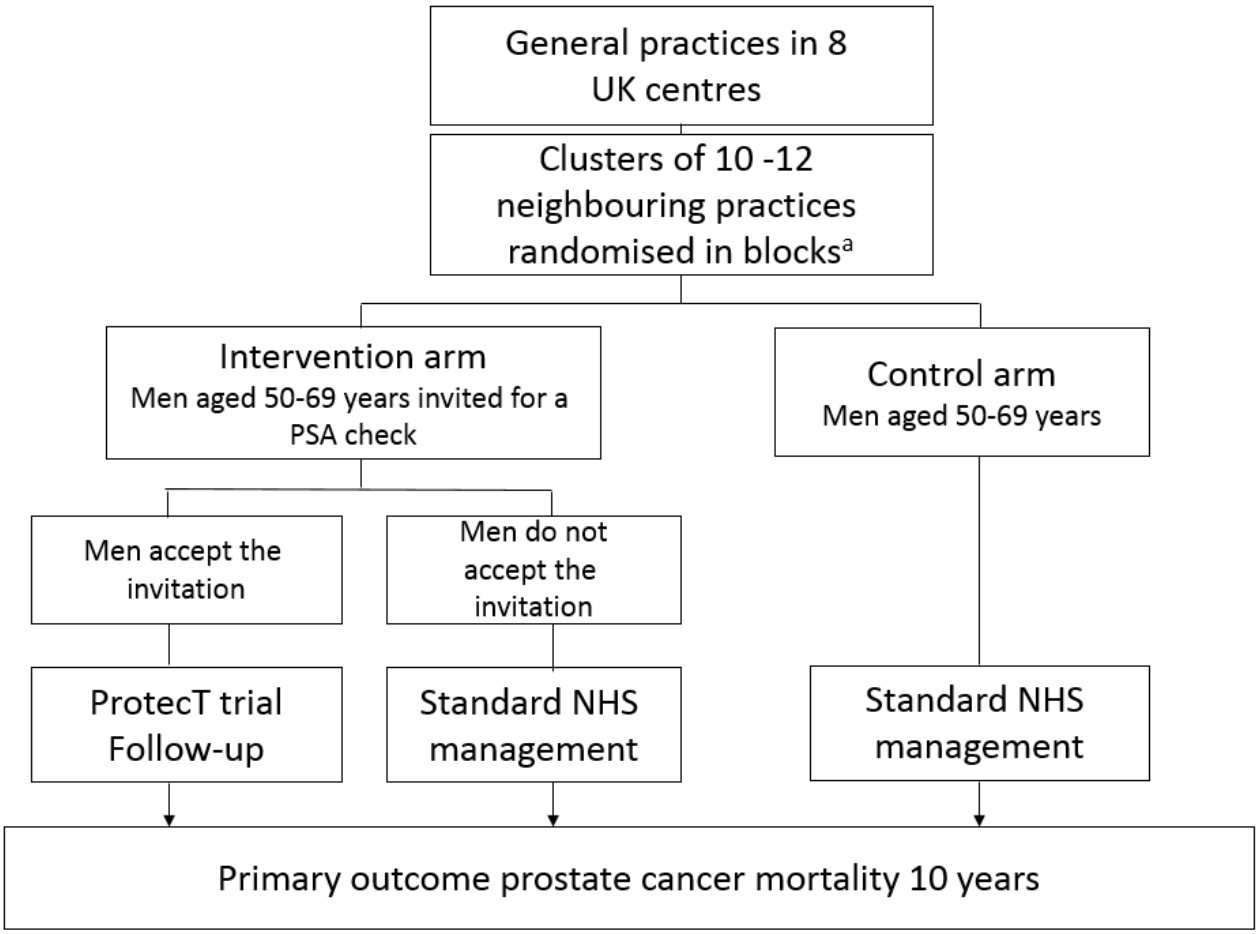
Martin, R., Donovan, J., Turner, E., Metcalfe, C., Young, G., Walsh, E., ... The CAP Trial Group (2018). Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality: The CAP Randomized Clinical Trial. *JAMA - Journal of the American Medical Association*, *319*(9), 883-895. https://doi.org/10.1001/jama.2018.0154

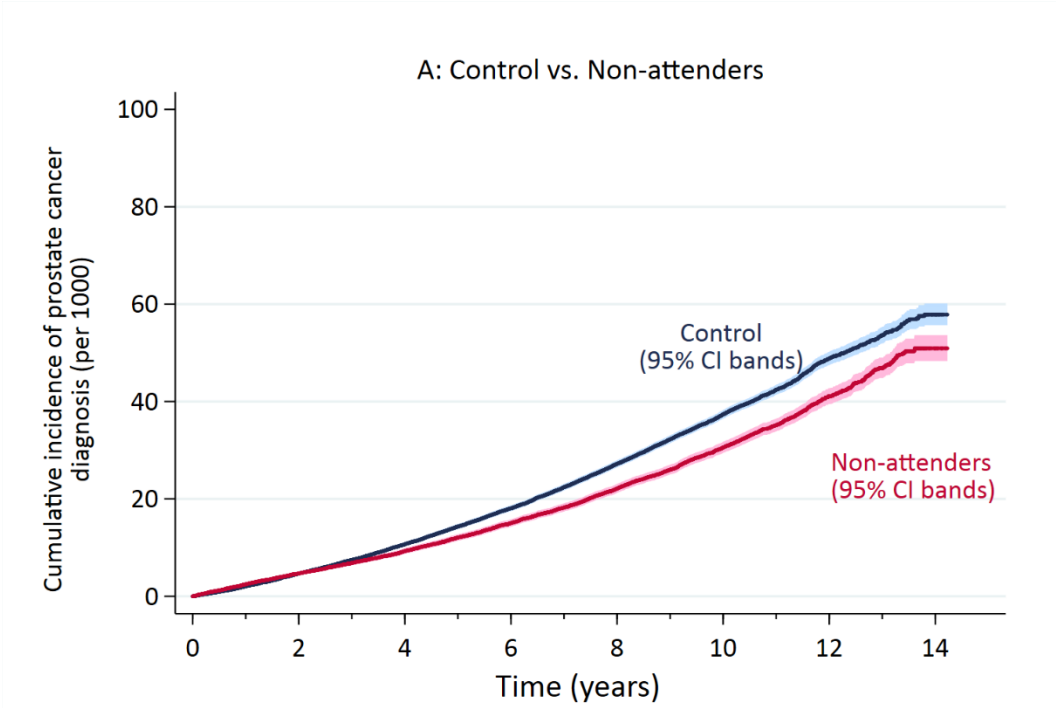
Supplementary Figure S1: Cluster randomized trial of PSA testing for Prostate cancer (CAP) trial design

