baseline characteristics	OR (95% CI)		
	5 $\alpha$ RI (n=47,874)	$\alpha$ -blockers (n=117,725)	Combination therapy (n=31,910)
<b>Age (years)</b>			
< 55	1 (ref)	1 (ref)	1 (ref)
55-64	1.33 (1.20-1.47)	1.44 (1.38-1.51)	1.11 (1.01-1.23)
65-74	1.66 (1.51-1.83)	1.59 (1.52-1.66)	1.12 (1.02-1.23)
75-84	2.08 (1.89-2.30)	1.47 (1.40-1.54)	1.10 (0.99-1.22)
$\geq$ 85	2.61 (2.31-2.94)	1.31 (1.22-1.40)	1.20 (1.04-1.38)
<b>Calendar year</b>			
1998-2001	1 (ref)	1 (ref)	1 (ref)
2002-2005	0.87 (0.82-0.92)	1.19 (1.15-1.23)	1.06 (0.99-1.13)
2006-2009	0.73 (0.69-0.77)	1.19 (1.14-1.23)	1.20 (1.12-1.29)
2010-2013	0.65 (0.61-0.70)	1.19 (1.15-1.24)	1.44 (1.33-1.55)
2014-2016	0.82 (0.75-0.90)	1.36 (1.29-1.43)	1.61 (1.46-1.78)
<b>Lifestyle variables</b>			
<b>BMI</b>			
$\geq$ 30 kg/m <sup>2</sup>	1 (ref)	1 (ref)	1 (ref)
< 30 kg/m <sup>2</sup>	1.05 (1.00-1.12)	0.89 (0.86-0.92)	0.92 (0.86-0.98)
Unknown	1.07 (1.00-1.14)	0.88 (0.84-0.91)	0.94 (0.88-1.02)
<b>Smoking</b>			
Ever smoker	1 (ref)	1 (ref)	1 (ref)
Never smoker	1.04 (1.00-1.09)	0.94 (0.92-0.97)	0.92 (0.87-0.97)
Unknown	0.99 (0.93-1.05)	0.92 (0.89-0.95)	0.93 (0.87-1.01)
<b>PSA testing in the previous year</b>			
0-4 ng/ml	1 (ref)	1 (ref)	1 (ref)
4-10 ng/ml	1.01 (0.93-1.09)	1.31 (1.25-1.38)	1.18 (1.08-1.28)
10-20 ng/ml	1.22 (1.06-1.40)	1.30 (1.18-1.43)	1.16 (0.99-1.36)
20+ ng/ml	1.14 (0.89-1.45)	1.60 (1.38-1.85)	1.29 (0.96-1.73)
Unknown	1.01 (0.97-1.07)	1.09 (1.06-1.12)	1.04 (0.99-1.10)
<b>General Practitioner Visits</b>			
0	1 (ref)	1 (ref)	1 (ref)
1-6	1.01 (0.97-1.06)	1.07 (1.05-1.10)	1.00 (0.96-1.05)
7-12	1.02 (0.92-1.13)	1.11 (1.04-1.18)	0.99 (0.88-1.12)
13-24	1.11 (0.93-1.33)	1.07 (0.95-1.20)	0.88 (0.72-1.09)
$\geq$ 25	0.93 (0.62-1.39)	1.04 (0.81-1.32)	0.92 (0.58-1.47)
<b>Charlson Comorbidity Index</b>			
0	1 (ref)	1 (ref)	1 (ref)
1	1.05 (1.00-1.10)	1.02 (0.99-1.05)	0.92 (0.87-0.98)
2+	1.12 (1.07-1.18)	1.04 (1.01-1.07)	0.95 (0.89-1.00)

**5 $\alpha$ RI:** Five alpha-reductase inhibitors;  **$\alpha$ -blocker:** Alpha blocker; **BMI:** Body mass index; **CI:** Confidence Interval; **n:** number; **OR:** Odds Ratio; **PSA:** Prostate-specific antigen; **SD:** Standard deviation; **UK:** United



Kingdom.

\* Adherence was defined as a percentage of days covered at 1 year of at least 80%.

**Supplementary Table 7.** Baseline characteristics of men with incident BPH in UK between 1998-2016, by treatment at cohort entry.

<b>Patients characteristics</b>	<b>5<math>\alpha</math>RIs (n=2,849)</b>	<b><math>\alpha</math>-blockers (n=23,586)</b>	<b>Combination treatments* (n=1,279)</b>	<b>No treatment (n=66,884)</b>	<b>Total (n=94,598)</b>
<b>Age, mean (SD)</b>	70.1 (10.1)	67.3 (10.2)	69.5 (9.8)	65.6 (10.4)	66.2 (10.4)
< 55	202 (7.1)	2,916 (12.4)	94 (7.4)	10,707 (16.0)	13,919 (14.7)
55-64	694 (24.4)	7,014 (29.7)	343 (26.8)	21,964 (32.8)	30,015 (31.7)
65-74	1,000 (35.1)	8,029 (34.0)	447 (35.0)	21,028 (31.4)	30,504 (32.3)
75-84	766 (26.9)	4,694 (19.9)	325 (25.4)	11,171 (16.7)	16,956 (17.9)
$\geq 85$	187 (6.6)	933 (4.0)	70 (5.5)	2,014 (3.0)	3,204 (3.4)
<b>Calendar year, n (%)</b>					
1998-2001	458 (16.1)	2,790 (11.8)	34 (2.7)	13,983 (20.9)	17,265 (18.3)
2002-2005	695 (24.4)	5,233 (22.2)	143 (11.2)	18,819 (28.1)	24,890 (26.3)
2006-2009	901 (31.6)	6,290 (26.7)	394 (30.8)	17,438 (26.1)	25,023 (26.5)
2010-2013	619 (21.7)	6,707 (28.4)	515 (40.3)	12,472 (18.7)	20,313 (21.5)
2014-2016	176 (6.2)	2,566 (10.9)	193 (15.1)	4,172 (6.2)	7,107 (7.5)
<b>Lifestyle variables</b>					
<b>BMI, n (%)</b>					
$\geq 30$ kg/m <sup>2</sup>	454 (15.9)	4,454 (18.9)	256 (20.0)	10,009 (15.0)	15,173 (16.0)
< 30 kg/m <sup>2</sup>	1,605 (56.4)	12,678 (53.8)	737 (57.6)	33,990 (50.8)	49,010 (51.8)
Unknown	790 (27.7)	6,454 (27.4)	286 (22.4)	22,885 (34.2)	30,415 (32.2)
<b>Smoking, n (%)</b>					
Ever smoker	1,631 (57.3)	13,509 (57.3)	759 (59.3)	34,239 (51.2)	50,138 (53.0)
Never smoker	774 (27.2)	6,454 (27.4)	415 (32.5)	17,527 (26.2)	25,170 (26.6)
Unknown	444 (15.6)	3,623 (15.4)	105 (8.2)	15,118 (22.6)	19,290 (20.4)
<b>PSA testing in the previous year, n (%)</b>					
0-4 ng/ml	934 (32.8)	8,606 (36.5)	454 (35.5)	11,912 (17.8)	21,906 (23.2)
4-10 ng/ml	304 (10.7)	1,830 (7.8)	173 (13.5)	5,254 (7.9)	7,561 (8.0)
10-20 ng/ml	79 (2.8)	350 (1.5)	49 (3.8)	1,521 (2.3)	1,999 (2.1)
20+ ng/ml	29 (1.0)	159 (0.7)	20 (1.6)	938 (1.4)	1,146 (1.2)
Unknown	1,503 (52.8)	12,641 (53.6)	583 (45.6)	47,259 (70.7)	61,986 (65.5)
<b>General practitioner visits, mean (SD)</b>					
0	1.6 (3.2)	1.4 (3.0)	1.6 (3.1)	1.1 (2.8)	1.2 (2.8)
1-6	1,571 (55.1)	13,736 (58.2)	698 (54.6)	42,072 (62.9)	58,077 (61.4)
7-12	1,110 (39.0)	8,797 (37.3)	511 (40.0)	22,480 (33.6)	32,898 (34.8)
13-24	128 (4.5)	773 (3.3)	51 (4.0)	1,717 (2.6)	2,669 (2.8)
$\geq 25$	33 (1.2)	238 (1.0)	16 (1.3)	516 (0.8)	803 (0.9)
<b>Charlson Comorbidity Score, n (%)</b>					
0	7 (0.3)	42 (0.2)	3 (0.2)	99 (0.2)	151 (0.2)
1	1,237 (43.4)	11,230 (47.6)	547 (42.8)	36,631 (54.8)	49,645 (52.5)
2	684 (24.0)	5,591 (23.7)	288 (22.5)	15,498 (23.2)	22,061 (23.3)
2+	928 (32.6)	6,765 (28.7)	444 (34.7)	14,755 (22.1)	22,892 (24.2)

