PSA Screening and 15-year Prostate Cancer Mortality: The CAP Randomized Clinical Trial

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Key points

Question: In men aged 50-69, does a single invitation for a prostate specific antigen (PSA) screening test reduce prostate cancer mortality at 15-year follow-up, compared to a control group that was not invited for testing?

Findings: In this cluster randomized trial of 415,357 men aged 50-69 randomized to a single invitation for PSA screening (N=195,912) or a control group without PSA screening (N=219,445) and followed-up for a median of 15-years, risks of death from prostate cancer were lower in the group invited to screening (0.69% vs. 0.78%; mean difference: 0.09%), compared to the control group.

Meaning: Compared to a control group without routine PSA testing, a single invitation for a PSA screening test reduced prostate cancer mortality at a median follow-up of 15 years, but the absolute mortality benefit was small.

Abstract (Word count 383)

IMPORTANCE The Cluster randomized trial of PSA testing for Prostate cancer (CAP) reported no effect of prostate specific antigen (PSA) screening on prostate cancer mortality at median 10-year follow-up (primary outcome), but the long-term effects of PSA screening on prostate cancer mortality remain unclear.

OBJECTIVE To evaluate the effect of a single invitation for PSA screening on the pre-specified secondary outcome of prostate cancer-specific mortality at a median of 15 years' follow-up, compared to a control group not invited for screening.

DESIGN, SETTING, PARTICIPANTS Cluster randomized trial of men aged 50-69 identified from 573 primary-care practices in England and Wales. Primary-care practices were randomized between 09/25/2001 and 08/24/2007 and men were enrolled between 01/08/2002 and 01/20/2009. Follow-up was completed on 03/31/2021.

INTERVENTION A single invitation for a PSA screening test with subsequent diagnostic tests if PSA≥3.0ng/ml, compared to standard practice (control).

MAIN OUTCOMES AND MEASURES The primary outcome was reported previously. Of eight prespecified secondary outcomes, results of four were reported previously. The four remaining pre-specified secondary outcomes at 15-year follow-up were prostate cancer-specific mortality, all-cause mortality, and prostate cancer stage and Gleason grade at diagnosis.

RESULTS Of 415,357 randomized men (mean [SD] age: 59.0 [5.6] years), 98% were analyzed in these analyses. Overall, 12,013 and 12,958 men with prostate cancers were diagnosed in the intervention and control groups (15-year cumulative risks 7.1% and 6.9% respectively).

At a median 15-year follow-up, 1,199 (0.69%) men in the intervention group and 1,451 (0.78%) men in the control group died of prostate cancer (rate ratio [RR] 0.92 [95% CI 0.85, 0.99]; p=0.03).

Compared to the control group, the PSA screening intervention increased detection of low-grade (Gleason score [GS]≤6; 2.2% versus 1.6%;p<0.001) and localized (T1/T2; 3.6% versus 3.1%;p<0.001) disease, but not intermediate (GS=7), high-grade (GS≥8), locally-advanced (T3) or distally-advanced

(T4/N1/M1) tumors. There were 45,084 all-cause deaths (23.2%) in the intervention group and 50,336 deaths (23.3%) in the control group respectively (RR 0.97 [95% CI 0.94, 1.01]; p=0.11). Eight deaths in the intervention and seven deaths in the control group were related to a diagnostic biopsy or prostate cancer treatment.

CONCLUSIONS AND RELEVANCE A single invitation for PSA screening, compared to standard practice without routine screening, reduced the secondary outcome of prostate cancer deaths at a median follow-up of 15-years. However, the absolute reduction in deaths was small.

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Introduction

In England, the number of men diagnosed with prostate cancer increased by 68% from 28,216 in 2001 to 47,479 in 2019,[1] reflecting population aging and increased prostate specific antigen (PSA) testing.[2] In the USA, approximately 3.3 million men currently live with a diagnosis of prostate cancer.[3] While low-risk prostate cancer progresses slowly and is associated with a low risk of mortality,[4-7] aggressive prostate cancer currently causes approximately 12,000 deaths in the UK and 34,700 deaths in the U.S. annually.[3,8] The goal of PSA screening is to reduce prostate cancer mortality by early detection of curable disease. However, uncertainty remains regarding the long-term effect of PSA-based screening on mortality.[9-11]

The CAP RCT (N=415,357) showed that, compared to a usual care (unscreened) control group, an invitation to a single PSA screen increased the number of prostate cancers diagnosed during the first 18 months of follow-up (the time period when PSA testing and subsequent biopsies for men with an elevated level of PSA took place). In this trial, rates of diagnosed prostate cancer were 2.2 per 1000 person-years in the control group and 10.4 per 1000 person-years in the intervention group (P<0.001).[10] However, at a median 10-year follow-up, the invitation for a single PSA screen did not reduce prostate cancer mortality, compared to the control group (0.29% vs. 0.30%; rate ratio: 0.96; 95%CI;0.85-1.08;p=0.5).[10] This report describes the effects of this single invitation to a PSA-screening test, with subsequent diagnostic tests if PSA>3.0ng/ml, on the pre-specified secondary outcome of prostate-cancer mortality at 15-year follow-up, compared to standard (unscreened) practice.[12]

Methods

The Derby National Research Ethics Service Committee East Midlands approved the study. The trial **Protocol** and the **statistical analysis plan** are available as Supplementary material to the primary outcome paper.[10] Participants were enrolled between 01/08/2002 and 1/20/2009. Final follow-up occurred 03/31/2021.

Men who attended PSA testing in the intervention group gave individual written informed consent via the ProtecT study.[13] Individual consent was not sought from men in the control group or from non-responders in the intervention group. Instead, approval for their identification and linkage to routine electronic records was obtained under Section-251 of the NHS Act 2006 from the UK Patient Information Advisory Group (now Confidentiality Advisory Group).[10] All clinical centers had local research governance approval.

Randomization

The study was a primary-care based cluster RCT that tested the effects of a single invitation for a PSA screening test (**eFigure 1**), compared to usual care (no screening), on the primary outcome of prostate-cancer mortality at a median follow-up of 10 years. The primary outcome has been reported.[10] Between 2001 and 2007, 785 eligible general practices in the catchment area of 8 hospitals across England and Wales (located in Birmingham, Bristol, Cambridge, Cardiff, Leeds, Leicester, Newcastle and Sheffield) were randomized before recruitment ('Zelen' design) to intervention or control groups and practices were invited to consent to participate. Randomization was blocked and stratified within groups of 10-12 neighboring practices, using a computerized random number generator. Because allocation preceded the invitation for practices to participate, it was not possible to conceal allocation. 573 (73%) practices, including 68% randomized to the intervention group and 78% randomized to the control group, agreed to participate **(Figure 1).**

Participants

Men aged 50-69 years in each participating randomized general practice were included. Men with prostate cancer on or before the randomization date and those registered as a patient with participating practices on a temporary or emergency basis were excluded.

Intervention

Men in practices randomized to the intervention received a single invitation for a PSA test after counselling. If the resulting PSA was 3.0-19.9ng/ml, they were offered 10-core transrectal ultrasound-guided biopsies. All laboratories participated in the UK National External Quality

Assessment Service (UK NEQAS) for PSA testing. Test results that did not meet laboratory quality assurance requirements, were lost, or if consent was ambiguous or if insufficient blood was obtained, were considered non-valid. Men in the intervention group diagnosed with localized prostate cancer were invited to participate in a second RCT, the ProtecT treatment trial (ISRCTN20141297) which randomized participants to active monitoring (consisting of regular PSA testing and clinical review), radical prostatectomy, or radical conformal radiotherapy with neo-adjuvant-androgen-deprivation (**eFigure 1**).[14] Men with a PSA ≥20ng/ml were referred to a urologist and received standard care.

Men in practices randomized to the control group received standard NHS management but did not receive a formal invitation for PSA testing as part of this study.[15] We assessed cumulative PSA testing for prostate cancer detection in the control group of CAP by longitudinal analysis of a national primary care database (N=434,236 men from 558 UK GP practices)[2].

Outcomes

The primary outcome of this clinical trial, 10-year prostate cancer mortality, was reported previously.[10] Pre-specified secondary outcomes were: definite or probable prostate cancer mortality at 15-year follow-up; all-cause mortality at 10-year follow-up; all-cause mortality at 15-year follow-up; all-cause mortality at 5-year follow-up; prostate cancer mortality at 5-year follow-up; disease grade and staging; cost-effectiveness; and health related quality of life. The protocol did not indicate the time point for assessing prostate cancer grade and staging; these were measured at median follow-up time points of 10-years and 15-year follow-up. Previously reported outcomes were all-cause mortality at 10-year follow-up,[10] disease grade and stage at 10-year follow-up,[10] cost-effectiveness[16] and health related quality of life.[17] The current report provides results for the remaining secondary outcomes of definite or probable prostate cancer mortality at 15-year follow-up, all-cause mortality at 15-year follow-up, and disease grade and stage at 15-year follow-up. All-cause and prostate cancer mortality at 5-year follow-up were not published separately, but five-year

follow-up data are shown in Kaplan Meier curves, both in the current paper and the publication of the 10-year primary outcome.[10]

Outcome ascertainment

Prostate cancer mortality at 15-year follow-up was ascertained with death certificates from the Office for National Statistics (ONS) at NHS England and adjudicated by an independent Cause of Death Evaluation (CoDE) committee using clinical information from hospital medical records and following a standardized protocol.[18,19] Prostate cancer stage and Gleason grade were obtained from the National Disease Registration Service[20] (NDRS, formerly Public Health England) at NHS England and Public Health Wales,[21] up to December 31st 2020.

Exploratory outcomes

Additional outcomes reported here that were described in the published original statistical analysis plan[10] were: i) mean age at diagnosis between allocated groups; and ii) a sensitivity analysis re-defining the primary outcome to include: (a) definite, probable, possible and treatment-related prostate cancer mortality; and (b) definite and treatment-related prostate cancer mortality.