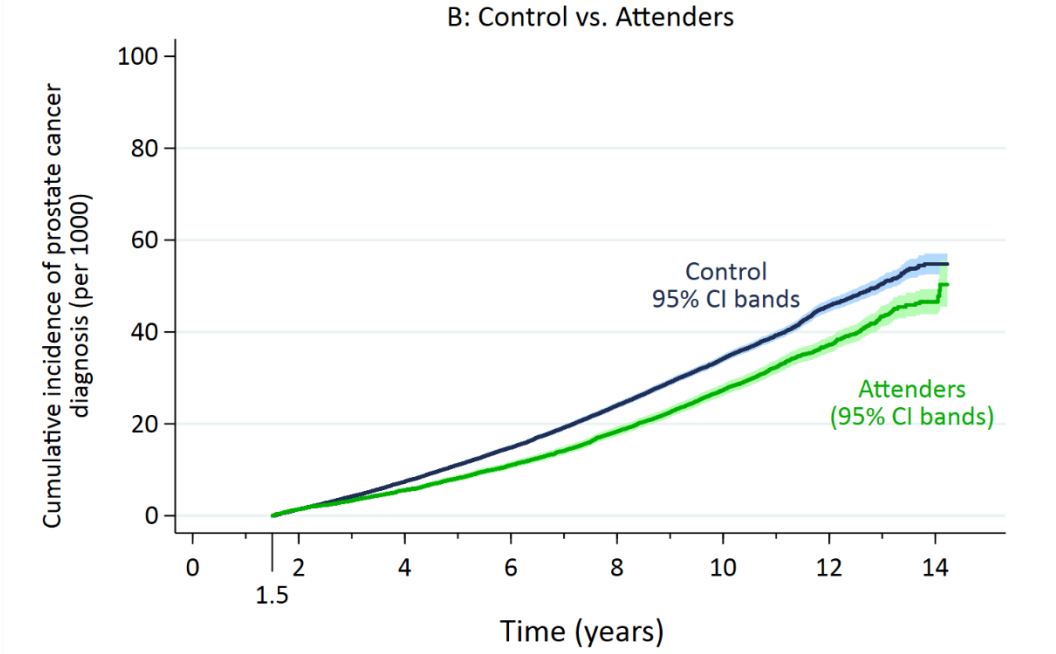


PSA: Prostate Specific Antigen

[a]Cluster randomization was blocked and stratified by geographical area as described previously.[1] A 9th centre was randomized (Edinburgh) but due to regulatory constraints we could not validate cause of death in individual unconsented men in the control arm, necessary for the primary analyses. These men were included in the ProtecT consented treatment trial as described in ProtecT publications,[2-4] but not in the CAP screening trial.[1]

Supplementary Figure S2: Cumulative incidence of prostate cancer in intervention-arm non-attenders for PSA screening vs controls (A) and in the post-screening phase (from 18 months post recruitment) amongst men who attended for PSA screening in the intervention-arm versus controls (B).