**5 $\alpha$ RI:** Five alpha-reductase inhibitors;  **$\alpha$ -blocker:** Alpha blocker; **BMI:** Body mass index; **CPRD:** Clinical Practice Research Datalink; **n:** number; **PSA:** Prostate-specific antigen; **SD:** Standard deviation; **UK:** United Kingdom.

\* Combination treatment included a five alpha-reductase inhibitors and alpha-blocker.

**Supplementary Table 8.** Temporal trends in the prescription of BPH medications among men with incident BPH in the UK from 1998-2016.

Incident Cohort (n=94,598)							
Types of prescription	Years	No. of prescription	Person-years (PYs)	Prescription per 100 PYs	Crude rate ratios (95% CI)	Crude rate ratio (95% CI) compared with preceding year	Adjusted rate ratio (95% CI) *
$\alpha$ -blockers only	1998-2000	27,625	14,262	193.0 (190.7-195.3)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	2001-2003	105,676	51,029	207.1 (205.8-208.3)	1.07 (1.06-1.09)	1.07 (1.06-1.09)	1.05 (1.03-1.06)
	2004-2006	191,115	89,787	212.9 (211.9-213.8)	1.10 (1.09-1.12)	1.03 (1.02-1.04)	1.06 (1.05-1.07)
	2007-2009	266,358	119,414	223.1 (222.2-223.9)	1.16 (1.14-1.17)	1.05 (1.04-1.05)	1.09 (1.08-1.11)
	2010-2012	317,557	134,731	235.7 (234.9-236.5)	1.22 (1.21-1.24)	1.06 (1.05-1.06)	1.14 (1.12-1.15)
	2013-2016	312,795	127,247	245.8 (245.0-246.7)	1.27 (1.26-1.29)	1.04 (1.04-1.05)	1.17 (1.16-1.18)
	1998-2016	1,221,026	536,471	227.6 (227.2-228.0)	---	---	---
5 $\alpha$ RI only	1998-2000	6,275	14,262	44.0 (42.9-45.1)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	2001-2003	19,537	51,029	38.3 (37.8-38.8)	0.87 (0.85-0.90)	0.87 (0.85-0.90)	0.81 (0.79-0.84)
	2004-2006	46,438	89,787	51.7 (51.3-52.2)	1.18 (1.14-1.21)	1.35 (1.33-1.37)	1.05 (1.02-1.07)
	2007-2009	74,897	119,414	62.7 (62.3-63.2)	1.43 (1.39-1.46)	1.21 (1.20-1.23)	1.22 (1.18-1.25)
	2010-2012	91,245	134,731	67.7 (67.3-68.2)	1.54 (1.50-1.58)	1.08 (1.07-1.09)	1.26 (1.23-1.29)
	2013-2016	85,244	127,247	67.0 (66.5-67.4)	1.52 (1.48-1.56)	0.99 (0.98-0.9985)	1.19 (1.16-1.22)
	1998-2016	323,636	536,471	60.3 (60.1-60.5)	---	---	---
$\alpha$ -blocker and 5 $\alpha$ RI combination therapy	1998-2000	800	14,262	5.6 (5.2-6.0)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	2001-2003	4,121	51,029	8.1 (7.8-8.3)	1.44 (1.33-1.55)	1.44 (1.33-1.55)	1.37 (1.27-1.48)
	2004-2006	21,478	89,787	23.9 (23.6-24.2)	4.26 (3.97-4.58)	2.96 (2.86-3.06)	3.91 (3.64-4.19)
	2007-2009	52,181	119,414	43.7 (43.3-44.1)	7.79 (7.26-8.35)	1.83 (1.80-1.86)	6.89 (6.43-7.39)
	2010-2012	85,362	134,731	63.4 (62.9-63.8)	11.29 (10.54-12.11)	1.45 (1.43-1.47)	9.68 (9.03-10.38)
	2013-2016	109,450	127,247	86.0 (85.5-86.5)	15.33 (14.30-16.44)	1.36 (1.35-1.37)	12.75 (11.89-13.66)
	1998-2016	273,392	536,471	51.0 (50.8-51.2)	---	---	---
Overall prescription of BPH drugs	1998-2000	34,600	14,262	242.6 (240.1-245.2)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	2001-2003	129,334	51,029	253.5 (252.1-254.8)	1.04 (1.03-1.06)	1.04 (1.03-1.06)	1.01 (0.9978-1.02)
	2004-2006	259,031	89,787	288.5 (287.4-289.6)	1.19 (1.18-1.20)	1.14 (1.13-1.15)	1.12 (1.11-1.13)
	2007-2009	393,436	119,414	329.5 (328.4-330.5)	1.36 (1.34-1.37)	1.14 (1.14-1.15)	1.25 (1.24-1.26)
	2010-2012	494,164	134,731	366.8 (365.8-367.8)	1.51 (1.50-1.53)	1.11 (1.11-1.12)	1.36 (1.35-1.38)
	2013-2016	507,489	127,247	398.8 (397.7-399.9)	1.64 (1.63-1.66)	1.09 (1.08-1.09)	1.45 (1.43-1.46)
	1998-2016	1,818,054	536,471	338.9 (338.4-339.4)	---	---	---

**5 $\alpha$ RI:** Five alpha-reductase inhibitors;  **$\alpha$ -blocker:** Alpha blocker; **CI:** Confidence interval; **CPRD:** Clinical Practice Research Datalink; **n:** number; **PYs:** Person Years; **UK:** United Kingdom; \*The rate ratio was adjusted for age with spline restricted (5%, 27.5%, 50%, 72.5%, 95%).

**Supplementary Table 9.** Trends in the prescription of BPH medications among men with incident BPH in the UK from 1998-2016, by age at cohort entry.