Post hoc outcomes

We estimated differences in the risks of prostate cancer diagnosis between the intervention and control groups at 18-months, 10-years and 15-years, to quantify changes in diagnosis rates over long-term follow-up. We calculated mean sojourn time (the period in which a tumor is asymptomatic but detectable by screening) from microsimulation using estimated transition parameters for single episodes of screening between ages 50 to 69 and over-diagnosis rates as the difference in the cumulative prostate cancer incidence between screened and unscreened groups over a lifetime (further methodological details in **Supplement 1**).[22,23]

Statistical Analysis

The intervention effect at a median 15-years follow-up (at March 31st 2021) was analysed comparing groups as randomized using random-effects Poisson regression to estimate prostate cancer-specific and all-cause mortality rate ratios (RRs) in intervention versus control practices, allowing for

clustering within GP practices and randomization strata. To allow for variation in the incidence of prostate cancer with age, follow-up for each participant was divided into periods within five-year age-groups. We present rates (per 1000 person-years) and Kaplan-Meier estimates of the cumulative risk (per 100 men) of prostate cancer diagnosis, and prostate cancer and all-cause mortality.

In pre-specified analyses described in the original statistical analyses plan, and available as Supplementary material to the primary outcome paper,[10] we: i) used instrumental methods (generalized method of moments estimator) to estimate the effect of attending the PSA screening clinic at a median 15-years, compared with men in the control group who would have attended the clinic if invited, adjusting for age-group and using robust standard errors to allow for variation between practices; ii) compared mean age, and prostate cancer clinical stage (T1/T2, T3 and T4/N1/M1 disease) and Gleason score (=6 [low-grade]; =7 [intermediate grade]; 8+ [high grade]) at diagnosis between intervention and control groups using ordered logistic regression.

Prespecified subgroup analyses investigated variation in the effect of screening on prostate cancer mortality by baseline age-group and quintiles of geographical area-based index of multiple deprivation, a measure of socioeconomic status. An interaction test p-value was used to evaluate the evidence against the null hypothesis of equal intervention effect across sub-groups.

In accordance with our original analysis plan,[10] we did not conduct multiple imputation analyses. The statistical analysis plan did not specify an intention to adjust p-values for multiple comparisons: conventional adjustments assumed statistical independence between estimates, which was not the case for analyses of the same outcome at 10 and 15 years. All statistical testing was for superiority and p-values were 2-sided. In interpreting the results, we focused on estimated effects and associated 95% CIs. Results were considered statistically significant if the P value was <.05 or not statistically significant if the P value was ≥.05. All trial analyses were conducted using Stata version 16.1 (StataCorp).

Results

Study Population

911 GP practices were randomized in 99 geographical areas. Of these, 126 were subsequently excluded as ineligible (**Figure 1**).[12] Consent rates were 68% (271/398) among eligible GP practices in the intervention group and 78% (302/387) among eligible GP practices in the control group. Overall, 415,357 men registered with these practices were eligible for the intervention (N=195,912) and control (N=219,445) groups. Follow-up data for cancer diagnosis and mortality at a median of 15 years after randomization were available for 408,721 of the eligible men (98%), including 189,326 (97%) randomized to the intervention and 219,395 (>99%) randomized to control (**Figure 1**). Baseline characteristics were similar between intervention and control groups at practice and individual level (**Table 1**). Among people randomized to the intervention who developed prostate cancer (N=12,013), 9.4% were missing data for cancer stage and 10.4% were missing data for Gleason grade. Among people randomized to the control group who developed prostate cancer (N=12,958), 7.8% were missing data for cancer stage and 11.2% were missing data for cancer Gleason grade.

Rates of PSA testing

Overall, 75,694 (40%) of men randomized to the intervention group underwent PSA-testing and 64,425 (34%) had a valid (as defined in the methods) test result. Of these, 6,855 (11%) had a PSA value between 3-19.9ng/ml and were eligible for the ProtecT trial. Of these, 5,848 (85%) had a prostate biopsy. Cumulative PSA testing for prostate cancer detection in the control-group was indirectly estimated at 10% to 15% over 10-years median follow-up.[2,10]

Prostate cancer deaths

After a median follow-up of 15.4 years (interquartile range, IQR: 14.2-16.4; range: 12.2, 19.2), there were 1,199 deaths due to prostate cancer (rate: 0.47 per 1000-person years) in the intervention group and 1,451 deaths (rate: 0.50 per 1000-person years) in the control-group: RR 0.92 (95% CI, 0.85 to 0.99; p=0.03) **(Table 2, Figure 2A**). At a median of 15-years' follow-up, the cumulative risks of

prostate cancer mortality were 0.69% in the intervention group and 0.78% in the control group [risk difference -0.09% (95% CI, -0.15 to -0.03, P=0.02)] (**Table 2, eTable 1**). Using instrumental variable analysis, the prostate cancer mortality rate ratio for the effect of screening amongst men attending PSA-testing clinics was 0.83 (95% CI 0.68, 1.00; p=0.053) (**Table 2**).

Overall survival

There were 45,084 total deaths in the intervention group and 50,336 total deaths in the control group (RR 0.97: 95% CI 0.94 to 1.01; p=0.11) (**Table 2, Figure 2B**). Other causes of death were similar between the two groups (**eTable 2**).

Prostate cancer grade and stage

Compared to control, men in the intervention group were at higher risk of diagnosis with low-grade (2.2% of men versus 1.6%; risk difference = 0.58%, 95% CI 0.50%, 0.67%), and at lower risk of high-grade (1.2% versus 1.3%; risk difference = -0.15%; 95% CI: -0.22% to -0.08%), prostate cancers over the 15-years follow-up (p for trend <0.001). There was a higher risk of localized (3.6% versus 3.1%; risk difference = 0.56%, 95% CI 0.44%, 0.67%) prostate cancers and a lower risk of advanced-stage tumors (0.9% versus 1.1%; risk difference = -0.16%; 95% CI: -0.22% to -0.10%) over the 15-years follow-up in the intervention versus control group (p for trend <0.001) (**eTable 3; eFigures 2** and **3**).

Exploratory results

The mortality results were similar when including in the outcome definition those prostate cancer-specific deaths judged as 'possible' by the Cause of Death Evaluation committee, and when restricting to those judged as 'definite' prostate cancer-specific deaths (**eTable 4**). There was little evidence that the intervention effect differed by age-group or socioeconomic status (p values for interaction ≥0.46) (**Table 3**). Compared to the control group, intervention group men were a mean 1.22 years younger at prostate cancer diagnosis (95% CI 1.02, 1.42; p<0.001) (**eTable 3)**.

Post hoc results

After a median 15-years follow-up, there were 12,013 (4.88 per 1000 person-years [cumulative risk: 7.1%]) prostate cancer diagnoses in the intervention group and 12,958 (4.60 per 1000 person-years

[cumulative risk: 6.9%]) in the control group **(Table 2, Figure 2C)**. Differences in the risks of prostate cancer diagnosis between the intervention and control groups varied markedly during follow-up: cumulative risk differences per 1000 men for the intervention versus control groups were 12.23 (95% CI: 11.63, 12.84) at 18-months, 4.80 (95% CI: 3.53, 6.07) at 10-years, 1.38 (95% CI: -0.38, 3.14) at 15-years and 0.86 (95% CI: -1.80, 3.53) at 18-years (**eTable 1**).

For age-groups 50-54 compared to 65-69 years, the mean sojourn time increased from 12.1 years to 15.3 years, and over-diagnosis from 9.2% to 20.8%, respectively (**eTable 5, eFigures 4-6**).

Adverse Events

Among the deaths due to prostate cancer, 8 (0.7%) in the intervention group and 7 (0.5%) in the control group were related to a diagnostic biopsy or prostate cancer treatment.[10] Other adverse events were reported previously.[9,11]

Discussion

In secondary analysis from this cluster RCT of 415,357 men aged 50-69, compared to usual care control, a single invitation to undergo a PSA test led to an absolute reduction in prostate cancer mortality of 0.09% after a median follow-up of 15 years. However, the magnitude of the effect was small. There was no effect on overall survival. Policy-makers considering screening for prostate cancer should consider this small reduction in deaths against the potential adverse effects associated with over-diagnosis and over-treatment of prostate cancer.[6,24]

This clinical trial previously reported no benefit of a single invitation to PSA screening on the primary outcome of prostate cancer mortality at a median follow-up of ten years.[10] PSA testing is increasingly common,[2] particularly among men over age 60,[2,25] and definitive evidence on the benefits and harms of PSA screening remain unclear.[24] Analyses reported here are important because of the need for a longer follow up period to evaluate the effect of PSA-detection of prostate cancers,[5] particularly because findings from the ProtecT trial showed no difference in mortality irrespective of treatment over 15 years.[6]

The magnitude of reduction in prostate cancer mortality was smaller than the *a priori* defined effect-size considered important for clinical and public health benefit.[12] The harms of PSA testing include over-diagnosis, biopsy complications,[9] adverse treatment-effects on urinary, sexual and bowel function,[11] and the potential to miss an aggressive prostate cancer.[10] This clinical trial's single invitation to a PSA screen aimed to minimize over-diagnosis and over-treatment compared with other screening trials, but overdiagnosis was still observed after 15-years median follow-up. The European Randomized Study of Prostate Cancer Screening (ERSPC) randomized clinical trial (N=162,243), which combined data from 7 centers with different protocols and screening strategies, reported that PSA screening conducted every 2-4 years (mean of 1.4 tests per participant) reduced prostate cancer mortality after 16 years (rate ratio: 0.80; 95% CI:0.72-0.89).[26] The Prostate, Lung, Colorectal and Ovarian (PLCO) randomized clinical trial (N=76,683) reported little evidence of prostate cancer mortality benefit after 17 years with annual PSA testing compared to usual care (rate ratio: 0.93; 95% CI 0.81-1.08),[27] but was limited by high rates of PSA testing in the control group (a mean of 2.7 routine PSA tests over the trial's 6 year intervention period[28]) and only 35% adherence to recommendations for diagnostic biopsy.[29] The Stockholm clinical trial compared one-time PSA screening, and diagnostic investigations if PSA>10ng/ml, with an unscreened control group. It demonstrated over-diagnosis of prostate cancer (persistent excess in cumulative prostate cancer incidence in the screening intervention group throughout follow-up), without reduced prostate cancer mortality after 20 years follow-up.[30] Multiple screens implemented in ERSPC and PLCO increased over-diagnosis,[31] with evidence of a strong positive correlation between the extent of the absolute prostate cancer mortality reduction achieved by the screening intervention and the extent of over-diagnosis (quantified as the risk difference in cumulative incidence of prostate cancer between the trial arms).[32]