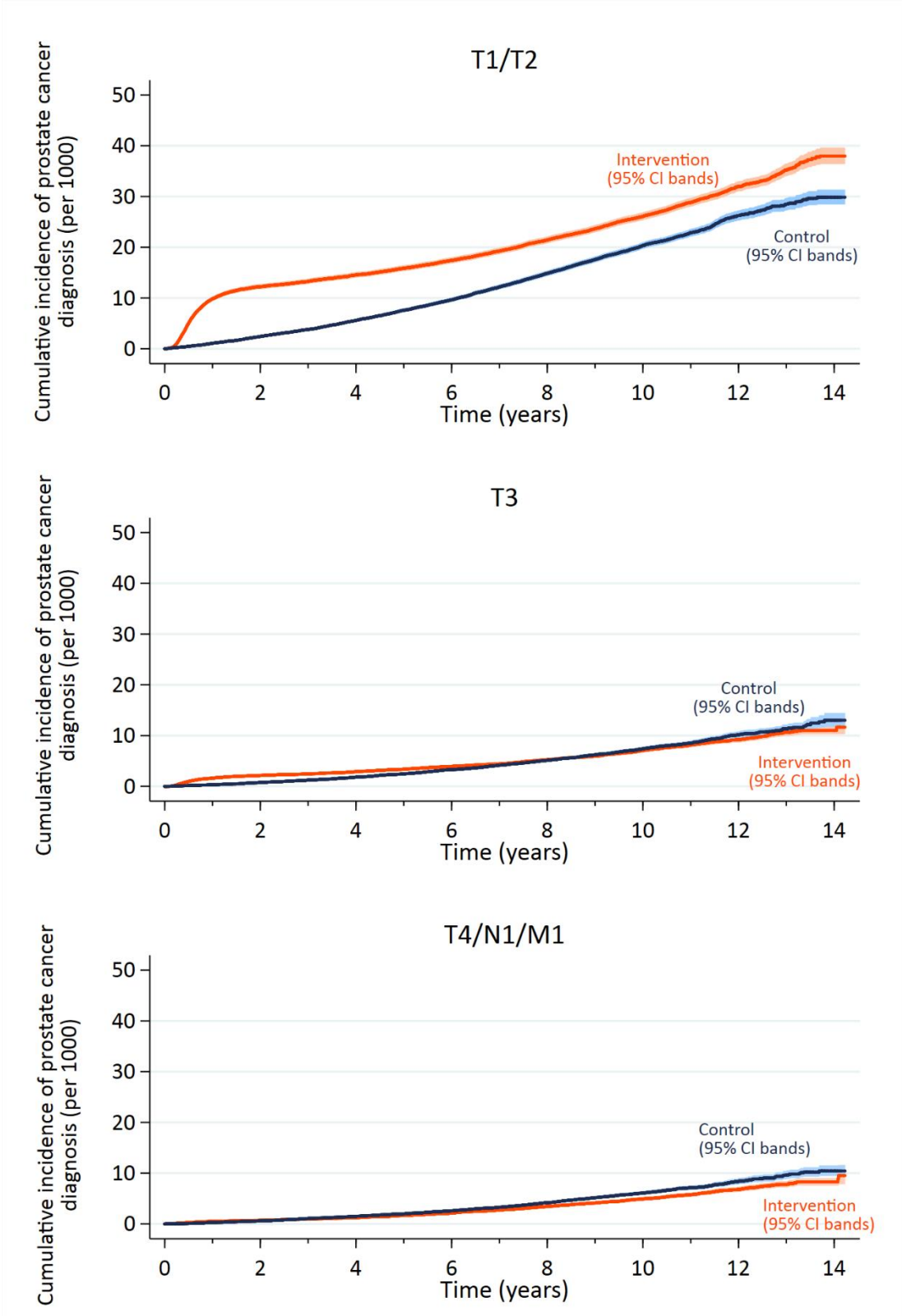




Number at risk at the start of each year (number of prostate cancer diagnoses in that year)																
Time (year)	**Median (IQR) follow up**	**0**	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
A: Control vs. non-attenders, crude rate difference -0.62 per 1000 (95% CI -0.76, -0.48)																
Non-attenders	9.82 (8.67, 10.92)	113,679 (280)	111,177 (243)	108,738 (233)	106,429 (257)	103,857 (291)	101,236 (299)	98,709 (317)	95,890 (376)	92,653 (334)	71,396 (283)	50,846 (200)	32,107 (151)	18,633 (78)	8,469 (25)	827 (0)
Control	9.68 (8.41, 11.27)	219,439 (455)	216,057 (555)	212,739 (597)	209,018 (663)	205,021 (749)	200,496 (758)	196,022 (858)	191,503 (929)	185,601 (881)	148,182 (669)	103,578 (406)	48,701 (206)	22,905 (90)	12,894 (37)	1,747 (0)
B: Control vs. attenders, crude rate difference -0.56 per 1000 (95% CI -0.70, -0.41)																
Attenders	10.38 (8.94, 11.88)		72,863 (102)	72,563 (138)	71,956 (164)	71,200 (186)	70,414 (200)	69,525 (218)	68,577 (292)	67,286 (259)	53,750 (230)	40,573 (178)	27,824 (115)	17,589 (76)	7,918 (18)	762 (3)
Control	9.89 (8.72, 10.93)		214,458 (300)	212,739 (597)	209,018 (663)	205,021 (749)	200,496 (758)	196,022 (858)	191,503 (929)	185,601 (881)	148,182 (669)	103,578 (406)	48,701 (206)	22,905 (90)	12,894 (37)	1,747 (0)

The graph in panel B show the cumulative incidence of prostate cancer diagnosis after the removal of the 18 month (1.5 year) 'screening phase', CI: confidence interval, IQR: interquartile range, [a]6months follow up only for panel B

Supplementary Figure S3: Cumulative incidence of prostate cancer by TNM stage at diagnosis.