<b>Incident Cohort (n=94,598)</b>					
<b>Types of prescription</b>	<b>Age (years)</b>	<b>No. of prescription</b>	<b>Person-years</b>	<b>Prescription rate per 100 per year (95% CI)</b>	<b>Crude rate ratio (95% CI)</b>
$\alpha$ -blockers only	40-54	54,824	45,536	120.4 (119.4-121.4)	1.00 (ref)
	55-64	270,107	142,187	190.0 (189.3-190.7)	1.58 (1.56-1.59)
	65-74	460,749	189,404	243.3 (242.6-244.0)	2.02 (2.00-2.04)
	75-84	347,374	128,080	271.2 (270.3-272.1)	2.25 (2.23-2.27)
	$\geq 85$	87,972	31,263	281.4 (279.5-283.3)	2.34 (2.31-2.36)
	$\geq 40$	1,221,026	536,471	227.6 (227.2-228.0)	---
5 $\alpha$ RIs only	40-54	5,325	45,536	11.7 (11.4-12.0)	1.00 (ref)
	55-64	41,978	142,187	29.5 (29.2-29.8)	2.52 (2.45-2.60)
	65-74	106,912	189,404	56.5 (56.1-56.8)	4.83 (4.70-4.96)
	75-84	124,948	128,080	97.6 (97.0-98.1)	8.34 (8.12-8.57)
	$\geq 85$	44,473	31,263	142.3 (140.9-143.6)	12.16 (11.82-12.52)
	$\geq 40$	323,636	536,471	60.3 (60.1-60.5)	---
$\alpha$ -blockers and 5 $\alpha$ RIs combination therapy	40-54	4,501	45,536	9.9 (9.6-10.2)	1.00 (ref)
	55-64	43,372	142,187	30.5 (30.2-30.8)	3.09 (2.99-3.18)
	65-74	99,108	189,404	52.3 (52.0-52.7)	5.29 (5.14-5.45)
	75-84	94,165	128,080	73.5 (73.1-74.0)	7.44 (7.22-7.66)
	$\geq 85$	32,246	31,263	103.2 (102.0-104.3)	10.44 (10.11-10.77)
	$\geq 40$	273,392	536,471	48.9 (50.8-51.2)	---
Overall prescription of BPH drugs	40-54	64,650	45,536	142.0 (140.9-143.1)	1.00 (ref)
	55-64	355,457	142,187	250.0 (249.2-250.8)	1.76 (1.75-1.78)
	65-74	666,769	189,404	352.0 (351.2-352.9)	2.48 (2.46-2.50)
	75-84	566,487	128,080	442.3 (441.1-443.4)	3.12 (3.09-3.14)
	$\geq 85$	164,691	31,263	526.8 (524.3-529.4)	3.71 (3.68-3.74)
	$\geq 40$	1,818,054	536,471	338.9 (338.4-339.4)	---

**5 $\alpha$ RI:** Five alpha-reductase inhibitors;  **$\alpha$ -blocker:** Alpha blocker; **CI:** Confidence interval; **CPRD:** Clinical Practice Research Datalink; **n:** number; **UK:** United Kingdom.

**Supplementary Table 10.** Temporal trends in the prescription of BPH medications among men with BPH in the UK from 1998-2016, with the preceding year used as the reference category for the estimation of period-specific rate ratios.

Prevalent Cohort (n=192,640)					
Types of prescription	Years	No. of prescription	Person-years (PYs)	Prescription per 100 PYs	Crude rate ratio (95% CI)*
$\alpha$ -blockers only	1998-2000	111,969	90,861	123.2 (122.5-124.0)	1.00 (ref)
	2001-2003	279,933	154,142	181.6 (180.9-182.3)	1.47 (1.46-1.48)
	2004-2006	447,361	209,460	213.6 (213.0-214.2)	1.18 (1.17-1.18)
	2007-2009	563,866	241,425	233.6 (233.0-234.2)	1.09 (1.09-1.10)
	2010-2012	625,615	251,131	249.1 (248.5-249.7)	1.07 (1.06-1.07)
	2013-2016	593,332	229,245	258.8 (258.2-259.5)	1.04 (1.04-1.04)
	1998-2016	2,622,076	1,176,264	222.9 (222.7-223.2)	---
5 $\alpha$ RI only	1998-2000	34,007	90,861	37.4 (37.0-37.8)	1.00 (ref)
	2001-2003	67,791	154,142	44.0 (43.7-44.3)	1.18 (1.16-1.19)
	2004-2006	129,016	209,460	61.6 (61.3-61.9)	1.40 (1.39-1.41)
	2007-2009	183,944	241,425	76.2 (75.8-76.5)	1.24 (1.23-1.25)
	2010-2012	206,030	251,131	82.0 (81.7-82.4)	1.08 (1.07-1.08)
	2013-2016	192,288	229,245	83.9 (83.5-84.3)	1.02 (1.02-1.03)
	1998-2016	813,076	1,176,264	69.1 (69.0-69.3)	---
$\alpha$ -blockers and 5 $\alpha$ RI combination therapy	1998-2000	4,442	90,861	4.9 (4.8-5.0)	1.00 (ref)
	2001-2003	15,771	154,142	10.2 (10.1-10.4)	2.09 (2.02-2.16)
	2004-2006	60,026	209,460	28.7 (28.4-28.9)	2.80 (2.75-2.85)
	2007-2009	128,545	241,425	53.2 (53.0-53.5)	1.86 (1.84-1.88)
	2010-2012	200,865	251,131	80.0 (79.6-80.3)	1.50 (1.49-1.51)
	2013-2016	243,548	229,245	106.2 (105.8-106.7)	1.33 (1.32-1.34)
	1998-2016	653,197	1,176,264	55.5 (55.4-55.7)	---
Overall prescription of BPH drugs	1998-2000	150,418	90,861	165.6 (164.7-166.4)	1.00 (ref)
	2001-2003	363,495	154,142	235.8 (235.1-236.6)	1.42 (1.42-1.43)
	2004-2006	636,403	209,460	303.8 (303.1-304.6)	1.29 (1.28-1.29)
	2007-2009	876,355	241,425	363.0 (362.2-363.8)	1.19 (1.19-1.20)
	2010-2012	1,032,510	251,131	411.1 (410.4-411.9)	1.13 (1.13-1.14)
	2013-2016	1,029,168	229,245	448.9 (448.1-449.8)	1.09 (1.09-1.09)
	1998-2016	4,088,349	1,176,264	347.6 (347.2-347.9)	---