Strengths

This study had several strengths. First, compared to randomizing individual patients, recruitment in general practice clusters is expected to minimize volunteer bias and reduce contamination in the

control group, in which the intervention effects also cause greater screening in the control group. Cumulative PSA testing in the control-arm of this clinical trial was indirectly estimated at 10% to 15% over 10-years median follow-up, consistent with current UK policy not to recommend screening. A *priori* estimates suggested that the effect on statistical power of ever undergoing PSA testing during follow-up in the control group (contamination) would be minimal unless the PSA testing rate reached 20%.[12] Second, all practices followed the same screening and diagnosis protocol, providing consistent results. Third, among those with an elevated PSA level, adherence with recommendations for biopsy was high at 85%, similar to ERSPC (81%) and higher than PLCO (35%). This feature of the clinical trial would likely improve screening's potential effectiveness, which depends on patients' willingness to undergo subsequent diagnostic tests. Fourth, the large sample size of this trial contributed to excellent statistical power to detect a clinically meaningful effect size (a prostate cancer mortality RR of 0.87), assuming a that PSA testing in the intervention-arm was between 35% and 50% and that less than 20% of the control group had PSA testing.[12] Fifth, the comprehensive national electronic health record linkage of all the men in this clinical trial helped attain a follow-up rate of 98% over the median 15 year follow-up period.

Limitations

This study had several limitations. First, the screening intervention involved a single invitation for a PSA screening test, which is not typical of organized screening programs. Some advanced prostate cancers that might have been identified in subsequent screening rounds were likely missed. Second, NHS electronic records were used to identify prostate cancer, resulting in missing data for clinical characteristics and possible delay in recording diagnoses. Third, prostate cancer mortality at 15 years was a secondary outcome. Fourth, after this clinical trial began, newer diagnostic methods[33] and more effective treatments for advanced and metastatic prostate cancer[34] have been identified. Fifth, few Black men, who are at higher risk of prostate cancer, were included.[35]

Conclusions

A single invitation for PSA screening, compared to standard practice without routine screening, reduced the secondary outcome of prostate cancer deaths at a median follow-up of 15-years. However, the absolute reduction in deaths was small.

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Role of the Funder/Sponsor

The funders and sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

[§]**CAP trial group**. Group members are listed in **Supplement 2**.

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548

Figure Titles and Footnotes

Figure 1: Recruitment, randomization, and flow of practices and patients in a trial of PSA testing for prostate cancer

Footnotes

Shaded boxes: Flow of GP practices through trial recruitment; unshaded boxes: flow of men through trial recruitment; [a] Pseudo-anonymised follow-up; [b] NHS digital national data opt-outs (previously type-2 opt-outs) preventing NHS data being used for research. https://www.nhs.uk/using-the-nhs/about-the-nhs/opt-out-of-sharing-your-health-records/

**Practices were randomized prior to invitation to take part in the trial. Randomization was blocked and stratified by geographical area based on groups of 10-12 neighboring primary care practices and using a computerized random number generator to allocate near-equal number of practices in each stratum to intervention and comparison groups. The intervention was a single invitation to prostate specific antigen (PSA) screening.*

***Numbers of men are as of November 2021 and are subject to small changes over time because of continued updates from NHSD e.g. changes to the trace status of the men (e.g. men newly successfully traced). Note that not all men traced at 15 years were traced at 10 years.*

Follow-up was through routine NHS electronic vital status and cancer registry databases for diagnoses and deaths notified by Nov 2021 but that occurred up to 31st March 2021.

Figure 2: The Effect of the Trial Intervention on the Cumulative Incidence of Prostate Cancer Mortality and Diagnosis, and All-Cause Mortality After a Median 15-Years Follow-Up. The intervention was a single invitation to PSA screening.

Figure 2A: Prostate cancer mortality, by group

Figure 2B: All-cause mortality, by group

Figure 2C: Prostate cancer detection, by group

Footnote
P-values from random-effects Poisson model (see Statistical Analysis section).

Table 1: Individual and practice level characteristics at baseline amongst consented GP practices and men included in the analysis (adapted from Turner et al[12] and Martin et al.[10])

	Intervention group	Control group
Individual Characteristics	n= 189,326 men	n= 219,395 men
Median age (IQR)	58.5 (54.3, 63.5)	58.6 (54.3, 63.5)
Median Index of Multiple Deprivation score, England (IQR)	17.5 (10.1, 33.2)	16.9 (9.8, 32.4)
Median Index of Multiple Deprivation score, Wales (IQR)	17.6 (9.2, 29.5)	13.7 (7.1, 29)
Urban area (%)[a]	163,701 (86%)	189,667 (86%)
Race (%White)[b]	98%[b]	Not available
Practice Characteristics	n= 271 practices	n= 302 practices
Median practice list size (IQR)[c]	6,300 (4,150, 9,107)	6,300 (3,793, 9,000)
Number of urban practices (%)	244 (90%)	267 (88%)
Number of multiple partner GP practices (%)	242 (89%)	267 (88%)
Single partner practices[d]	21 (8%)	29 (10%)
Small practices (2-3)	60 (22%)	61 (20%)
Medium/large practices (4+)	128 (47%)	146 (48%)
Missing	62 (23%)	66 (22%)
Median QOF points achieved (%)[e] (IQR); n	98.9 (97.4, 99.6); 224	99 (97.4, 99.7); 266
Median Index of Multiple Deprivation score, England (IQR); n	21.8 (12.7, 44.1); 231	23.6 (13.3, 46.7); 271
Median Index of Multiple Deprivation score, Wales (IQR); n	18.8 (11.9, 22.9); 40	20.1 (7.6, 34.5); 31
Mean prevalence[f], %		
All cancers (s.d)	0.6 (0.3)	0.5 (0.2)
Diabetes (s.d)	3.6 (1.0)	3.7 (1.0)
Obesity (s.d)	8.0 (2.8)	7.8 (2.8)
Coronary heart disease (s.d)	4.1 (1.4)	3.9 (1.3)

Index of Multiple Deprivation, a measure of relative deprivation for small areas: a higher score indicates more deprivation, range 0-100. English and Welsh IMD scores are not directly comparable and are reported separately. The Index of Multiple Deprivation for the practice refers to the area of the practice not where patients live; QOF = Quality and Outcomes Framework, a system for performance management and payment of GPs based on the quality of their care: data are % of total QOF points achieved; IQR = interquartile range (25th percentile, 75th percentile); s.e. = standard error; [a]Rural/urban classification 2004, a measure of population density and sparseness, urban defined as areas >10,000 people; [b]Race/ethnicity for men attending the intervention group PSA test clinic were ascertained by a nurse using a standardized questionnaire as one of a range of baseline characteristics to assess generalisability.[13] Race/ethnicity were defined using UK Office for National Statistics Census categories and recoded as White and Other (all other categories collapsed due to low numbers of non-White participants). Race/ethnicity data were not available from NHS routine data we had access to at the time, so we could not compute these data for the control group. [c]The total number of individuals registered at GP practices (primary care practices). [d]Single partner GP practices are primary care practices with a single General Practitioner registered and practicing from there. [e]Based on 2007/2008 data,

England only. Quality and Outcomes Framework (QoF) scores are measured from 135 indicators and one measure of depth of care (holistic care) and are split across clinical, organisational, patient experience and additional services domains (maximum score 1,000 points). [f] *The prevalence of medical conditions across practices obtained from the clinical domain indicators of QoF: practices reported counts of patients with each condition and practice list size, enabling calculation of mean prevalence.*

Table 2: Effect of the trial intervention on prostate cancer specific and all-cause mortality and prostate cancer diagnosis by random allocation and by instrumental variable analysis, after a median 15-years of follow-up (median 10-year estimate can be obtained from Martin et al[10]).