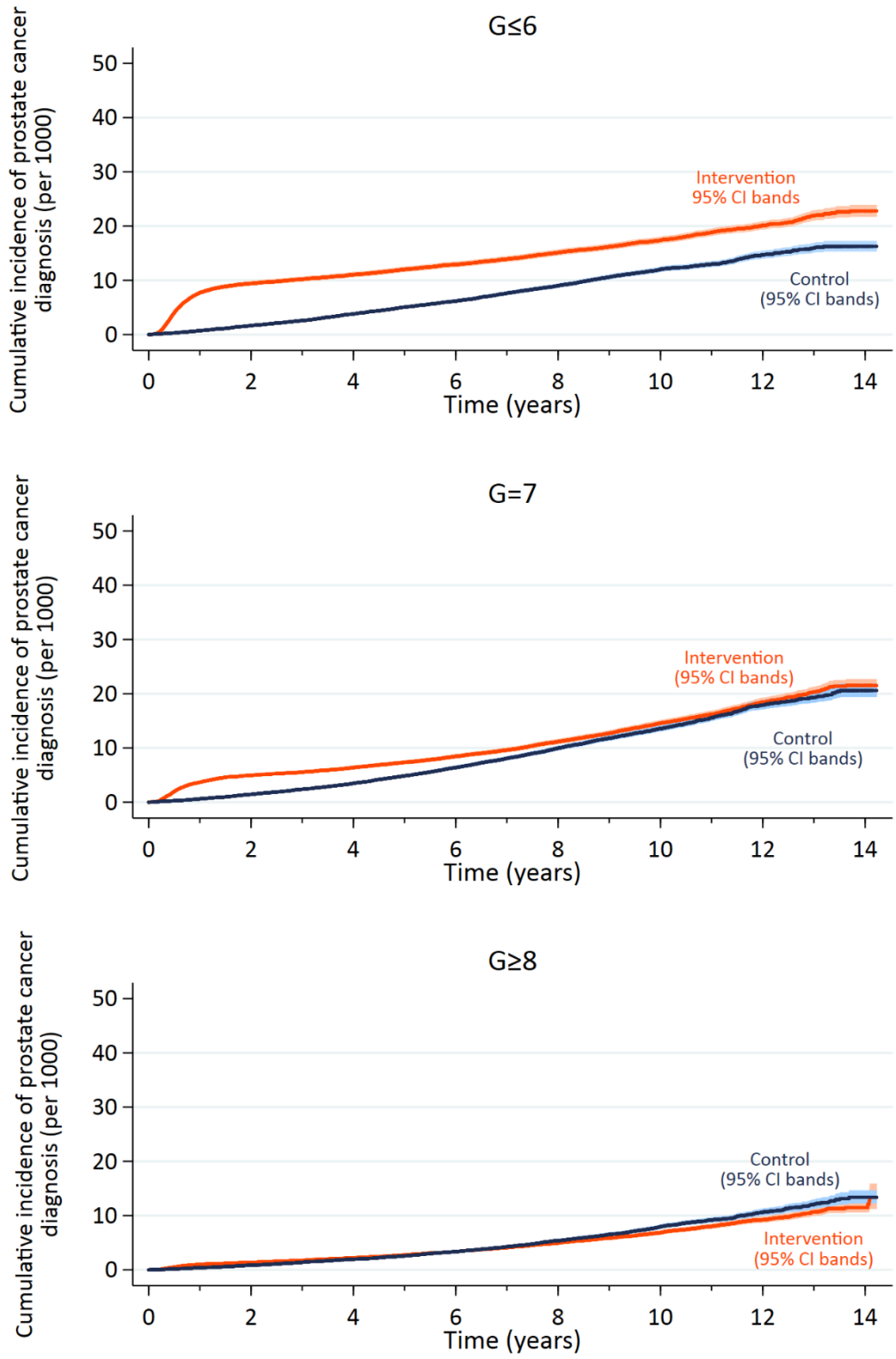


Number at risk at the start of each year (number of prostate cancer diagnoses in that year)																
Years	**Median (IQR) follow up**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Intervention		189,386	184,549	181,301	178,385	175,057	171,650	168,234	164,467	159,939	125,146	91,419	59,931	36,222	16,387	1,589
Stage T1/T2	2.96 (0.61, 7.51)	(1852)	(441)	(187)	(229)	(235)	(265)	(313)	(359)	(330)	(269)	(215)	(151)	(78)	(30)	(0)
Stage T3	5.45 (1.21, 8.57)	(303)	(97)	(56)	(76)	(85)	(97)	(81)	(135)	(105)	(117)	(85)	(50)	(37)	(5)	(1)
Stage T4/N1/M1[a]	6.85 (4.08, 9.00)	(93)	(39)	(46)	(51)	(71)	(82)	(100)	(117)	(97)	(86)	(64)	(51)	(27)	(7)	(2)
Control		219,439	216,057	212,739	209,018	205,021	200,496	196,022	191,503	185,601	148,182	103,578	48,701	22,905	12,894	1,747
Stage T1/T2	6.18 (3.65, 8.27)	(240)	(283)	(293)	(365)	(413)	(413)	(500)	(511)	(469)	(353)	(195)	(106)	(41)	(13)	(0)
Stage T3	6.62 (4.00, 8.68)	(69)	(97)	(99)	(120)	(131)	(165)	(167)	(183)	(185)	(152)	(88)	(52)	(21)	(12)	(0)
Stage T4/N1/M1[a]	6.77 (4.02, 8.62)	(60)	(72)	(96)	(85)	(103)	(121)	(136)	(172)	(167)	(116)	(83)	(36)	(23)	(7)	(0)

CI: confidence interval; [a]If any of these conditions were satisfied patients were categorized as T4, e.g. a patient with T3, N0 and M1 would be T4/N1/M1.

Intevention vs control groups: T1/T2: Difference per 1000 = 6.97, 95% CI (6.05, 7.89); T3: Difference per 1000 = -0.00 (95% CI -0.51, 0.51); T4/N1/M1: Difference per 1000 = -0.91 (95% CI -1.36, -0.46)

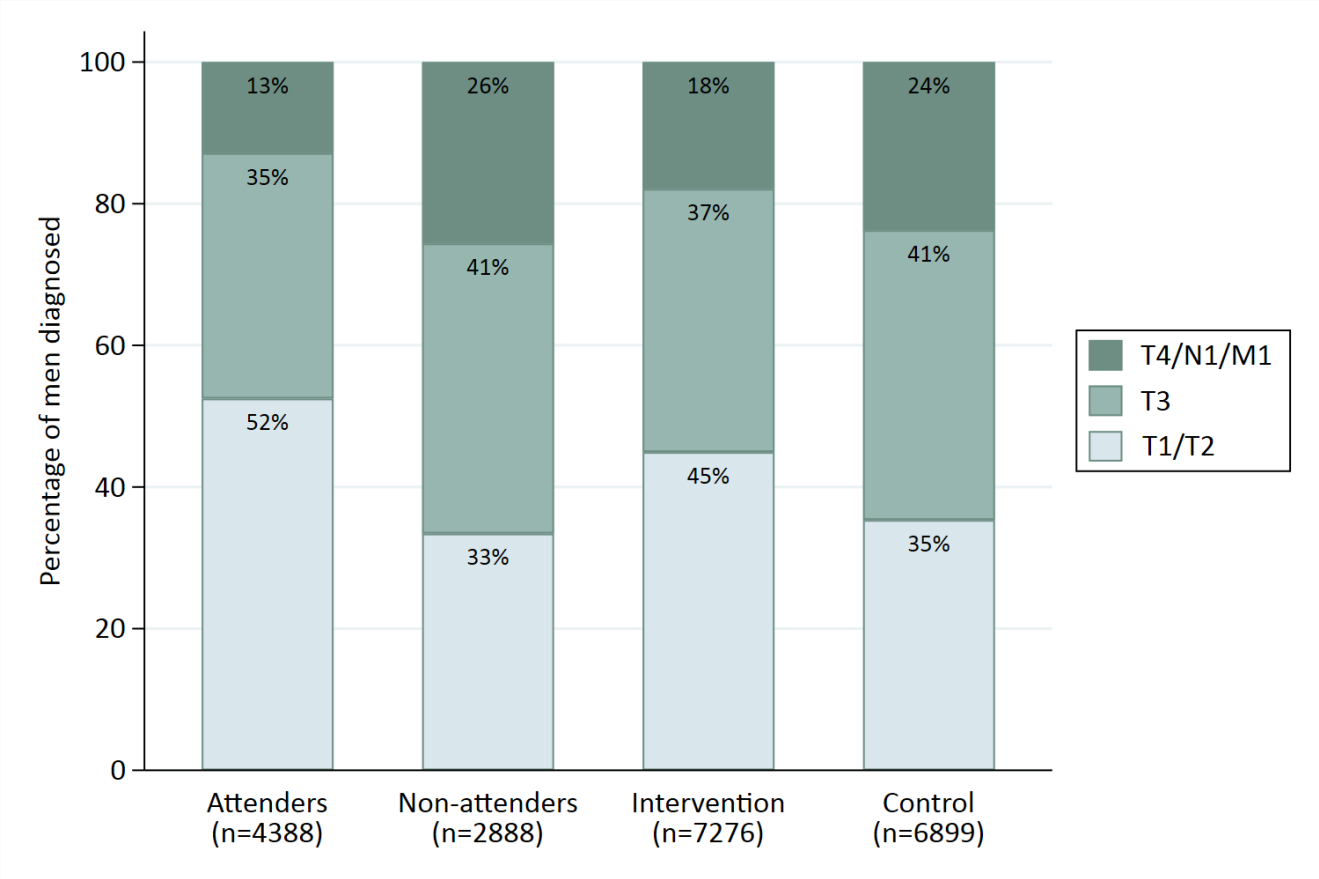
Supplementary Figure S4: Cumulative incidence of prostate cancer by Gleason score at diagnosis.