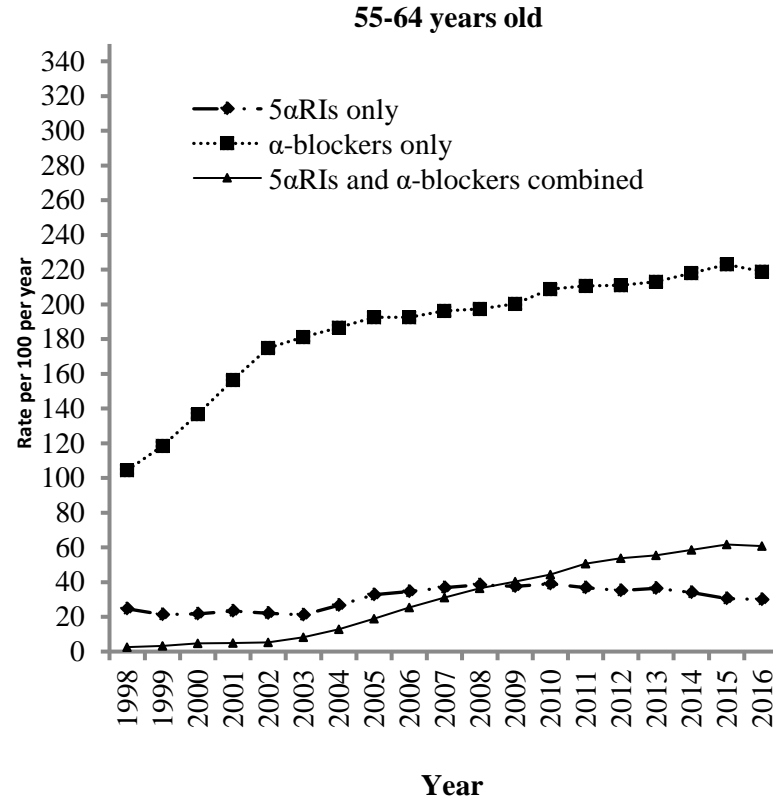
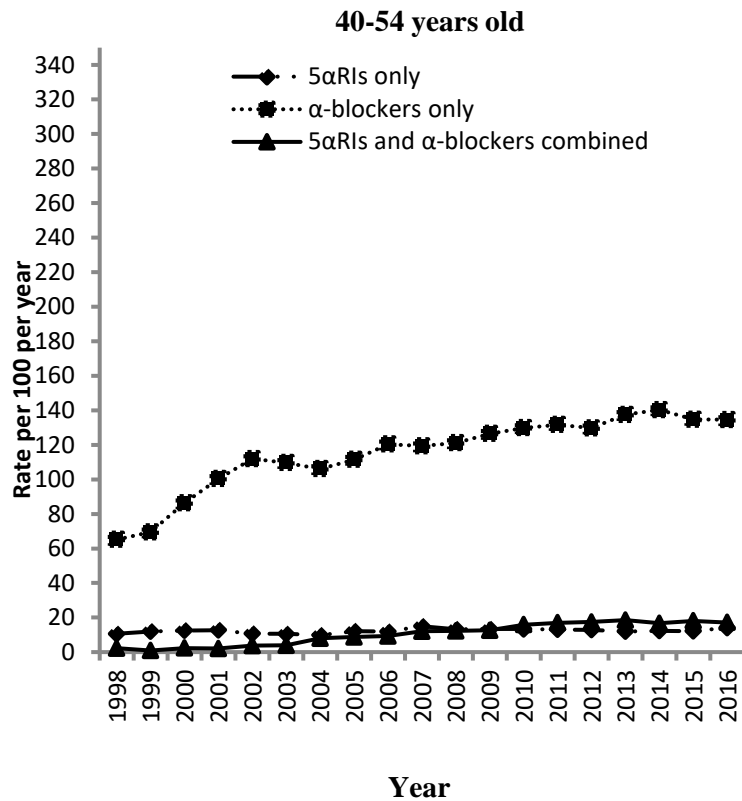
**5 $\alpha$ RI:** Five alpha-reductase inhibitors;  **$\alpha$ -blocker:** Alpha blocker; **UK:** United Kingdom;

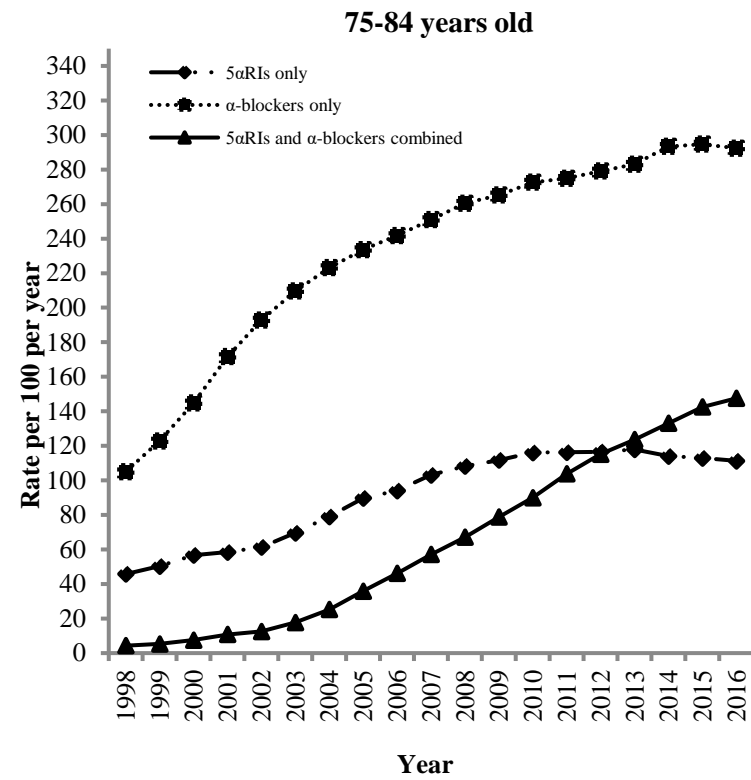
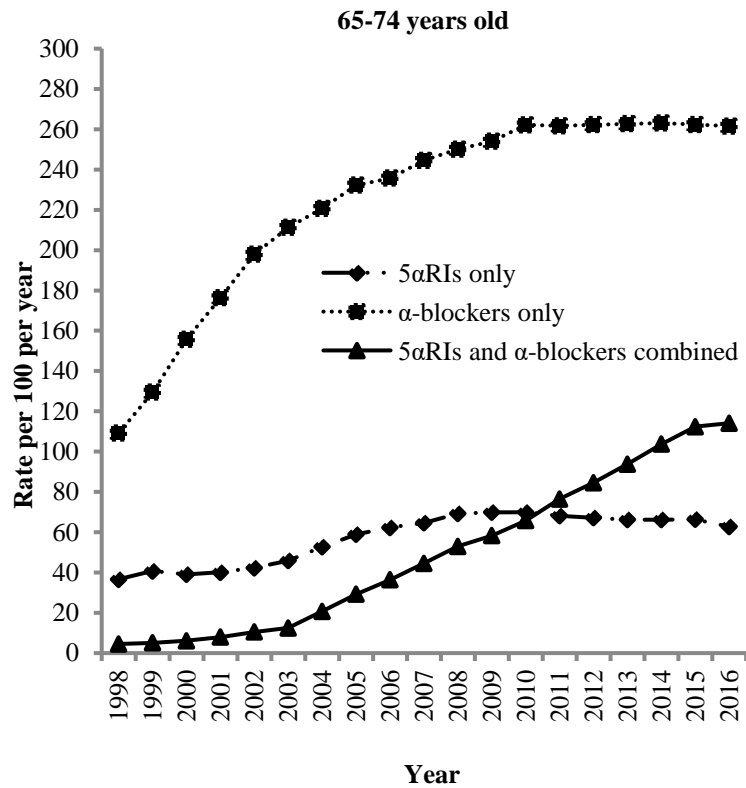
\* Rate ratios estimated with the preceding period as the reference category.