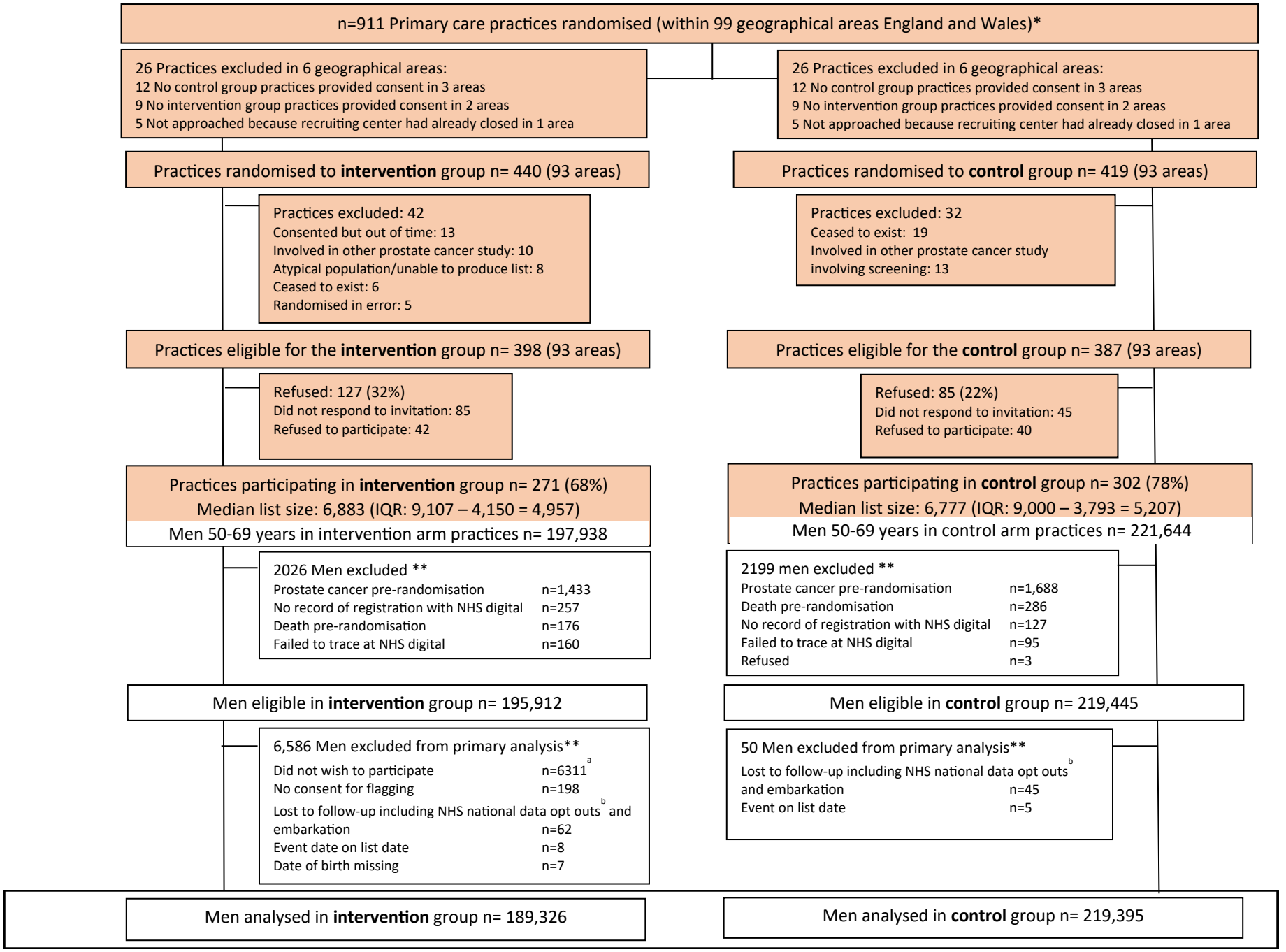
	Intervention group n=189,326; 2,543,298 person years)			Control group (n=219,395; 2,885,418 person-years)			Estimated effect of intervention versus control		
	Events	Rate/1000 person years (95% CI)	Risk [%] at 15 years (95% CI)[a]	Events	Rate/1000 person years (95% CI)	Risk [%] at 15 years (95% CI)[a]	Risk difference [%] at 15 years (95% CI)	Rate ratio (95% CI)[b]	P value[b,c]
15-year prostate cancer mortality[d]									
As randomized	1,199	0.47 (0.45, 0.50)	0.69 (0.65, 0.73)	1,451	0.50 (0.48, 0.53)	0.78 (0.73, 0.82)	-0.09 (-0.15, -0.03)	0.92 (0.85, 0.99)	0.033
IV analysis[e]		-	-	-	-	-	-	0.83 (0.68, 1.00)	0.053
15-year all-cause mortality									
As randomized	45,084	17.7 (17.6, 17.9)	23.2 (23.0, 23.4)	50,336	17.4 (17.3, 17.6)	23.3 (23.1, 23.5)	-0.07 (-0.35, 0.21)	0.97 (0.94, 1.01)	0.11
IV analysis[e]		-	-	-	-	-	-	1.01 (0.91, 1.12)	0.85
15-year prostate cancer diagnoses									
As randomized	12,013	4.88 (4.80, 4.97)	7.08 (6.95, 7.21)	12,958	4.60 (4.52, 4.68)	6.94 (6.82, 7.06)	0.14 (-0.04, 0.31)	1.06 (1.02, 1.09)	0.001

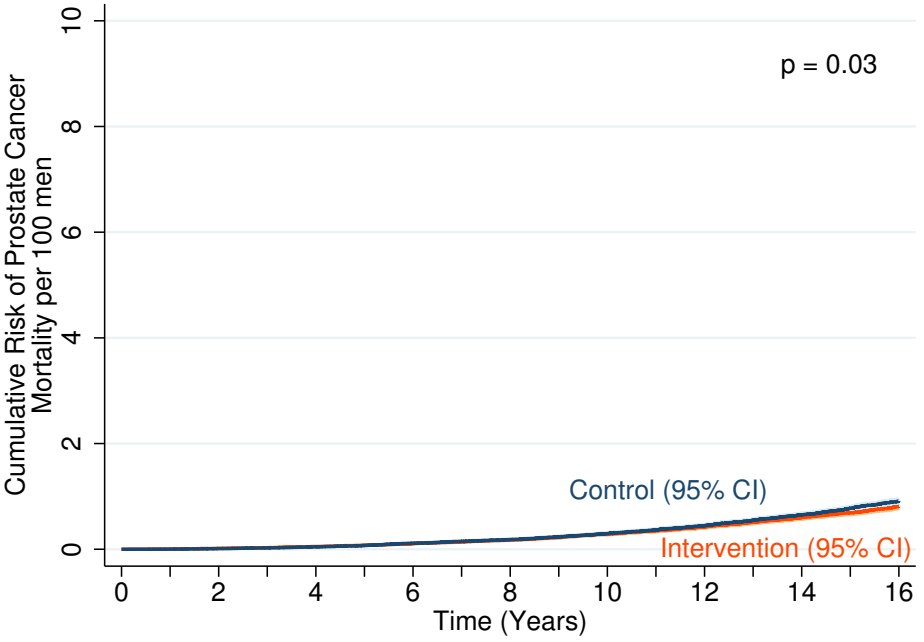
CI = confidence interval. IV: Instrumental variable. Median follow-up time was 15.43 years (interquartile range: 14.23-16.43; range: 12.19, 19.23). The intervention was a single invitation to PSA screening. [a]The numbers of deaths for the cumulative 15-year risk by intervention versus control group are 1,018 and 1,288, respectively. [b]Adjusted for current age using a lexis diagram approach; variation between randomisation cluster and GP practice accommodated by random effects in a three-level model. [c]Likelihood ratio test of the null hypothesis "no difference between the groups". [d]Defined as definite or probable prostate cancer death or intervention related death by an independent cause of death committee. [e]Instrumental variable analysis to estimate the effect of screening amongst those attending the PSA testing clinic, using a generalized method of moments (gmm) estimator with random allocation as the instrumental variable.

Table 3: Exploratory analysis of prostate cancer mortality rate ratios comparing intervention versus control groups, by age and deprivation scores, after a median 15-years follow-up

	Intervention group (n=189,326) Person years = 2,543,298			Control group (n=219,395) Person-years = 2,885,418			Estimated effect of intervention versus control		
	Deaths	Rate/1000 person years (95% CI)	Risk [%] at 15 years (95% CI)	Deaths	Rate/1000 person years (95% CI)	Risk [%] at 15 years (95% CI)	Risk difference [%] at 15 years (95% CI)	Rate ratio (95% CI)[a]	P value for interaction[a]
Age at baseline									
50-54	132	0.17 (0.14, 0.20)	0.22 (0.18, 0.27)	154	0.18 (0.15, 0.21)	0.25 (0.21, 0.30)	-0.03 (-0.09, 0.03)	0.96 (0.76, 1.22)	0.75
55-59	251	0.33 (0.29, 0.38)	0.47 (0.41, 0.54)	300	0.35 (0.31, 0.39)	0.54 (0.47, 0.61)	-0.07 (-0.16, 0.02)	0.92 (0.78, 1.10)	
60-64	368	0.64 (0.58, 0.71)	0.97 (0.87, 1.09)	465	0.70 (0.64, 0.77)	1.10 (1.00, 1.22)	-0.13 (-0.28, 0.02)	0.90 (0.77, 1.04)	
65-69+	448	1.05 (0.96, 1.15)	1.61 (1.45, 1.78)	532	1.07 (0.99, 1.17)	1.76 (1.60, 1.93)	-0.15 (-0.38, 0.08)	0.98 (0.86, 1.12)	
IMD area deprivation tertile England[b]									
Most affluent	326	0.44 (0.40, 0.50)	0.61 (0.54, 0.69)	425	0.47 (0.43, 0.52)	0.71 (0.64, 0.79)	-0.11 (-0.21, 0.00)	0.92 (0.79, 1.07)	0.46
Mid-level	373	0.51 (0.46, 0.56)	0.76 (0.68, 0.85)	463	0.53 (0.49, 0.58)	0.84 (0.76, 0.93)	-0.08 (-0.20, 0.04)	0.94 (0.82, 1.07)	
Most deprived	351	0.48 (0.44, 0.54)	0.74 (0.66, 0.83)	444	0.55 (0.50, 0.61)	0.86 (0.77, 0.95)	-0.11 (-0.23, 0.01)	0.85 (0.74, 0.99)	
IMD area deprivation tertile Wales[c]									
Most affluent	45	0.41 (0.31, 0.55)	0.52 (0.37, 0.73)	43	0.34 (0.25, 0.46)	0.47 (0.34, 0.65)	+0.05 (-0.19, 0.28)	1.16 (0.76, 1.77)	0.84
Mid-level	48	0.37 (0.28, 0.49)	0.62 (0.46, 0.84)	36	0.40 (0.29, 0.56)	0.60 (0.43, 0.84)	+0.02 (-0.25, 0.30)	0.89 (0.55, 1.43)	
Most deprived	56	0.49 (0.37, 0.63)	0.66 (0.49, 0.89)	39	0.41 (0.30, 0.56)	0.72 (0.52, 1.02)	-0.07 (-0.38, 0.25)	1.23 (0.82, 1.85)	

