

The influence of age and the presence of prostate cancer on prostate volume, PSA and PSA-D

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Conflict of Interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Statement of originality

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54 **Abstract**

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56 *Purpose/Background*

57 Few studies have mapped prostate volume (PV) changes across the lifespan of asymptomatic patients. In this study we
58 assessed PV changes with age in symptomatic and asymptomatic men with and without clinically significant prostate cancer
59 (csPCa). In symptomatic patients, we additionally analysed the effect of age and csPCa on PSA and PSA-density (PSA-D) and
60 compared these to current NICE-recommended PSA age-range thresholds.

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62 *Methods*

63 This single-centre retrospective cross-sectional study included 2,512 men: 760 asymptomatic, disease-free men and 1,752
64 patients referred on a PCa diagnostic pathway. MRI-derived whole-gland PV was recorded for all patients. A machine-
65 learning pipeline with k-fold cross validation modelled relationships between PV and age.

66
67 *Results*

68 In asymptomatic men (median PV 25.4ml), mean PV per age-group increased non-linearly with age, from 18.7ml at an
69 increase of 0.10ml/year aged 18, to 41.3ml at 0.68ml/year aged 89, with increased rate of change from 48.9 years. Significant
70 positive relationships were shown between PSA and age in patients with and without csPCa ($r^2=0.09$ vs 0.13 , respectively),
71 with PSA increasing by mean 0.17ng/ml/year across groups. csPCa patients had consistently higher PSA levels. PSA-D
72 showed significant age-related linear increases in csPCa, but remained consistently lower in those without csPCa at all ages
73 ($0.10\text{-}0.11\text{ ng/ml}^2$), allowing differentiation at a threshold of $>0.15\text{ ng/ml}^2$.

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75 *Conclusion*

76 In asymptomatic men, prostate volume changed non-linearly with age. Age-related PSA thresholds are supported, however, a
77 static PSA-D threshold of 0.15 ng/ml^2 can be applied across all age-ranges.

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80 **Key words**

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82 PSA; PSA density; prostate cancer; prostate volume; MRI prostate
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109 **Key Points**

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- 111 In asymptomatic men, prostate volume changed non-linearly with age, with an increased rate of change from 48.9 years.
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- 113 In symptomatic men, prostate volume was significantly lower in patients with csPCa than symptomatic non-cancer patients,
- 114 and increased more slowly with age.
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- 116 Patients with csPCa had significantly higher PSA-D, and higher PSA.
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- 118 The use of different age-related PSA thresholds is supported, in line with current NICE guidance.
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- 120 For all age-ranges, the static PSAD threshold of 0.15 ng/ml² could be applied to support csPCa detection.
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Introduction

Prostate cancer (PCa) is the most common male cancer in the United Kingdom, and is the fifth highest cause of mortality for men worldwide(1). Furthermore, both PCa incidence and mortality have been shown to increase with age(2), with incidence expected to increase with an ageing global population.

The first investigation performed when PCa is suspected clinically, is a prostate-specific antigen (PSA) test. PSA alone has a low specificity for the diagnosis of PCa, and may be raised due to benign prostatic hyperplasia (BPH)(3), increased age, infection, inflammation, and trauma(4). The increase of PSA with age is thought to be driven by an increase in prostate size in the ageing male, and particularly an increase in the quantity of PSA-producing glandular tissue, alongside a breakdown of the physiological barriers restricting leakage of PSA from within the prostatic ductal system(5). This has led to the adoption of age-specific prostate specific antigen (PSA) thresholds as recommended by NICE(6), however these have not been accurately mapped in the existing literature(7,8).

In the current PCa diagnostic pathway, a PSA test is followed by a prostate MRI(6) to determine the need for subsequent biopsy and enable accurate gland volume assessment. With prostate volume (PV), PSA density (PSA-D) can be calculated, which has been shown to be more accurate than PSA alone(9,10), and can be used to augment clinical decision making. However, for PSA-D, age-related thresholds have not yet been established. Furthermore, it is unclear how prostate volume differs between men that are asymptomatic and disease-free, symptomatic and disease-free, or patients with indolent or clinically significant cancer. Addressing this knowledge gap may lead to a more personalised use of PSA or even PSA-D thresholds specific to age, rather than a universal threshold.

In this study, we assessed age-specific changes in MRI-derived prostate volume in a large cohort of symptomatic and asymptomatic men with and without PCa to derive age-specific PSA and PSA-density threshold levels.