**Supplementary Table 11.** Temporal trends in the prescription of BPH medications among men with BPH in the UK from 1998-2016, with combination therapy sub-classified by formulation (combination pill versus two classes prescribed on the same day).

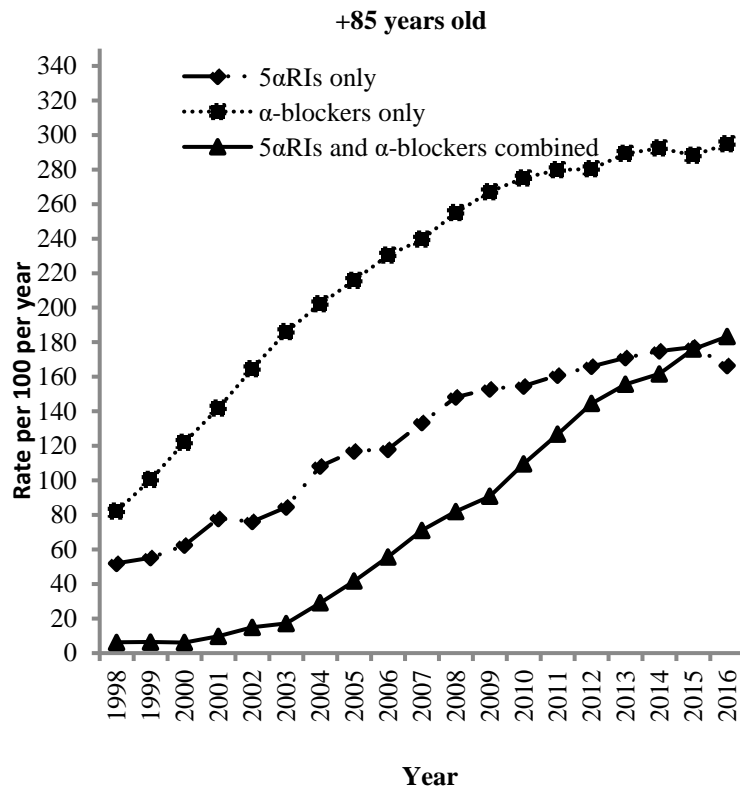
Types of prescription	Years	Number of prescriptions*	Person-year	Prescription rate per 100 per year (95% CI)
$\alpha$ -blockers only	1998-2000	111,969	90,861	123.3 (122.5-124.0)
	2001-2003	279,933	154,142	181.6 (180.9-182.3)
	2004-2006	447,361	209,460	213.6 (213.0-214.2)
	2007-2009	563,866	241,425	233.6 (233.0-234.2)
	2010-2012	625,615	251,131	249.1 (248.5-249.7)
	2013-2016	593,332	229,245	258.8 (258.2-259.5)
	<b>1998-2016</b>	<b>2,622,076</b>	<b>1,176,264</b>	<b>222.9 (222.7-223.2)</b>
5 $\alpha$ RIs only	1998-2000	34,007	90,861	37.4 (37.0-37.8)
	2001-2003	67,791	154,142	44.0 (43.7-44.3)
	2004-2006	129,016	209,460	61.6 (61.3-61.9)
	2007-2009	183,944	241,425	76.2 (75.8-76.5)
	2010-2012	206,030	251,131	82.0 (81.7-82.4)
	2013-2016	192,288	229,245	83.9 (83.5-84.3)
	<b>1998-2016</b>	<b>813,076</b>	<b>1,176,264</b>	<b>69.1 (69.0-69.3)</b>
$\alpha$ -blocker and 5 $\alpha$ RI combination therapy: combination pills	1998-2000	0	90,861	---
	2001-2003	0	154,142	---
	2004-2006	0	209,460	---
	2007-2009	0	241,425	---
	2010-2012	11,404	251,131	4.5 (4.5-4.6)
	2013-2016	33,023	229,245	14.4 (14.3-14.6)
	<b>1998-2016</b>	<b>44,427</b>	<b>1,176,264</b>	<b>3.8 (3.7-3.8)</b>
$\alpha$ -blocker and 5 $\alpha$ RI combination therapy: same date	1998-2000	4,442	90,861	4.9 (4.8-5.0)
	2001-2003	15,771	154,142	10.2 (10.1-10.4)
	2004-2006	60,026	209,460	28.7 (28.4-28.9)
	2007-2009	128,545	241,425	53.2 (53.0-53.5)
	2010-2012	189,461	251,131	75.4 (75.1-75.8)
	2013-2016	210,525	229,245	91.8 (91.4-92.2)
	<b>1998-2016</b>	<b>608,870</b>	<b>1,176,264</b>	<b>51.8 (51.6-51.9)</b>
Overall prescription of BPH drugs	1998-2000	150,418	90,861	165.6 (164.7-166.4)
	2001-2003	363,495	154,142	235.8 (235.1-236.6)
	2004-2006	636,403	209,460	303.8 (303.1-304.6)
	2007-2009	876,355	241,425	363.0 (362.2-363.8)
	2010-2012	1,032,510	251,131	411.1 (410.4-411.9)
	2013-2016	1,029,168	229,245	448.9 (448.1-449.8)
	<b>1998-2016</b>	<b>4,088,349</b>	<b>1,176,264</b>	<b>347.6 (347.2-347.9)</b>

**5 $\alpha$ RI:** Five Alpha Reductase Inhibitors;  **$\alpha$ -blocker:** Alpha Blocker; **BPH:** Benign Prostatic Hyperplasia; **CI:** Confidence interval; **CPRD:** Clinical Practice Research Datalink; **n:** number; **UK:** United Kingdom.