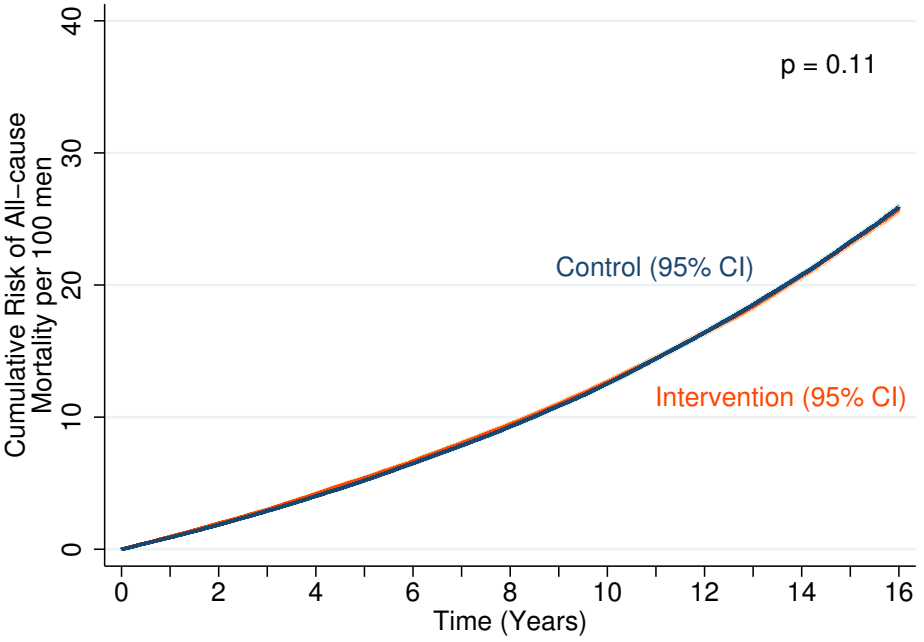
[a]Adjustment for age stratum and practice cluster effects apart from age which was not adjusted for age stratum. [b]Index of Multiple Deprivation. Scores range from 0 to 100 with higher scores indicating higher levels of deprivation. Tertile 1 has scores ranging from 1.08 to 12.17, tertile 2 has scores ranging 12.18 to 25.95 and tertile 3 has scores ranging from 25.97 to 79.98. [c]Scores range from 0 to 100 (England and Wales do not share the same scale) with higher scores indicating higher levels of deprivation. Tertile 1 has scores ranging from 1.40 to 10.30, tertile 2 has scores ranging 10.40 to 23.30 and tertile 3 has scores ranging from 23.40 to 78.90.


n=911 Primary care practices randomised (within 99 geographical areas England and Wales)*
26 Practices excluded in 6 geographical areas:
12 No control group practices provided consent in 3 areas
9 No intervention group practices provided consent in 2 areas
5 Not approached because recruiting center had already closed in 1 area
26 Practices excluded in 6 geographical areas:
12 No control group practices provided consent in 3 areas
9 No intervention group practices provided consent in 2 areas
5 Not approached because recruiting center had already closed in 1 area
Practices randomised to intervention group n= 440 (93 areas)
Practices randomised to control group n= 419 (93 areas)
Practices excluded: 42
Consented but out of time: 13
Involved in other prostate cancer study: 10
Atypical population/unable to produce list: 8
Ceased to exist: 6
Randomised in error: 5
Practices excluded: 32
Ceased to exist: 19
Involved in other prostate cancer study involving screening: 13
Practices eligible for the intervention group n= 398 (93 areas)
Practices eligible for the control group n= 387 (93 areas)
Refused: 127 (32%)
Did not respond to invitation: 85
Refused to participate: 42
Refused: 85 (22%)
Did not respond to invitation: 45
Refused to participate: 40
Practices participating in intervention group n= 271 (68%)
Median list size: 6,883 (IQR: 9,107 – 4,150 = 4,957)
Men 50-69 years in intervention arm practices n= 197,938
Practices participating in control group n= 302 (78%)
Median list size: 6,777 (IQR: 9,000 – 3,793 = 5,207)
Men 50-69 years in control arm practices n= 221,644
2026 Men excluded **
Prostate cancer pre-randomisation n=1,433
No record of registration with NHS digital n=257
Death pre-randomisation n=176
Failed to trace at NHS digital n=160
2199 men excluded **
Prostate cancer pre-randomisation n=1,688
Death pre-randomisation n=286
No record of registration with NHS digital n=127
Failed to trace at NHS digital n=95
Refused n=3
Men eligible in intervention group n= 195,912
Men eligible in control group n= 219,445
6,586 Men excluded from primary analysis**
Did not wish to participate n=6311 a
No consent for flagging n=198
Lost to follow-up including NHS national data opt outs b and embarkation n=62
Event date on list date n=8
Date of birth missing n=7
50 Men excluded from primary analysis**
Lost to follow-up including NHS national data opt outs b and embarkation n=45
Event on list date n=5
Men analysed in intervention group n= 189,326
Men analysed in control group n= 219,395



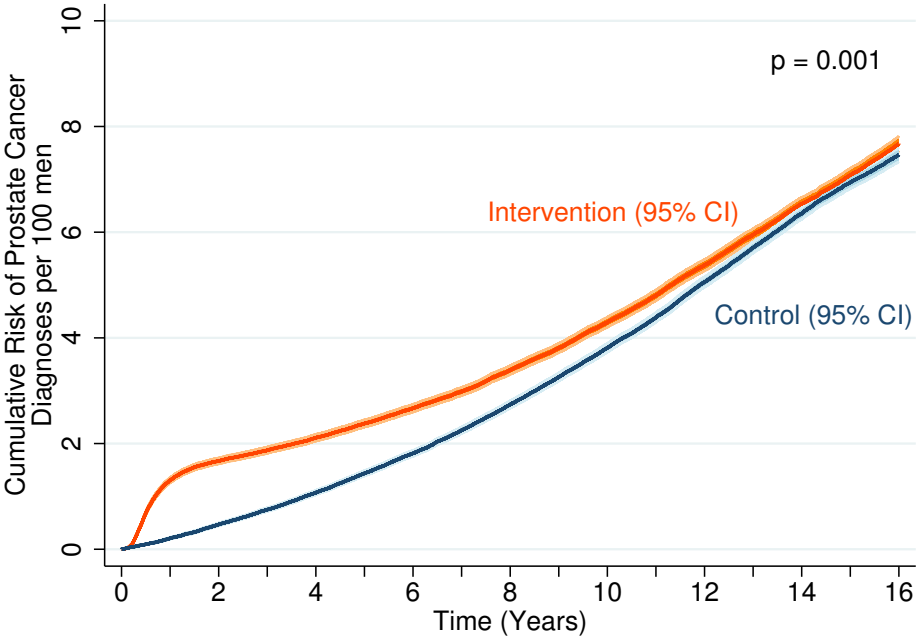
Number at risk

Intervention :	189326	177962	164154	146469	51975
Control :	219395	206205	189599	166375	40988



Number at risk

Intervention :	189326	177962	164154	146469	51975
Control :	219395	206205	189599	166375	40988



Number at risk

Intervention :	189326	174289	158876	139138	48427
Control :	219395	204203	184887	158863	38396

Supplemental Online Content

Martin RM, Turner EL, Young GJ, et al; CAP Trial Group. Prostate-specific antigen screening and 15-year prostate cancer mortality. *JAMA.* Published online April 10, 2024. doi:10.1001/jama.2024.4011

This supplemental material has been provided by the authors to give readers additional information about their work.

Methods used to estimate overdiagnosis and mean sojourn time.

We simulated a cohort of three million men aged 50-69 years and followed to death, calibrated against CAP data – prostate cancer incidence rate, and cancer-specific and all-other cause mortality rates (**eFigure 4**) and age at death (**eFigure 5**). We applied multistate survival model with parametric hazards and the following states: healthy, screen-detectable, screen-detected, clinically diagnosed, cancer-specific death, and all-other cause deaths, to estimate the natural history parameters and time to death after a cancer diagnosis (**eFigure 6**). The transition between healthy and screen-detectable states was assumed to follow the Weibull distribution, while other transitions were assumed to follow the Gompertz distribution. We estimated the transition hazards between the states and the misclassification of states (i.e., 1-episode sensitivity[1]) by maximising the likelihood functions.[2] We derived the mean sojourn time and overdiagnosis from microsimulation using the estimated transition parameters and one-off screening between ages 50 to 69 and assuming 85% of men with elevated PSA level undertake biopsy. We calculated the sojourn time as the length of time in the screen-detectable state given a transition to a clinically diagnosed state (i.e. the time by which diagnosis is advanced by screening [lead time]). We estimated overdiagnosed cases as the difference in cumulative prostate cancer incidence between screened and unscreened groups over lifetime. The probability of overdiagnosis was the fraction overdiagnosed among screen-detected cases.

Supplementary Tables

eTable 1: Prostate cancer-specific diagnoses and mortality and all-cause mortality at 10-years, 15-years and 18-years post-randomisation (and at 18 months for prostate cancer diagnoses) by random allocation and an as randomized estimate of the difference between groups.