Number at risk at the start of each year (number of prostate cancer diagnoses in that year)																
Years	**Median (IQR) follow up**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Intervention		189,386	184,549	181,301	178,385	175,057	171,650	168,234	164,467	159,939	125,146	91,419	59,931	36,222	16,387	1,589
Gleason ≤6	1.40 (0.52, 6.42)	(1452)	(311)	(144)	(151)	(167)	(156)	(168)	(197)	(160)	(132)	(110)	(63)	(43)	(9)	(0)
Gleason 7	5.07 (0.97, 8.18)	(691)	(235)	(103)	(150)	(172)	(186)	(197)	(255)	(224)	(199)	(131)	(105)	(47)	(15)	(0)
Gleason ≥8	6.38 (3.03, 8.82)	(184)	(70)	(71)	(81)	(93)	(104)	(123)	(138)	(133)	(108)	(91)	(59)	(35)	(10)	(3)
Control		219,439	216,057	212,739	209,018	205,021	200,496	196,022	191,503	185,601	148,182	103,578	48,701	22,905	12,894	1,747
Gleason ≤6	5.69 (3.24, 7.99)	(159)	(202)	(192)	(249)	(259)	(225)	(284)	(264)	(270)	(181)	(76)	(53)	(23)	(3)	(0)
Gleason 7	6.28 (3.90, 8.30)	(136)	(176)	(201)	(226)	(277)	(309)	(329)	(360)	(314)	(228)	(154)	(75)	(26)	(12)	(0)
Gleason ≥8	6.72 (3.91, 8.74)	(86)	(103)	(109)	(116)	(127)	(158)	(174)	(213)	(194)	(178)	(97)	(43)	(27)	(11)	(0)

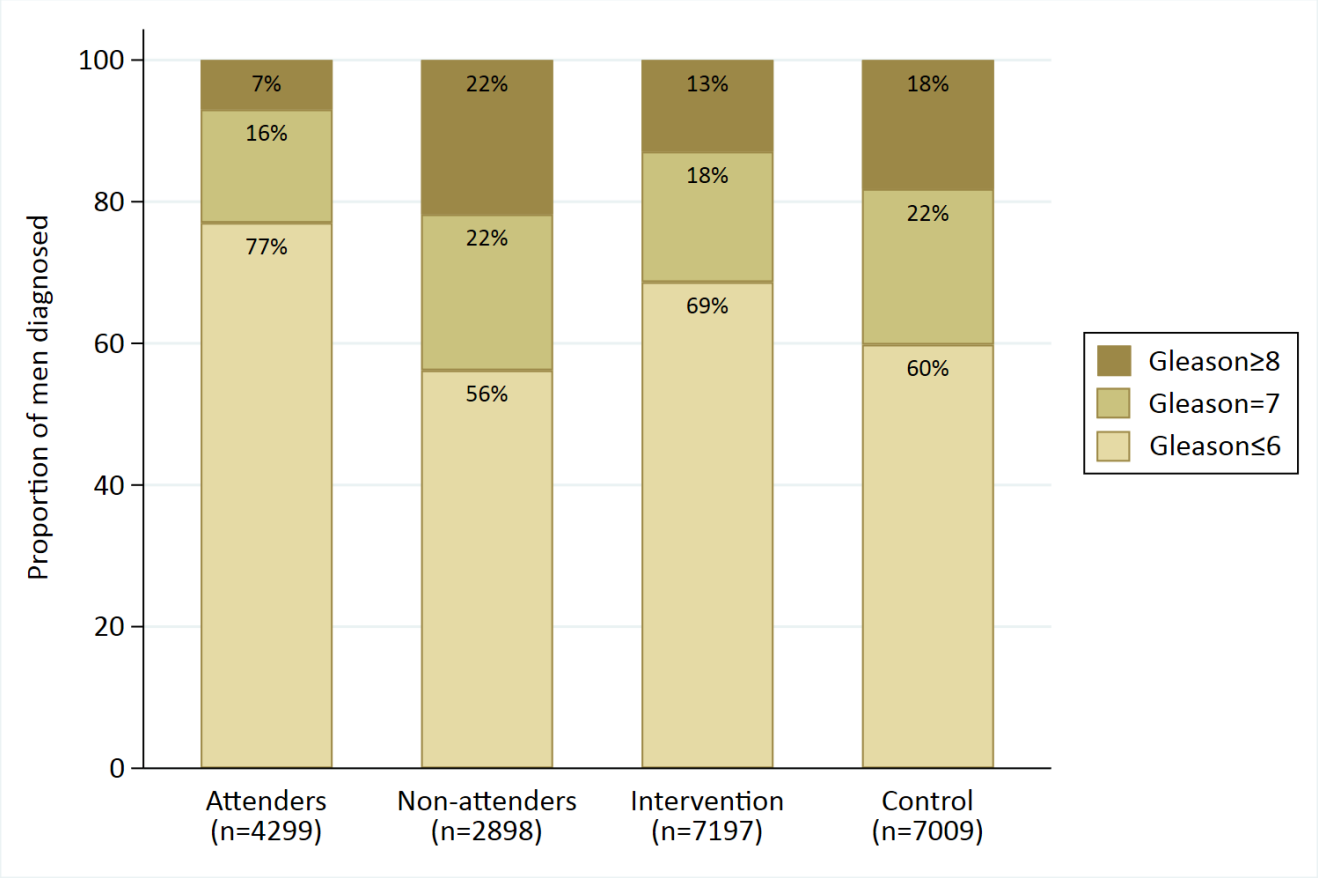
CI: confidence interval; Intevention vs control groups:Gleason≤6: Difference per 1000 = 6.11, 95% CI (5.38, 6.84); Gleason=7: Difference per 1000 = 1.44 (95% CI 0.73, 2.16); Gleason≥8: Difference per 1000 = -0.58 (95% CI -1.09, -0.06)