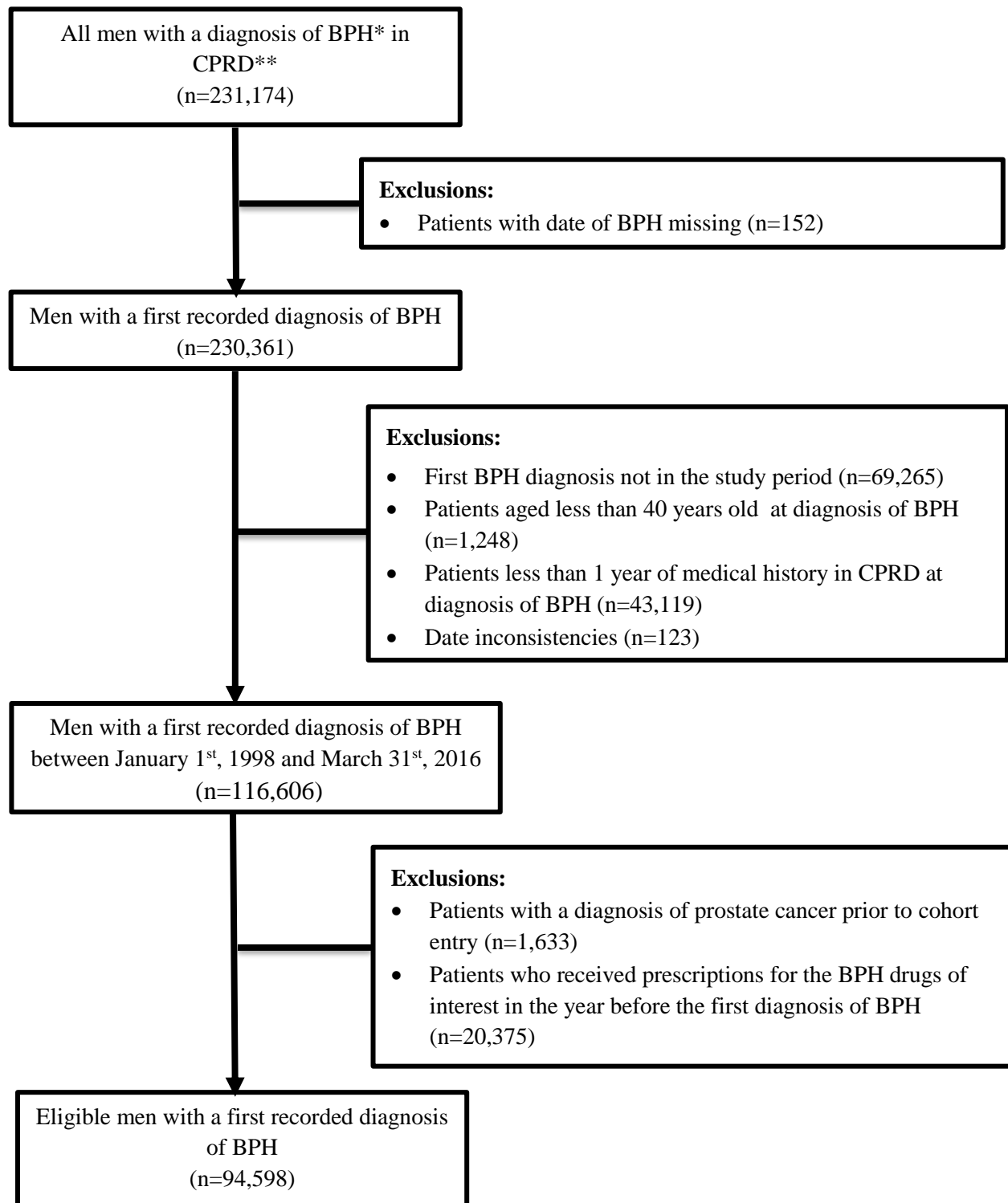




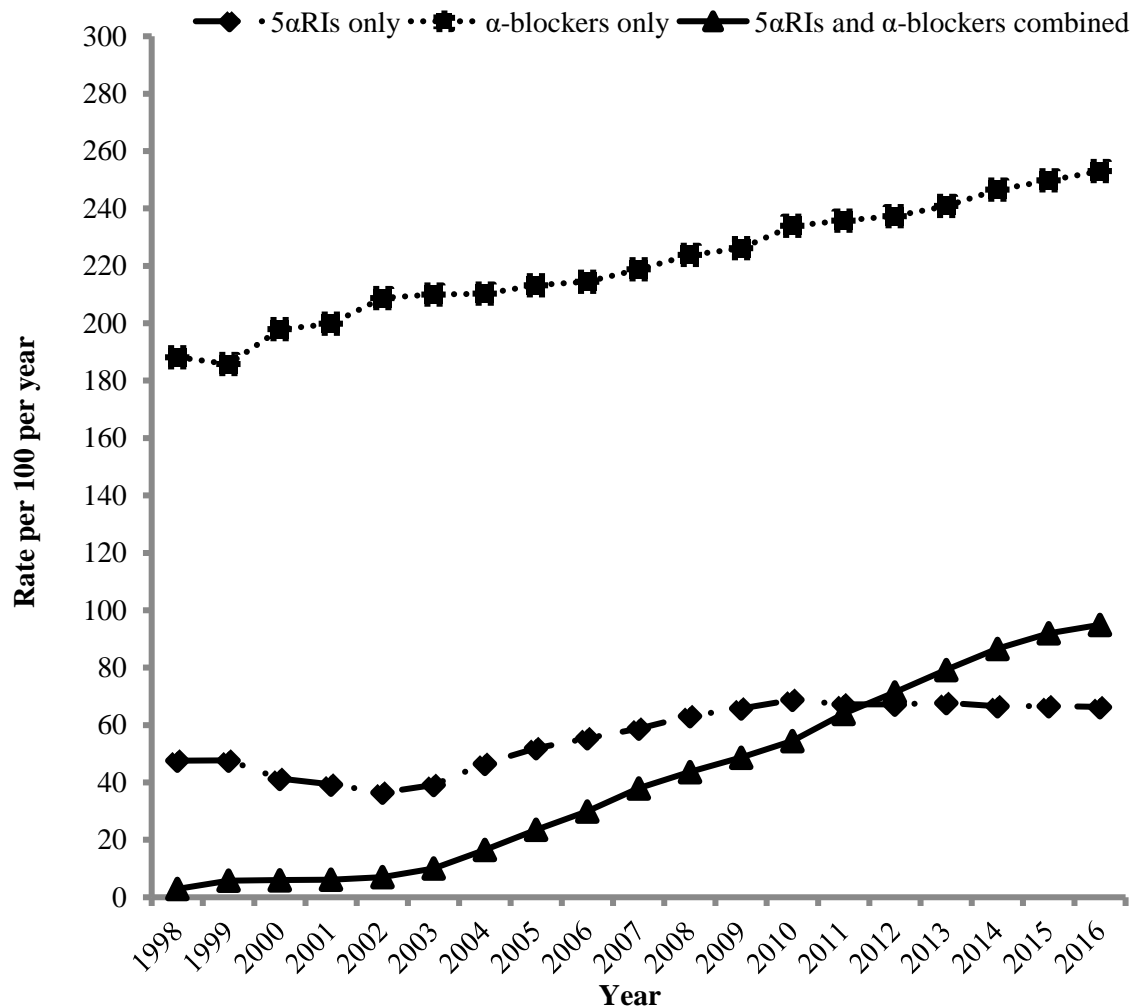




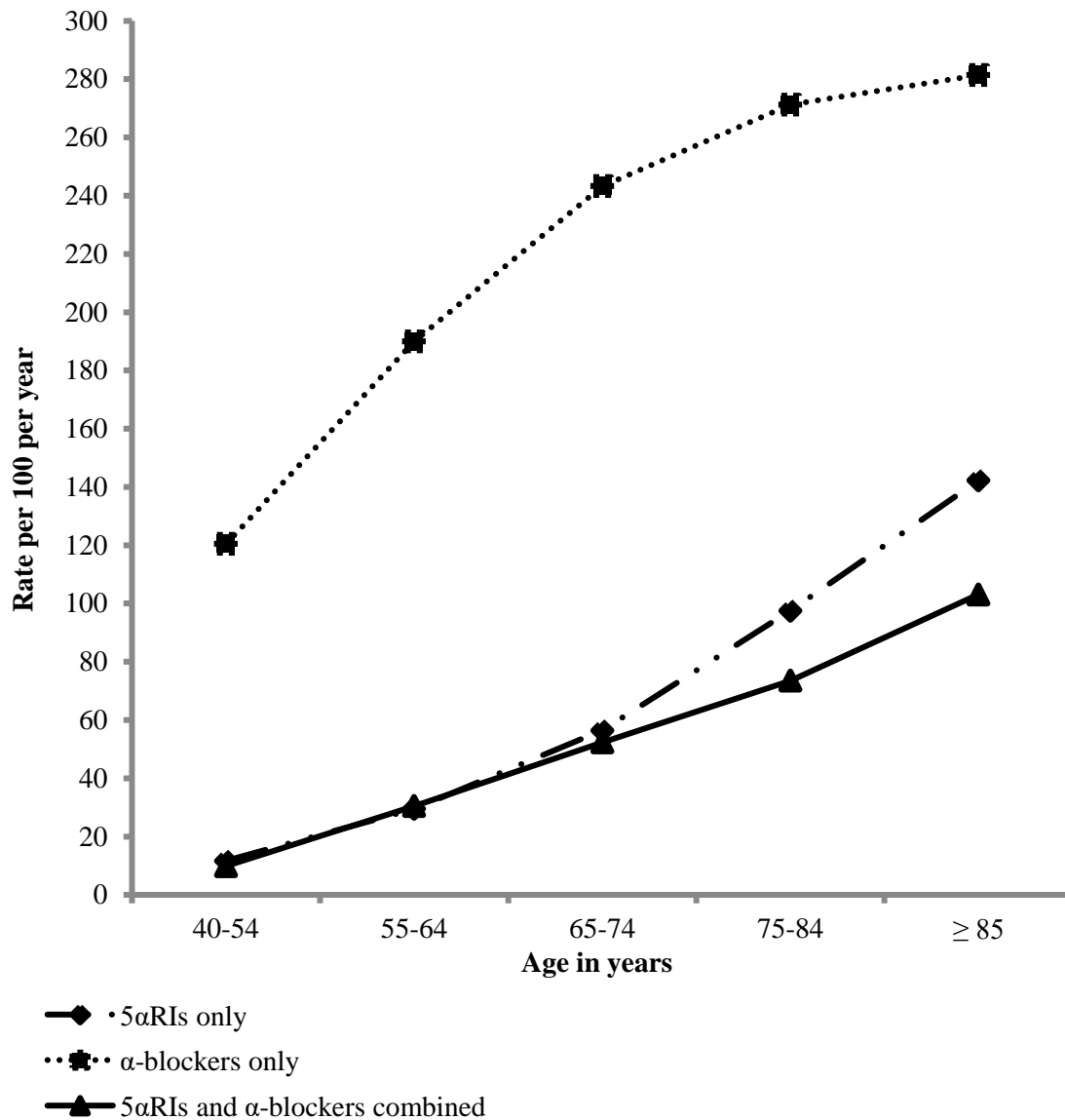
**Supplementary Figure 1:** Temporal trends in the prescription of BPH medications across age strata among men with BPH in the UK from 1998-2016.



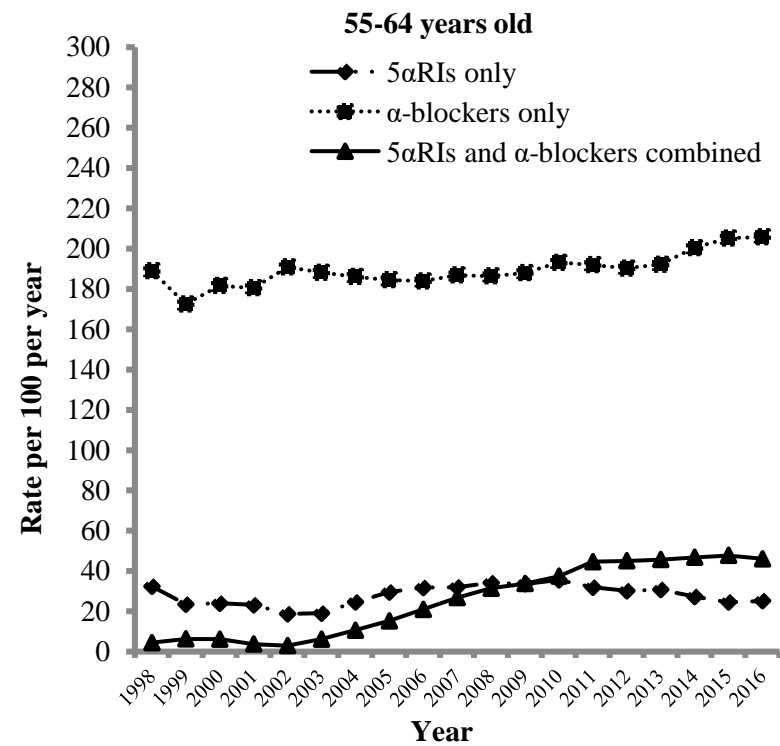