	Intervention group *(n=189,326)*		**Control group** *(n=219,395)*		
	N	**Cumulative risk per 1000 men (95% CI)**	**N**	**Cumulative risk per 1000 men (95% CI)**	**Cumulative risk difference per 1000 men (95% CI)**
Prostate cancer mortality					
At 10-years	488	2.89 (2.65, 3.16)	575	2.95 (2.72, 3.21)	-0.06 (-0.41, 0.29)
At 15-years	1,018	6.90 (6.48, 7.34)	1,288	7.76 (7.34, 8.21)	-0.86 (-1.48, -0.25)
At 18-years	1,185	10.92 (10.14, 11.76)	1,440	12.09 (11.19, 13.07)	-1.17 (-2.41, 0.07)
All-cause mortality					
At 10-years	23,212	126.30 (124.79, 127.83)	26,581	125.37 (123.97, 126.79)	0.92 (-1.15, 3.00)
At 15-years	40,001	232.08 (230.06, 234.12)	46,073	232.75 (230.86, 234.65)	-0.68 (-3.46, 2.10)
At 18-years	44,747	316.15 (313.03, 319.29)	50,045	320.46 (316.91, 324.03)	-4.27 (-9.01, 0.47)
Prostate cancer diagnoses					
At 18-months	2,912	15.51 (14.96, 16.08)	711	3.28 (3.05, 3.53)	12.23 (11.63, 12.84)
At 10-years	7,558	42.92 (41.98, 43.88)	7,554	38.12 (37.28, 38.97)	4.80 (3.53, 6.07)
At 15-years	11,291	70.78 (69.51, 72.08)	12,368	69.40 (68.21, 70.62)	1.38 (-0.38, 3.14)
At 18-years	12,001	86.30 (84.53, 88.12)	12,938	85.44 (83.48, 87.44)	0.86 (-1.80, 3.53)

N is numbers of deaths and diagnoses as shown in the row headers. CI: Confidence interval. This table differs from Table 2, in that it reports cumulative risks at specific time points (10, 15 and 18 years), while Table 2 reports the data after a median 15 years of follow-up (range: 12.2 to 19.2 years).

eTable 2: Underlying causes of death[a] in intervention versus control groups at 15-year median follow-up (not including prostate cancer).

Cause of death	Intervention n (%)	Control n (%)
Any (not incl. prostate cancer)	43,885 (100%)	48,885 (100%)
Other cancers	16,553(38%)	18,440 (38%)
Circulatory diseases	12,419 (28%)	13,662 (28%)
Respiratory disease	5,287 (12%)	5,796 (12%)
Digestive disease	2,316 (5%)	2,612 (5%)
Infectious disease	385 (1%)	402 (1%)
Genitourinary diseases	445 (1%)	503 (1%)
Blood, immune, endocrine	644 (1%)	736 (2%)
Nervous system disease	1,862 (4%)	2,217 (5%)
Accident	1,126 (3%)	1,278 (3%)
Other	2,705(6%)	3,074 (6%)
No ICD10 code	143 (<1%)	165 (<1%)

[a]*Underlying cause of death for non-prostate cancer deaths was determined by death certificate.*

There were 95,420 all-cause deaths in total, including 308 deaths without an ICD10 code and 2,650 prostate cancer deaths (N=92,462 non prostate cancer deaths with an ICD-10 code).

eTable 3. Effect of the CAP trial intervention on characteristics of prostate cancer cases at diagnosis[a]

		Intervention group			Controls
		Attended PSA clinic 75,694	Did not attend PSA clinic 113,632	All invited 189,326	219,395
Number of prostate cancers (%)[b]		6,554 (8.7%)	5,459 (4.8%)	12,013 (6.3%)	12,958 (5.9%)
Clinical characteristics at diagnosis					
Person-years of follow up		1,043,530	1,416,377	2,459,907	2,815,181
Rate per 1000-person years		6.28 (6.13, 6.43)	3.85 (3.75, 3.96)	4.88 (4.80, 4.97)	4.60 (4.52, 4.68)
Mean age (SD)		67.28 (6.54)	69.21 (5.91)	68.16 (6.33)	69.38 (5.90)
Median years between randomization and diagnosis (IQR)		5.90 (0.67, 11.26)	9.15 (5.25, 12.15)	7.84 (1.69, 11.76)	8.93 (5.29, 12.02)
Grade (%)					
	Grade recorded[c]	5,991 (91.4%)	4,769 (87.4%)	10,760 (89.6%)	11,501 (88.8%)
	≤6[b]	2,704 (3.6%)	1,407 (1.2%)	4,111 (2.2%)	3,482 (1.6%)
	7[b]	2,305 (3.0%)	2,097 (1.8%)	4,402 (2.3%)	5,082 (2.3%)
	3+4	*1,011 (1.3%)*	*1,074 (0.9%)*	*2,085 (1.1%)*	*2,708 (1.2%)*
	4+3	*468 (0.6%)*	*570 (0.5%)*	*1,038 (0.5%)*	*1,443 (0.7%)*
	Unknown[d]	*826 (1.1%)*	*453 (0.4%)*	*1,279 (0.7%)*	*931 (0.4%)*
	≥8[b]	982 (1.3%)	1,265 (1.1%)	2,247 (1.2%)	2,937 (1.3%)
Stage (%)					
	Stage recorded[c]	5,952 (90.8%)	4,933 (90.4%)	10,885 (90.6%)	11,945 (92.2%)
	T1/T2[b]	4,227 (5.6%)	2,647 (2.3%)	6,874 (3.6%)	6,746 (3.1%)
	T3[b]	1,160 (1.5%)	1,146 (1.0%)	2,306 (1.2%)	2,871 (1.3%)
	T4/N1/M1[b]	565 (0.7%)	1,140 (1.0%)	1,705 (0.9%)	2,328 (1.1%)

The intervention was a single invitation to PSA screening. The PSA clinic was the clinic men were invited to have the PSA test explained, consider having a PSA test and give written informed consent with a 24-hour period cooling off period.
IQR = interquartile range (25th percentile, 75th percentile). CI = confidence interval. [a]Diagnoses were collected from routine data sources, NHS England data were used in the first instance (n=23,415 cancers) and additional cases were included if present in data provided by Public Health Wales (n=930) or the National Disease Registration Service (NDRS, formerly Public Health England) (n=626). [b]Denominators are column header totals. [c]Denominators are N of prostate cancers in each column. [d]Missing primary and secondary Gleason grade to enable 3+4 and 4+3 subdivision.

eTable 4: Sensitivity analyses employing alternative definitions of prostate cancer deaths.

	Intervention group *(n=189,326)* Person years=2,543,298		**Control group** *(n=219,395)* Person years=2,885,418		**As randomized estimate**	
	Events	**Rate/1000 person years (95% CI)**	**Events**	**Rate/1000 person years (95% CI)**	**Rate ratio (95% CI)**	**P value[a]**
Including 'possible' prostate cancer death[d]	1230	0.48 (0.46, 0.51)	1498	0.52 (0.49, 0.55)	0.91 (0.85, 0.99)	P=0.020
Definite prostate cancer death only[e]	1028	0.40 (0.38, 0.43)	1254	0.43 (0.41, 0.46)	0.91 (0.84, 0.99)	P=0.030

[a]Likelihood ratio test of the null hypothesis "no difference in prostate cancer mortality between the groups", adjusted for randomisation cluster and age using a lexis diagram approach. [b]Defined as definite, probable or possible prostate cancer death or intervention related death by an independent cause of death committee. [c]Defined as definite prostate cancer death or intervention related death by an independent cause of death committee.

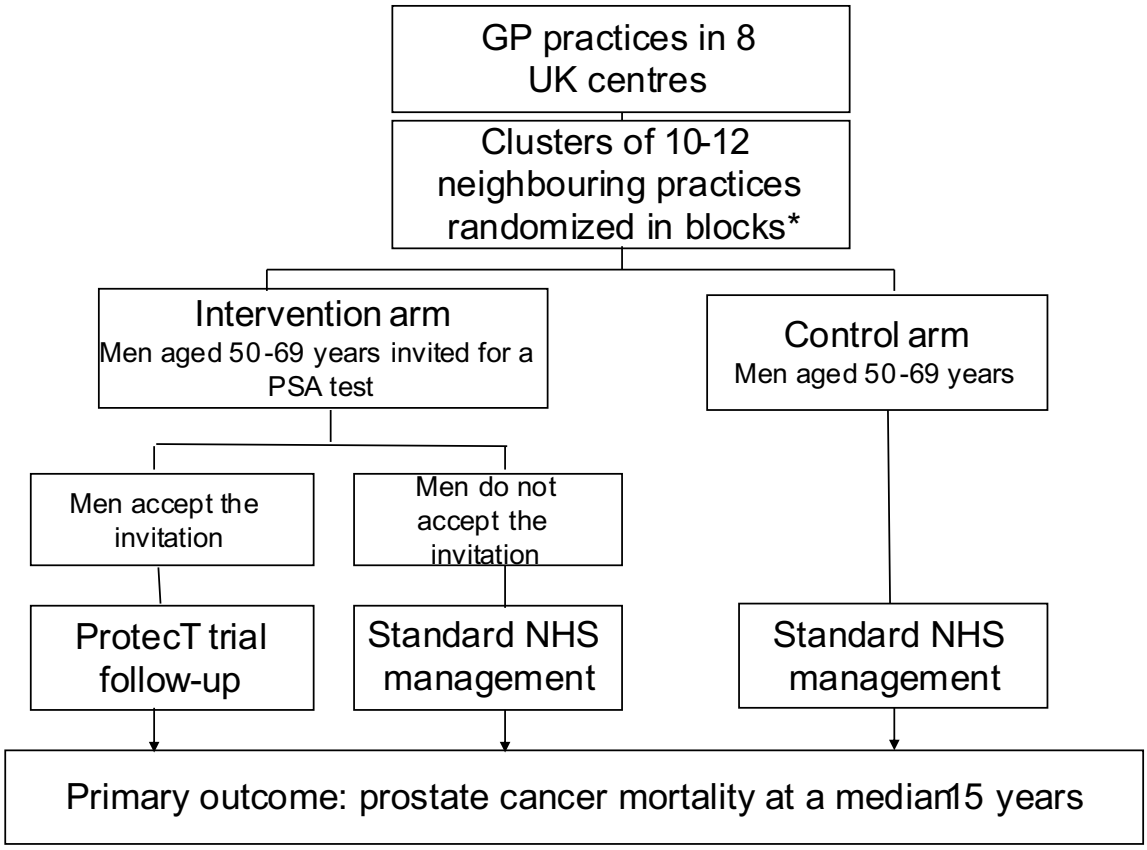
eTable 5: Estimated mean and median sojourn time and probability of overdiagnosis.