Supplementary Figure S5: Prostate cancer diagnoses categorized by TNM stage[a] across the trial groups (control group; all men in the intervention group [labelled 'Intervention']; men in the intervention group who attended for PSA screening [labelled 'Attended']; and men in the intervention group who did not attend for PSA screening [labelled 'Not attended'])



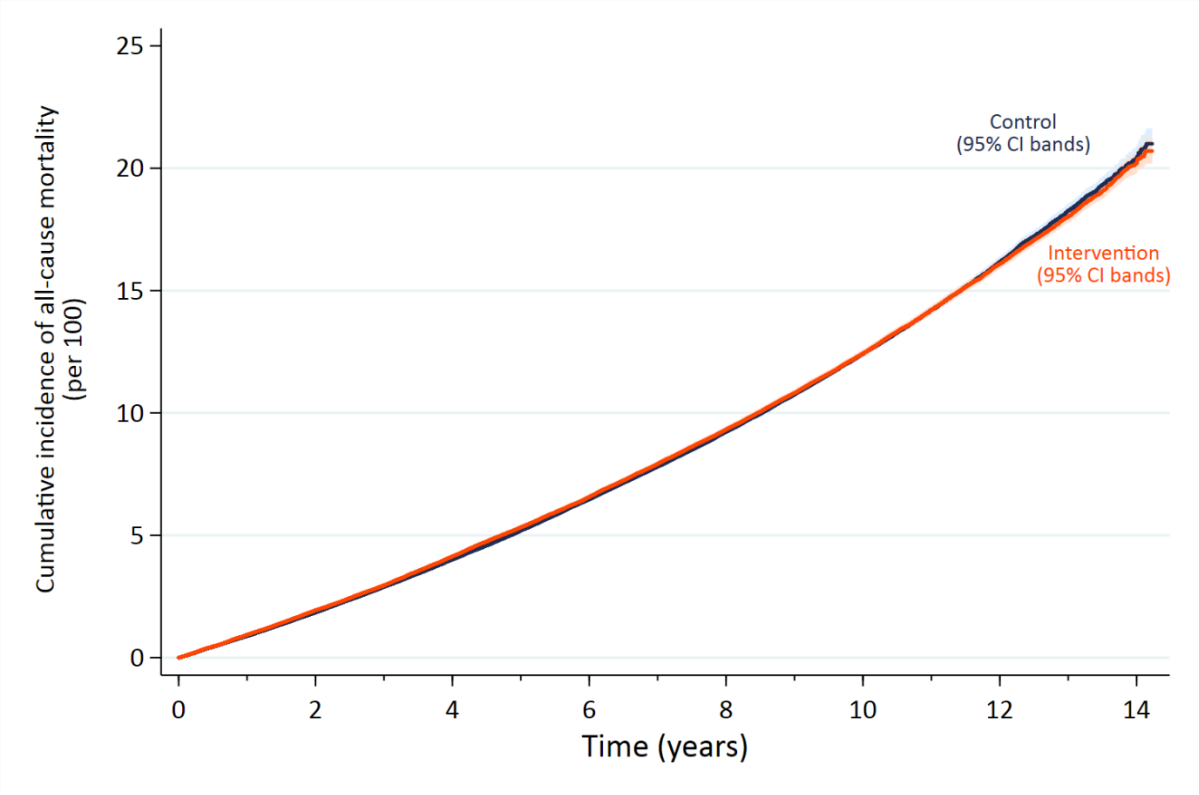
[a]A man was given a stage of T4/N1/M1 if he had been diagnosed with stage T4 or was positive for metastases (M1) or nodes (N1). If a man had stage T3 but did not have metastates (M0) or nodes (N0) then the diagnosis was categorized as T3. Any diagnoses categorized as T1 or T2 (with no metastasis or nodes) were placed in the T1/T2 category.

Supplementary Figure S6: Prostate cancer diagnoses categorized by Gleason score[a] across the trial groups (control group; all men in the intervention group [labelled 'Intervention']; men in the intervention group who attended for PSA screening [labelled 'Attended']; and men in the intervention group who did not attend for PSA screening [labelled 'Not attended'])



[a]Gleason score was calculated as the summation of the primary and secondary Gleason grades. The score was then broken down into less than or equal to an overall score of 6, equal to 7, or greater than or equal to 8.

Supplementary Figure S7: Effect of the Cluster randomized trial of PSA testing for Prostate cancer (CAP) trial intervention on the cumulative incidence of all-cause mortality



Number at risk at the start of each year (number of deaths in that year)[a]																
Time (year)	**Median (IQR) follow up**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
A: Intervention vs. control, crude rate difference 0.23 per 1000 (95% CI -0.00, 0.46)																
Intervention	10.03 (8.80, 11.50)	189,386 (1,772)	186,989 (1,888)	184,370 (1,900)	181,778 (2,212)	178,777 (2,215)	175,750 (2,302)	172,702 (2,479)	169,353 (2,581)	165,313 (2,500)	129,718 (2,028)	95,089 (1,629)	62,558 (1,085)	38,003 (620)	17,273 (238)	1,649 (10)
Control	9.92 (8.74, 10.93)	219,439 (1,941)	216,504 (2,089)	213,705 (2,290)	210,530 (2,404)	207,112 (2,547)	203,235 (2,723)	199,382 (2,849)	195,578 (3,003)	190,408 (2,963)	152,725 (2,435)	107,186 (1,748)	50,531 (747)	23,811 (471)	13,468 (187)	1,816 (9)