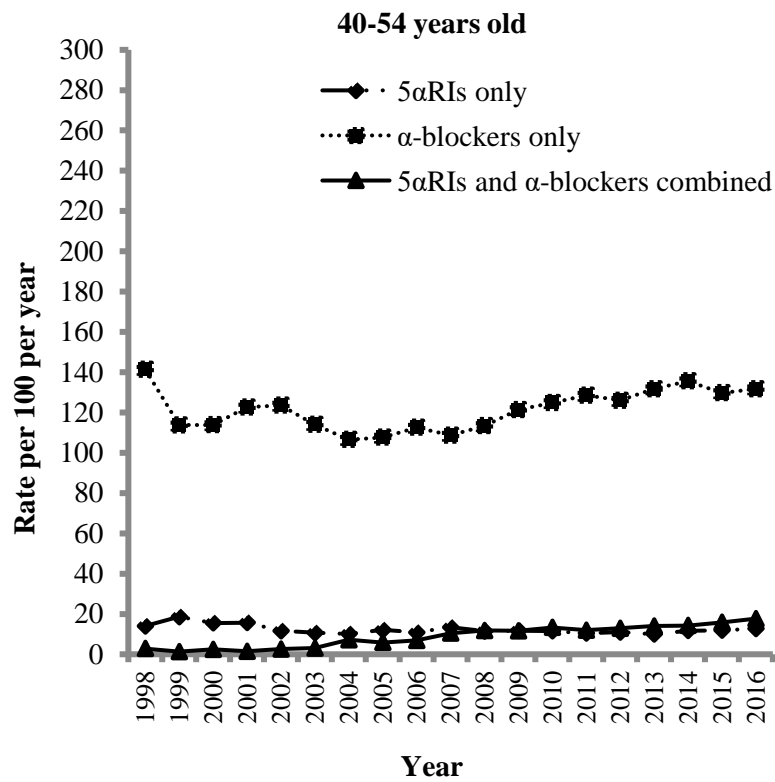
**Supplementary Figure 2.** Flow diagram describing the construction of cohort of men with incident BPH in the UK between 1998-2016 \*Benign Prostatic Hyperplasia \*\* Clinical Practice Research Datalink