Patients

This single-centre retrospective study was approved by the local ethics committee (anonymised), with the need for written informed consent waived. Patient populations were defined as below (**Figure S1**). The symptomatic cohort included patients referred to urology with a suspicion of prostate cancer based on lower urinary tract symptoms (LUTS), and/or raised PSA, and/or an abnormal digital rectal examination. The asymptomatic cohort had no known prostatic or LUTS, and no previous investigations or treatment for benign or malignant prostatic disease.

1. Asymptomatic, disease-free men (Cohort 1)

We performed a search of the local electronic medical record system for male patients aged 18-89 undergoing MRI of the pelvis for any indication between January 2019 to December 2021 (n=2788). This is a wider age range than our symptomatic cohort, as this is a physiological dataset aiming to represent normal prostate growth across adulthood. The purpose is to provide contextual comparison to the symptomatic group and investigate the need for the existing different age-related thresholds for normal PSA values (which are based on expected increase in volume in age). Exclusion criteria were: age (<18 and ≥90, n=140), repeat images (n=211), suspicion or confirmation of prostate pathology (from past medical history, indication that PSA level was tested, radiological evidence, biopsies, n=1229), incomplete MRI coverage of prostate (n=415).

2. Symptomatic patients (Cohort 2)

A separate search of the electronic database was performed for patients undergoing prostate MRI for suspected prostate cancer for patients aged 40-79 from October 2015 to November 2021 (n=2196). Patients on this Prostate Diagnostic Cancer Pathway were symptomatic for PCa, with raised absolute serum PSA on two consecutive tests 4-6 weeks apart, with or without LUTS or an abnormal digital rectal examination. Raised PSA was defined as >3.0 ng/ml for patients aged 50-69, clinical discretion being used for patients outside of this range, but <30 ng/ml as beyond this level patients were at higher risk of metastatic disease, at which point staging investigations would have been more appropriate than MRI. Exclusion criteria were: patients with a previous history of prostate cancer (n=7), repeat imaging (n=95); insufficient clinical data available (n=4); prior treatment for benign prostatic disease (including TURP, HoLEP or Rezum; taking finasteride or dutasteride; n=51); MRI Likert scores of 4 or 5 without a biopsy being performed (n=16); inflammatory change ≤6 months post-MRI (either clinically diagnosed or based on biopsy; n=185); age (<40 and >79, n=3). Total PSA levels were recorded based on the sample taken within 3 months of MRI and, in cases of multiple readings, the one closest to the time of imaging. All patients underwent 1.5T or 3T scanning (GE Healthcare, USA) following a PI-RADS compliant protocol and including T1, multiplane T2, diffusion-weighted imaging and dynamic contrast-enhanced MRI [Ref].

Methods

Prostate volumes

Prostate volumes derived from T2-weighted images in two different planes were selected, and the maximum anteroposterior (a), transverse (b) and longitudinal (c) diameters were measured directly on the MRI slices and applied to the clinically approved elliptical formula: $PV (mL) = 0.00052 * a * b * c$ (11). The data was stratified by age groups conforming to those used by NICE(7) (**Table S1**). For both cohorts, age group-specific outliers (n=33 from cohort 1; n=83 from cohort 2), were calculated as $x > mean + 2sd$ or $x < mean - 2sd$.

Data analysis

The volumes for each group were plotted against age, and a machine-learning pipeline (repeated k-fold cross validation) was used to ascertain which, of several fits (polynomials orders 1-20 and a spline regression) would best describe the relationship between PV and age in this data and unseen data, for each group. From this, models were made that best described PV cross-sectionally over the age ranges of each cohort that would also take into account the data of future patients (**Supplemental Methods**). If repeated k-fold cross validation suggested a model that was non-linear, the R² of that regression was tested for statistical significance over a linear model with paired t-tests, nested model f-tests and the effect size calculated with Cohen's d. This approach was taken to avoid the classical overfitting that accompanies classical descriptive statistics. For the asymptomatic disease-free group, this age range was the entire adult lifetime, to inform our understanding of baseline prostate physiology. To determine how prostate volume changes with different presentations and pathology, we then use this same machine-learning analysis to describe the volume changes in our diseased groups.

In the symptomatic groups, we analysed PSA with linear regression to determine how it is affected by both age, and disease severity. We then determined how PSA-D was influenced by the same variables, again with linear regression and compared our findings to the current NICE thresholds. For the symptomatic groups, the data was narrowed down to the age ranges that are currently most relevant as periods of disease occurrence. Logistic regression analysis was done to test the ability of volume for predicting csPca. Youden's index was calculated to determine the optimal PSA-D threshold.