Supplementary Table S1: Data flow amongst participants in the Cluster randomized trial of PSA testing for Prostate cancer (CAP) trial intervention-arm[1] compared with the previously published *ProtecT* trial[2-4]

	ProtecT	CAP intervention-group[a]		
	Total N	Total N	Prostate cancer diagnoses	Prostate cancer deaths[b]
PSA test non-attenders	128,522	113,679	3,367	361
PSA test attenders	100,444	75,707	4,687	188
No PSA taken/no valid test	18,014	11,271	527	42
Valid test	82,430	64,436	4,160	146
PSA<3ng/ml	73,538	57,326	1,172	68
PSA ≥20ng/ml	280	218	196	19
No result	46	35	4	0
3≤PSA<20ng/ml (eligible for biopsy within ProtecT)	8,566	6,857	2,788	59
No biopsy	1,152	1,007	174	15
Biopsy	7,414	5,850	2,614	44
Negative biopsy result	4,518	3,546	365	4
Positive biopsy result	2,896	2,304	2,249[c]	40
Randomised-group	1,643	1,216	1,184	8
Preference-group[d]	997	733	721	9
Advanced cancer	267	164	164	18
Excluded, localised cancer	290	190	179	5
Two-arm randomization[e]	24	1	1	0

The flow of participants in the intervention arm is detailed: column 2 (ProtecT) shows the Ns reported in the previously published *ProtecT* trial; column 3 shows the N for those who are included in the intervention arm in CAP; columns 4 and 5 show the prostate cancer diagnoses and prostate cancer deaths in men as they flow through the stages of the trial. PSA: Prostate specific antigen.

[a]Excludes the *ProtecT* Edinburgh centre, feasibility practices and early *ProtecT* phase practices not randomised into CAP. [b]Definite, probable or intervention related prostate cancer death

[c]There were 55 patients that were not flagged by routine data sources as having been diagnosed. Inclusion of these in a sensitivity analysis did not alter any results.

[d]Eligible for randomization into the ProtecT trial but declined to be randomly assigned and expressed a preference for a particular treatment
[e]Eligible for randomization into the ProtecT trial but agreed to be randomized to two of the three treatment groups only; radiotherapy and radical prostatectomy

Supplementary Table S2: Sensitivity analysis based on comparing alternative definitions of prostate cancer mortality in intervention vs. control groups at 10-year median follow-up

	Intervention group *(n=189,386)* Person years=1,853,167		Control group *(n=219,439)* Person years=2,095,405					Instrumental variable estimate[a]	
	Deaths (%)	Rate per 1000 person-years (95% CI)	Deaths (%)	Rate per 1000 person-years (95% CI)	Rate difference per 1000 men (95% CI)	Rate ratio (95% CI)[b]	P value[b]	Rate ratio (95% CI)	P value
Defined as definite, probable or **possible** prostate cancer death or IRD[c]	*560 (0.30%)*	*0.30 (0.28, 0.33)*	*655 (0.30%)*	*0.32 (0.29, 0.34)*	*-0.015 (-0.050, 0.020)*	*0.95 (0.84, 1.08)*	*0.42*	*0.91 (0.65, 1.27)*	*0.58*
Defined as **definite only** prostate cancer death or IRD[c]	*436 (0.23%)*	*0.24 (0.21, 0.26)*	*510 (0.23%)*	*0.24 (0.22, 0.27)*	*-0.008 (-0.039, 0.022)*	*0.97 (0.85, 1.12)*	*0.69*	*0.93 (0.66, 1.32)*	*0.69*
Defined as definite or probable prostate cancer deaths or IRD, and also including deaths in the presence of castrate resistant prostate cancer[c]	*593 (0.31%)*	*0.32 (0.30, 0.35)*	*699 (0.32%)*	*0.33 (0.31, 0.36)*	*-0.014 (-0.049, 0.022)*	*0.96 (0.86, 1.08)*	*0.497*	*0.93 (0.68, 1.27)*	*0.64*

CI: confidence interval; IRD: intervention related death

[a]Analysis to obtain the causal effect of screening amongst those attending the prostate specific antigen (PSA) testing clinic using a generalized method of moments (gmm) estimator with random allocation as an instrumental variable.

[b]Likelihood ratio test of the null hypothesis "no difference in prostate cancer mortality between the groups", adjusted for randomisation cluster and age stratum.

[c]As determined by the independent cause of death committee

Supplementary Table S3: Underlying causes of death[a] in intervention versus control groups at 10-year median follow-up (not including prostate cancer)

Cause of death	Intervention n (%)	Control n (%)
Any (not incl. prostate cancer)	24,910 (100%)	27,659 (100%)
Other cancers	9,984 (40%)	11,066 (40%)
Ischemic heart disease	1,141 (5%)	1,287 (5%)
Stroke	4,763 (19%)	5,217 (19%)
Other circulatory diseases	1,648 (7%)	1,767 (6%)
Respiratory disease	2,754 (11%)	3,100 (11%)
Digestive disease	1,437 (6%)	1,576 (6%)
Infectious disease	233 (1%)	237 (1%)
Blood, immune, endocrine	497 (2%)	561 (2%)
Nervous system disease	807 (3%)	960 (3%)
Accident	660 (3%)	777 (3%)
Other	986 (4%)	1,111 (4%)

[a]*Causes of death were determined by death certificate*

Supplementary Table S4: Effect of the Cluster randomized trial of PSA testing for Prostate cancer (CAP) intervention on characteristics of prostate cancer cases at diagnosis, by time-period (≤18 vs. >18 months)