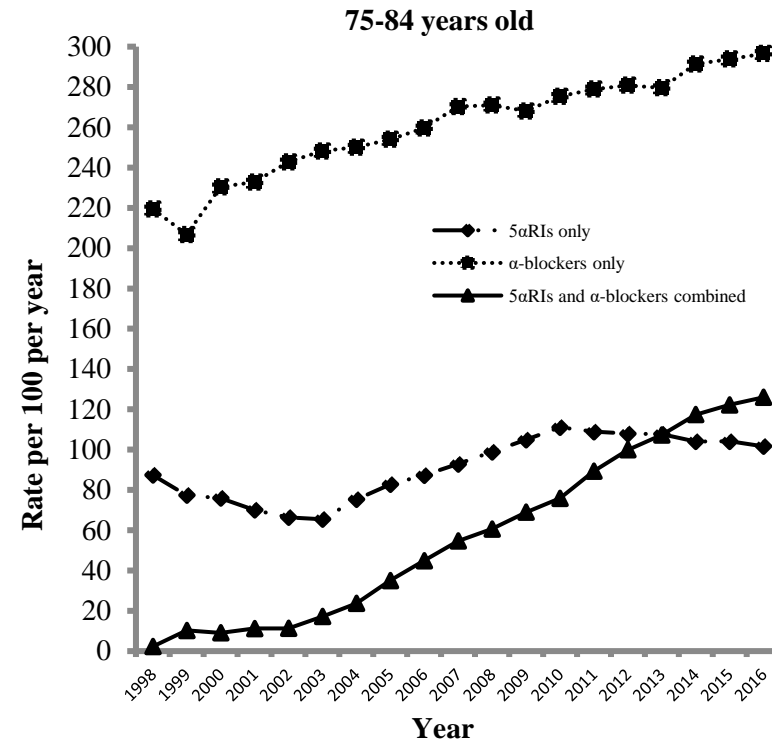
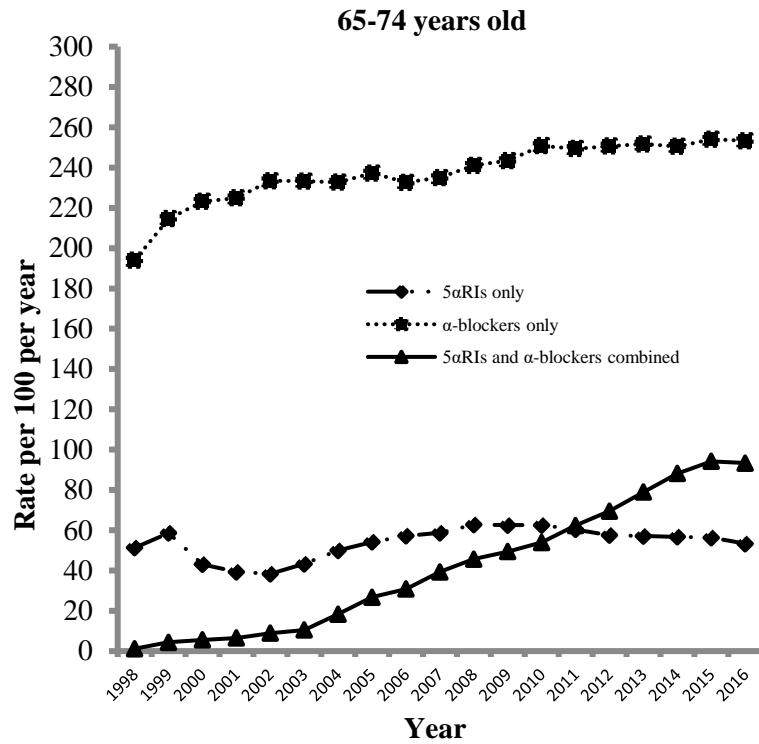


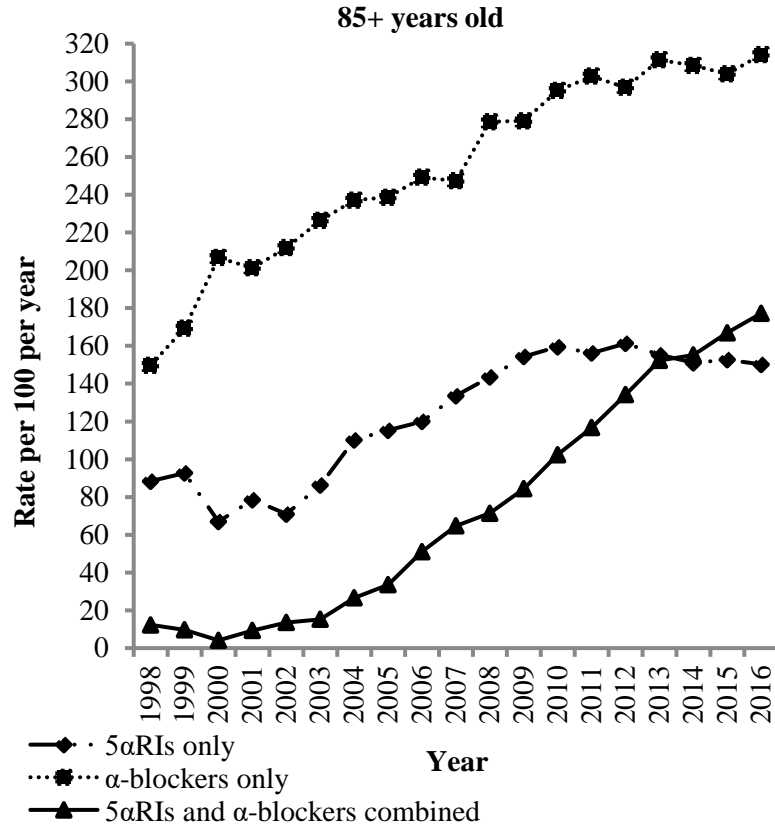
**Supplementary Figure 3.** Prescription rates of BPH medications over time among men with incident BPH in the UK between 1998 and 2016.



**Supplementary Figure 4.** Prescription rates of BPH medications by age among men with incident BPH in the UK between 1998 and 2016.







**Supplementary Figure 5:** Temporal trends in the prescription of BPH medications across age strata among men with incident BPH in the UK from 1998-2016.

**Supplementary Methods 1.** Definition of BPH medications (prescription) adherence in men with BPH in the UK between 1998 and 2016

We measured adherence of Benign Prostatic Hyperplasia (BPH) medication (prescription) with the Proportion of Days Covered (PDC) as recommended by the American Pharmacists Association<sup>1</sup> (ASA) and the Pharmacy Quality Alliance (PQA).<sup>2</sup>

$$\text{PDC} = \frac{\text{Number of Days in Period (Covered)}}{\text{Number of Days in Period}}$$

Where,

**Number of Days in Period:** We defined adherence in a one-year time window (period) starting from the time of prescription to the end of one year, death, end of the study, or the diagnosis of prostate cancer whichever came first. We assessed the robustness of adherence with a two-year time window.

**The number of days in period (covered):** We defined by continuous prescription of BPH medications with 30 days of grace period from the first prescription to the end of one year, death, end of the study, or the diagnosis of prostate cancer whichever came first. In the sensitivity analysis, the continuous prescription was assessed in a two-year time window.

The resulting PDC ranges from 0 to 1. A value of 1 corresponds to 100% adherence.

## REFERENCES

1. Measuring Adherence. 2020. (Accessed June 3, 2020, at [https://www.pharmacist.com/measuring-adherence#:~:text=Proportion%20of%20Days%20Covered%20\(PDC\)&text=The%20organization%20determined%20that%20the,or%2080%25%20of%20days%20covered.](https://www.pharmacist.com/measuring-adherence#:~:text=Proportion%20of%20Days%20Covered%20(PDC)&text=The%20organization%20determined%20that%20the,or%2080%25%20of%20days%20covered.))
2. PQA measure overview. 2020. (Accessed June 3, 2020, at <https://www.pqaalliance.org/adherence-measures.>)