All the statistical and graphical analyses were performed using the coding languages 'R' (version 4.5.1) and GraphPad Prism (version 9.3.1). The symptomatic cohort (cohort 2) was grouped based on their MRI and biopsy results: clinically significant

254 prostate cancer (csPCa) if Gleason Score (GS) ≥ 7 on biopsy; clinically insignificant prostate cancer (Gleason score 3+3)), or
255 benign: if negative MRI i.e. Likert score of 1 or 2 without biopsy, or GS 6 on biopsy; or clinically benign. Clinically benign was
256 defined as any patient who did not have proven PCa at the time of the investigation. This means they had a biopsy result reported
257 as histologically benign, or Atypical Small Acinar Proliferation (ASAP) or Prostatic Intraepithelial Neoplasia (PIN) without a
258 Gleason scale cancer. A biopsy was offered to patients with a Likert score or 1-2 and PSAD >0.15 ng/mL², Likert score of 3
259 and PSAD >0.12 ng/mL² or a score of 4-5 (12). Patients with a Likert score 1-3 MRI and no biopsy were followed up for a
260 minimum of 6 months and had at least one subsequent PSA reading [Ref]. Overall, the groups were as follows: asymptomatic
261 disease free, symptomatic benign, symptomatic low-grade cancer, symptomatic clinically significant (medium-high grade
262 cancer). Comparisons between the asymptomatic and symptomatic groups were made (between age groups 40-79, to avoid
263 mixing age effects with disease effects) using the Kruskal-Wallis test with the Dunn-Bonferroni post hoc test, to ascertain which
264 groups were significantly different from each other.
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266 Results

267 Demographics

268 Cohorts one and two this had final populations of n=760 and n=1752, respectively, for analysis.

269 In our asymptomatic cohort for volume analysis (n=760), the cohort had an age (in years) mean of 52.9, median of 53 and
270 minimum-maximum range of 18-89.

271 In our symptomatic cohort for volume analysis (n=1752), the cohort had an age mean of: 64.5, median of 65, range of 42-79.
272 PSA (in ng/ml) mean of 7.2, median of 6.2, range of 0.67-23.4. 992 biopsies (56.6%) were benign, 760 (43.4%) showed a
273 Gleason score of $\geq 3+3$ disease, while 585 (77% of total cancers) harboured clinically significant cancer (GS $\geq 3+4$).
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279 PSA

280 Significant positive linear relationships were shown between PSA and age in patients both with and without csPCa ($r^2 = 0.09$ vs
281 0.13 , $P < 0.0001$ respectively), with csPCa patients having higher PSA levels (Figure 1, Table S2). There is an overlap of 95%
282 confidence intervals below approximately 51 years, and so difference between PSA below this age may lose statistical
283 significance. Between patients with and without csPCa, rate of change in PSA with age was not significantly different ($p=0.34$),
284 and hence a combined gradient could be calculated, showing a gradational PSA increase of 0.17 ng/ml/year.

285 Prostate volume

286 1. Asymptomatic, disease-free prostates (Cohort 1)

287 The median PV of the cohort was 25.4ml. Mean PV per age-group continuously increased over the age-range, from 18.7ml to
288 41.3ml (Table 1, Figure S2), with a significant positive correlation between PV and age, confirmed by Spearman's rank of
289 $\rho=0.56$, $p<0.0001$. Prostate growth was estimated from the substitution of age into the differentiation of the equation of our
290 quadratic model and increased continuously from 0.10ml/yr at age 18 to 0.68ml/yr at age 89 (Table S3). With repeated k-fold
291 cross validation, these prostate volumes are best modelled by a quadratic curve ($R^2 = 0.32$) (Figure S4). This was verified to be
292 a statistically significant improvement on the linear model (f-test $p<0.005$), with a large effect size (Cohen's $d = 4.3$). This
293 translates to 32% of the variation in PV being accounted for by the variation in age. Therefore, in asymptomatic men free of
294 prostatic disease, prostate volume changes non-linearly over the entire adult lifetime (Figure 2). From the spline model we could
295 identify that a distinct change in the increment of PV increase occurs at 48.8 years (± 5.14) (Figure S4). Overall, however,
296 further repeated cross-validation revealed that the quadratic model slightly surpassed the spline in its ability to fit the data (the
297 latter $R^2 = 0.31$).