		Intervention group *(n=189,386)*			Controls *(n=219,439)*
		Attended PSA clinic (*n=75,707*)	Did not attend PSA clinic (*n=113,679*)	All invited	7853 (3.6%)
Number of prostate cancers (%):		4687 (6.2%)	3367 (3.0%)	8054 (4.3%)	
Clinical characteristics at diagnosis for those diagnosed within 18 months of randomization					
Number of prostate cancers/number at risk (%)		2,508/75,707 (3.31%)	404/113,679 (0.36%)	2,912/189,386 (1.54%)	710/219,439 (0.32%)
Person years of follow up		111,375	168,013	279,388	326,081
Rate per 1000 person-years (95% CI)		22.52 (21.65, 23.42)	2.40 (2.18, 2.65)	10.42 (10.05, 10.81)	2.18 (2.02, 2.34)
Grade (%)	≤6	1,497 (1.98%)	166 (0.15%)	1,663 (0.86%)	250 (0.11%)
	7	732 (0.97%)	124 (0.11%)	856 (0.45%)	215 (0.10%)
	≥8	169 (0.22%)	56 (0.05%)	225 (0.12%)	131 (0.06%)
	No record	110 (0.15%)	58 (0.05%)	198 (0.10%)	114 (0.05%)
Stage (%)	T1/T2	1,949 (2.57%)	205 (0.18%)	2,154 (1.14%)	364 (0.17%)
	T3	310 (0.41%)	60 (0.05%)	370 (0.20%)	107 (0.05%)
	T4/N1/M1	59 (0.08%)	58 (0.05%)	117 (0.06%)	96 (0.04%)
	No record	190 (0.25%)	81 (0.07%)	271 (0.14%)	143 (0.07%)
Clinical characteristics at diagnosis for those diagnosed over 18 months after randomization					
Number of prostate cancers/number at risk (%)		2179/72,863 (2.99%)	2963/110,017 (2.69%)	5142/182,880 (2.81%)	7143/214,458 (3.33%)
Person years of follow up		639,198	889,445	1,528,643	1,737,831
Rate per 1000 person-years (95% CI)		3.41 (3.27, 3.56)	3.33 (3.21, 3.45)	3.36 (3.27, 3.46)	4.11 (4.02, 4.21)
Grade (%)	≤6	800 (1.06%)	800 (0.70%)	1,600 (0.84%)	2,190 (1.00%)
	7	794 (1.05%)	1,060 (0.93%)	1,854 (0.98%)	2,608 (1.19%)
	≥8	396 (0.52%)	682 (0.60%)	1,078 (0.57%)	1,505 (0.69%)

		Intervention group *(n=189,386)*			Controls *(n=219,439)*
		Attended PSA clinic (*n=75,707*)	Did not attend PSA clinic (*n=113,679*)	All invited	7853 (3.6%)
Number of prostate cancers (%):		4687 (6.2%)	3367 (3.0%)	8054 (4.3%)	
	No record	189 (0.25%)	421 (0.37%)	610 (0.32%)	840 (0.38%)
Stage (%)	T1/T2	1,359 (1.80%)	1,425 (1.25%)	2,784 (1.47%)	3,828 (1.74%)
	T3	380 (0.50%)	579 (0.51%)	959 (0.51%)	1,433 (0.65%)
	T4/N1/M1	242 (0.32%)	571 (0.50%)	813 (0.43%)	1,181 (0.54%)
	No record	198 (0.26%)	388 (0.34%)	586 (3.09%)	701 (0.32%)

Supplementary Table S5: Summary description of intervention related deaths as determined by the Independent Cause of Death Committee[5]

Post-operative (n=5)	Post chemotherapy (n=2)	Post radiation (n=2)	Post hormones (n=3)	Post investigative procedures, e.g. biopsy (n=3)
Sudden death 5 days after Radical Prostatectomy	Sepsis	Proctitis	Cardiovascular event	Transurethral resection of bladder tumor (TURBT), transurethral resection of the prostate (TURP) & pelvic mass biopsy conducted a few days prior to death
Perforated diverticular disease	Neutropenic sepsis	Hemorrhagic cystitis	Cardiac event	Post biopsy complications
Bleeding			Pulmonary embolism	Deterioration of existing kidney disease linked to CT scan
Renal failure				
Sepsis				

Orange shading = deaths in the intervention-group; blue shading = deaths in the control-group.

Supplementary Table S6: Characteristics of CAP[1], ERSPC[6] and PLCO[7] randomized trials of prostate cancer screening

	CAP	ERSPC	PLCO
Performance Characteristics			
Number in intervention arm	189,386	72,952	38,343
Number in control arm	219,439	89,353	38,350
Mean age at baseline [a] (years)	59.0	61.5	NA
Number PSA-tested in intervention-group	67,312	59,923	≈32,600
Proportion PSA-tested in intervention-group	36%	64%[b]	85%
Recommend PSA threshold for biopsy referral	3ng/ml	3-4ng/ml (variable across countries)	4ng/ml
Rates of biopsy in men with raised PSA	85%	86%	41%[8]
PSA contamination amongst controls (screening in the control arm)	≈10-15% asymptomatic PSA tests with screening intent[9]	ERSPC Rotterdam ≈15% asymptomatic PSA tests after randomization[10]	PLCO≈50% per year[7]
Prostate cancer detection in the control group	7853/219439 3.6% over 10 years	4307/89353 4.8% over 9 years	2974/38350 7.8% over 7-10 years
Prostate cancer detection in the intervention group	8054/189386 4.3% over a median of 10 years	5990/72,952 8.2% over a median of 9 years[6]	3452/38343 9.0% over 7-10 years[7]
Characteristics of diagnosed prostate cancers in controls[c]			
Gleason grade ≤6	35%	55%	62%
Gleason grade 7	41%	29%	27%
Gleason grade ≥8	24%	16%	12%
Stage T1/2	60%	79%	95%
Characteristics of diagnosed prostate cancers in the intervention group[c]			
Gleason grade ≤6	45%	72%	67%
Gleason grade 7	37%	20%	24%
Gleason grade ≥8	18%	7%	9%
Stage T1/2	69%	90%	97%
Mean age at prostate cancer diagnosis (yrs)	67	61	NK

CAP: Cluster randomized trial of PSA testing for Prostate cancer, ERSPC: European Randomised Study of Screening for Prostate Cancer, PLCO: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, NA: not available, PSA: Prostate specific antigen, [a]CAP mean age at invitation; ERSPC mean age at randomization. [b]In ERSPC centers where randomization was based on men identified from population registries and consented post-randomization (as in CAP), the participation rate in the screening arm varied from 59% to 69% (mean: 64%) (compliance was considerably higher in centers with pre-randomization consent).[11] [c]Figures for ERSPC and PLCO were derived from those reported in order to remove 'missing/not yet reported' from the denominator.

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