Age group				
	Mean sojourn time (years)	**95% confidence interval (years)**	**Median sojourn time (years)**	**Interquartile range (years)**
50-54	12.1	12.1 – 12.2	10.6	5.0 – 17.5
55-59	13.2	13.1 – 13.2	11.9	5.5 – 19.3
60-64	14.2	14.2 – 14.3	13.0	5.9 – 21.4
65-69	15.3	15.2 – 15.3	13.8	6.2 – 23.4
50-69	**13.4**	**13.4 -13.4**	**12.0**	**5.5 -19.8**
	Mean overdiagnosis %	**95% confidence interval (%)**	**Median overdiagnosis %**	**Interquartile range %**
50-54	9.2	8.9 – 9.4	9.3	8.0 – 10.4
55-59	13.3	13.1 – 13.5	13.4	12.4 – 14.3
60-64	17.1	17.0 – 17.3	17.2	16.4 – 17.9
65-69	20.8	20.6 – 21.0	20.8	20.0 – 21.3
50-69	**15.0**	**14.4 – 15.5**	**14.8**	**13.6 – 15.8**

The sojourn time represents the duration of the preclinical screen-detectable period for each of the 3 million men who transition from screen-detectable to clinically diagnosed state. Sojourn time varies between individuals.
*****Overdiagnosis estimates are based on simulation of 200 cohorts of 3 million men aged 50 to 69 followed to death. The episode sensitivity[1] (the ability of the full diagnostic process – testing and biopsy – to find cancer in the detectable preclinical phase) increased from 50.0% to 85.3% for ages 50 to 69.

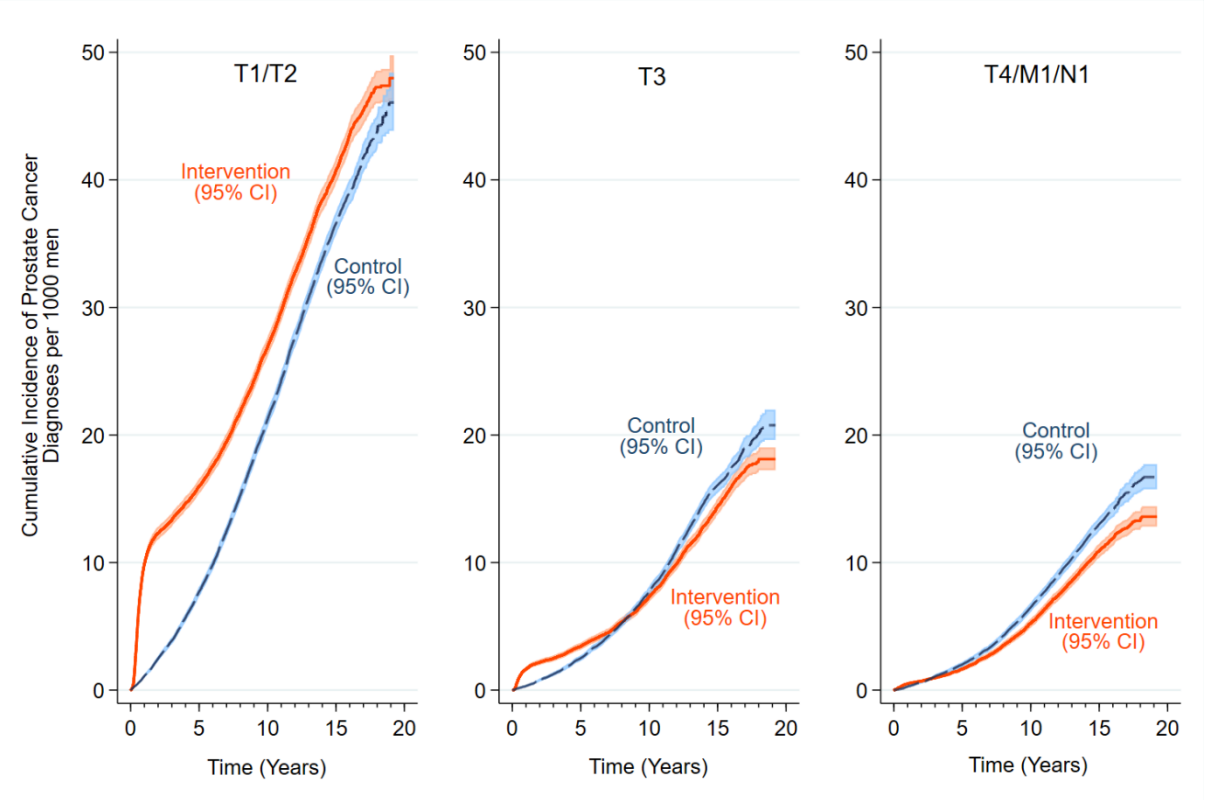
Supplementary Figures

eFigure 1: CAP trial design.



CAP is a UK-wide cluster RCT in which 573 GP practices in 8 UK centres (Sheffield, Newcastle, Bristol, Birmingham, Cardiff, Leeds, Cambridge, Leicester) were randomised and consented to either PSA testing and prostate cancer diagnosis (ProtecT trial) or the routine-practice comparison arm. Pre-specified Prostate cancer mortality outcomes were collected at a median 10-years (reached 31st March 2016) and 15-years (reached 31st March 2021) follow-up.

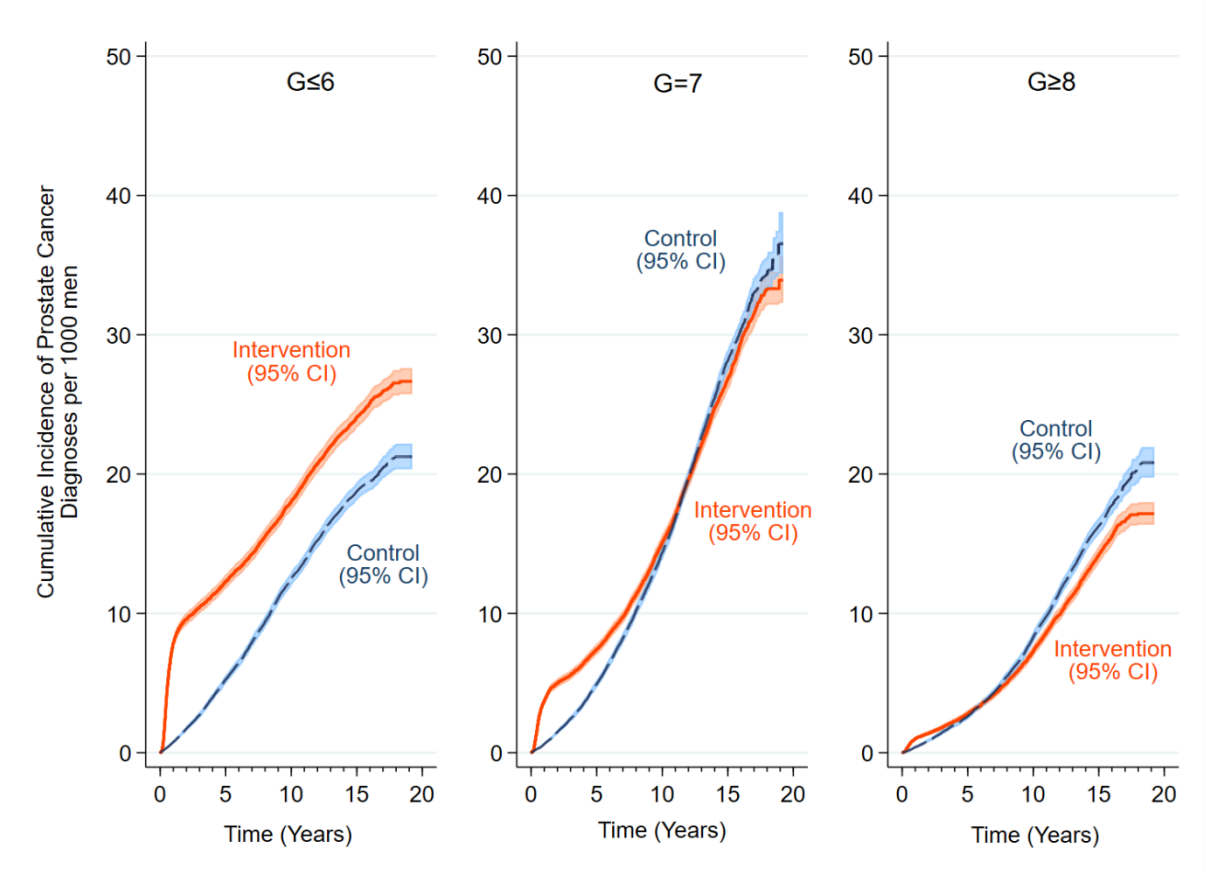
eFigure 2: Cumulative incidence of prostate cancer by TNM stage at diagnosis.



Number at risk at the start of each two-year period (number of prostate cancer diagnoses in that period)												
Time (year)	**Median (IQR) follow up**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**
A: Clinical stage T1/T2												
Intervention	14.20 (11.42, 16.04)	189,326 (2302)	180,957 (418)	174,289 (514)	167,024 (697)	158,876 (805)	149,145 (868)	139,138 (763)	103,163 (386)	48,427 (119)	12,794 (2)	0 (0)
Control	14.35 (11.09, 15.67)	219,395 (531)	212,352 (665)	204,203 (844)	194,558 (1,044)	184,887 (1,083)	172,125 (1079)	158,863 (936)	119,810 (459)	38,396 (94)	9,687 (11)	0 (0)
B: Clinical stage T3												
Intervention	14.20 (11.42, 16.04)	189,326 (404)	180,957 (136)	174,289 (183)	167,024 (220)	158,876 (302)	149,145 (374)	139,138 (388)	103,163 (230)	48,427 (68)	12,794 (1)	0 (0)
Control	14.35 (11.09, 15.67)	219,395 (168)	212,352 (223)	204,203 (300)	194,558 (357)	184,887 (447)	172,125 (547)	158,863 (541)	119,810 (230)	38,396 (52)	9,687 (6)	0 (0)
C: Clinical stage T4/M1/N1[a]												
Intervention	14.20 (11.42, 16.04)	189,326 (131)	180,957 (97)	174,289 (152)	167,024 (223)	158,876 (266)	149,145 (316)	139,138 (309)	103,163 (161)	48,427 (46)	12,794 (4)	0 (0)
Control	14.35 (11.09, 15.67)	219,395 (133)	212,352 (181)	204,203 (227)	194,558 (314)	184,887 (397)	172,125 (417)	158,863 (402)	119,810 (207)	38,396 (47)	9,787 (3)	0 (0)

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

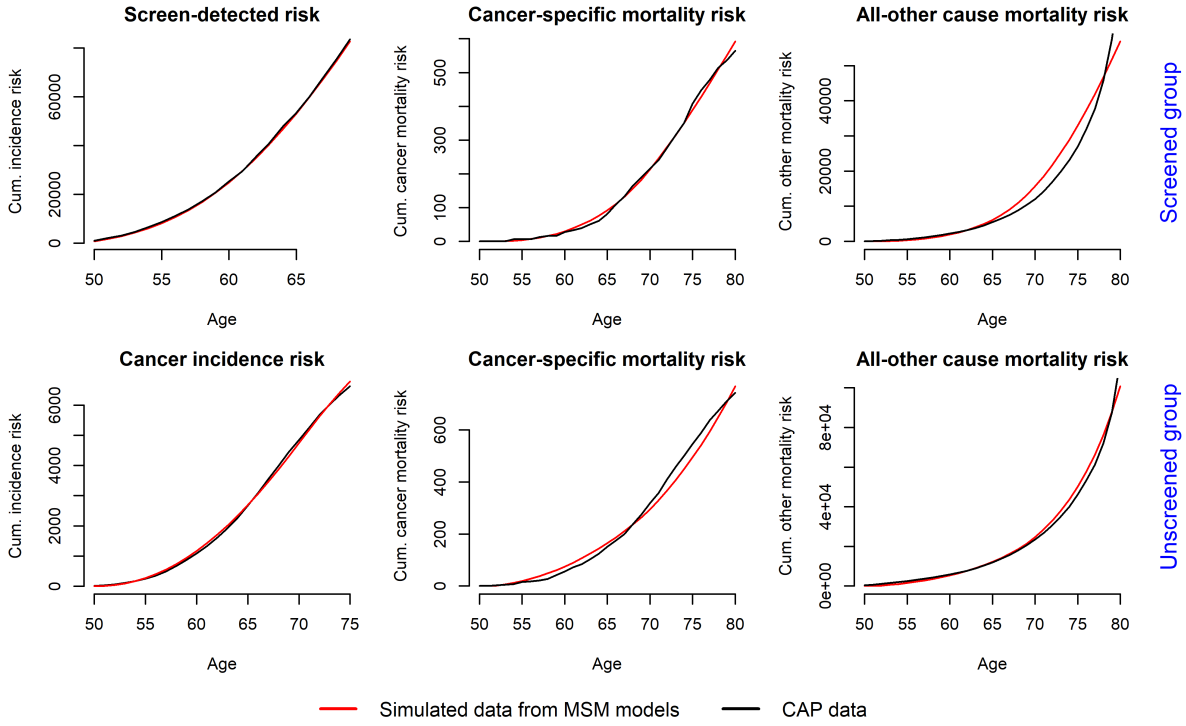
eFigure 3: Cumulative incidence of prostate cancer by Gleason score at diagnosis.



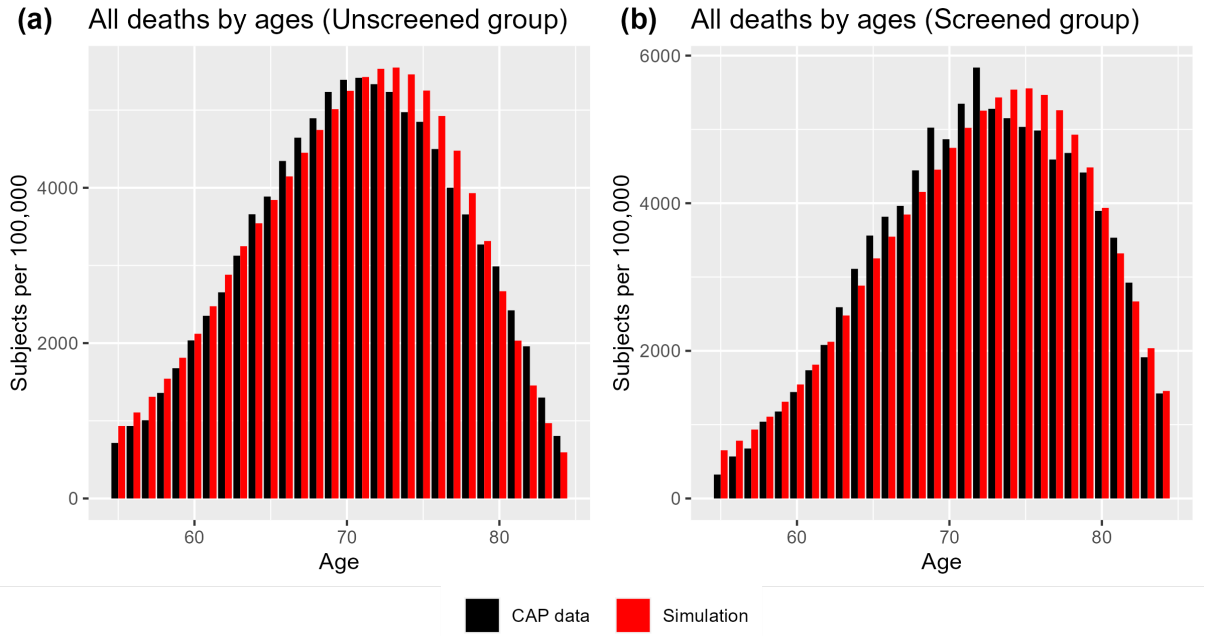
Number at risk at the start of each two-year period (number of prostate cancer diagnoses in that period)												
Time (year)	**Median (IQR) follow up**	**0[b]**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**
A: Gleason≤6												
Intervention	14.20 (11.42, 16.04)	189,326 (1790)	180,957 (313)	174,289 (330)	167,024 (378)	158,876 (390)	149,145 (402)	139,138 (307)	103,163 (153)	48,427 (47)	12,794 (1)	0 (0)
Control	14.35 (11.09, 15.67)	219,395 (374)	212,352 (458)	204,203 (503)	194,558 (565)	184,887 (556)	172,125 (463)	158,863 (373)	119,810 (157)	38,396 (33)	9,687 (0)	0 (0)
B: Gleason 7												
Intervention	14.20 (11.42, 16.04)	189,326 (930)	180,957 (256)	174,289 (366)	167,024 (460)	158,876 (578)	149,145 (664)	139,138 (676)	103,163 (352)	48,427 (118)	12,794 (2)	0 (0)
Control	14.35 (11.09, 15.67)	219,395 (317)	212,352 (432)	204,203 (593)	194,558 (705)	184,887 (754)	172,125 (899)	158,863 (863)	119,810 (426)	38,396 (84)	9,687 (9)	0 (0)
C: Gleason≥8												
Intervention	14.20 (11.42, 16.04)	189,326 (257)	180,957 (155)	174,289 (198)	167,024 (266)	158,876 (342)	149,145 (389)	139,138 (375)	103,163 (208)	48,427 (57)	12,794 (0)	0 (0)
Control	14.35 (11.09, 15.67)	219,395 (193)	212,352 (288)	204,203 (288)	194,558 (391)	184,887 (503)	172,125 (539)	158,863 (502)	119,810 (236)	38,396 (52)	9,687 (5)	0 (0)

CI: confidence interval, IQR: interquartile range

eFigure 4: Comparing simulated data to empirical data for the cumulative prostate cancer incidence and cancer-specific and all-other cause mortality risk among the screened men and the unscreened group. Average of 200 simulations of three million men aged 50-69 years with one-off screening in the screened group.

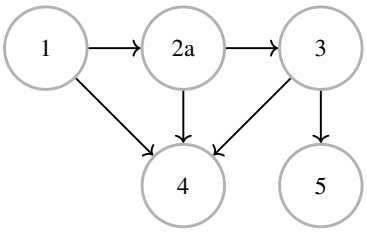


eFigure 5: Comparison number of subjects per 100, 000 cohorts at death from all causes by ages between simulated data and CAP data. Average of 200 simulations of three million men aged 50-69 years with one-off screening in the screened group.

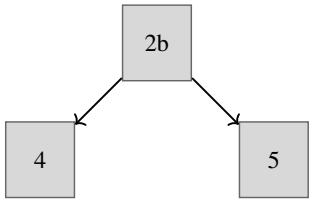


eFigure 6: Transition diagram for multi-state survival models a. Natural history model with states 1-Healthy, 2a – Screen-detectable, 3-clinically diagnosed, 4-all-other cause death, 5-cancer-specific death; b. survival model for screen-detected cancers with states 2b-screen-detected, 4-all-other cause death, 5-cancer-specific death.

Model a.



Model b.



Supplementary Material References

1. Hakama M, Auvinen A, Day NE, Miller AB. Sensitivity in cancer screening. *Journal of Medical Screening* 2007; **14**(4): 174-7.
2. Bhatt R, van den Hout A, Pashayan N. A multistate survival model of the natural history of cancer using data from screened and unscreened population. *Stat Med* 2021; **40**(16): 3791-807.