298 2. Prostates symptomatic for PCa (Cohort 2)

299 The symptomatic group had a higher median PV of 52.0ml. As in the asymptomatic cohort, PV increased with age. Repeated
300 K-fold cross validation suggested that the symptomatic benign group was best modelled by a fifth order polynomial, which was
301 a statistically significant improvement (f-test $p<0.05$) with a modest effect size (Cohen's $d = 2.2$). However, unlike the
302 quadratic model for the asymptomatic data, a polynomial of this order is inappropriate for interpretation clinically, and the
303 marginal gain in explained variance does not justify the substantial increase in model complexity. By the principle of parsimony,
304 a linear model ($R^2 = 0.20$) would afford minimal loss in predictive performance, but improved interpretability and clinical utility.
305 The csPCa group was also best modelled linearly ($R^2=0.07$), though PV was consistently lower and increased with age at a
306 slower rate. The optimal model for clinically insignificant cancer predicted by repeated k-fold cross validation was a quadratic
307 ($R^2=0.18$), however this was not a statistically significant improvement on the linear model (f-test $p=0.2991$). Overall, all the
308 symptomatic cohorts are modelled in this study with a linear regression (Figure S4).

309 Aside from age, the second variable of disease severity, also influenced volume (Figure 2). The Kruskal-Wallis rank sum test,
310 after age-matching (40-79 years) indicated that there were significant differences in volume between our 4 groups (chi-squared
311 $= 805.23$, $p\text{-value} < 0.0001$). The post-hoc pairwise comparisons using the Bonferroni correction revealed that for each pair, all
312 possible comparisons were statistically significant (Table S4). Notably, there was still a clear distinction between the prostate
313 volumes in clinically insignificant and clinically significant cancer (adjusted $p\text{-value} < 0.01$) and between clinically insignificant
314 and symptomatic non-cancer (adjusted $p\text{-value} < 0.001$).
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316 Based on logistic regression with asymptomatic men excluded, our results demonstrated that as volume increases by one
317 millilitre in symptomatic men, the odds of having csPCa rises by a factor of 0.97 (0.963 to 0.973). This would indicate that as
318 volume increases, the odds of having csPCa decrease. For a 10ml increase, the odds would be approximately 72% of the original
319 odds (a 28% reduction).
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Age ranges (yrs.)	Mean prostate volume (ml) +- standard error				N=				PSA thresholds (micrograms/L), as defined by NICE ⁷
	Asymptomatic disease free	Symptomatic non-cancer	Clinically Insignificant cancer	Clinically Significant cancer	Asymptomatic disease free	Symptomatic non-cancer	Clinically Insignificant cancer	Clinically Significant cancer	
18-29	18.7 (+ 0.47)	-	-	-	88	-	-	-	Use clinical judgement
30-39	21.6 (+ 0.48)	-	-	-	112	-	-	-	Use clinical judgement
40-49	23.2 (+ 0.55)	31.5 (+1.56)	31.9 (+4.74)	34.8 (+4.40)	117	35	7	6	>2.5
50-59	27.0 (+ 0.62)	56.7 (+1.19)	44.1 (+2.83)	39.4 (+1.72)	150	281	37	75	>3.5
60-69	32.2 (+ 1.06)	66.8 (+ 1.09)	52.1 (+2.15)	43.6 (+1.01)	128	520	94	313	>4.5
70-79	36.4 (+ 1.32)	87.8 (+ 2.67)	68.0 (+5.25)	53.3 (+1.96)	126	156	37	191	>6.5
80-89	41.3 (+2.87)	-	-	-	39	-	-	-	Use clinical judgement

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Table 1- Age stratified prostate volumes, together with the number of patients within each group, and NICE thresholds for PSA stratified by age-group

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PSA-Density

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Only the csPCa group showed a significant linear increase in PSA-D with age ($r^2 = 0.007$ vs 0.001 , $P = 0.046$ vs 0.202 , respectively) of $0.0017 \text{ ng/ml}^2/\text{year}$. The causes of raised PSA-D are multifactorial, but this suggests that, critically, for men with csPCa, 0.7% of this variation in PSA-D can be explained by age ($p=0.046$). For those without csPCa, PSA-D remained consistently lower than csPCa at all ages 42-79 at around 0.114 ng/ml^2 at age 42 ($0.10 - 0.12 \text{ ng/ml}^2$ 95% CIs) to 0.10 ng/ml^2 at age 79 ($0.09 - 0.11 \text{ ng/ml}^2$ 95% CIs). This allowed those with and without csPCa to be clearly distinguished using the suggested NICE clinical threshold of 0.15 ng/ml^2 (**Figure 3**), **sensitivity for which was calculated as 61.7 (57.5-65.6%), and specificity 85.4 (83.2-87.3%)**. However, 0.13 ng/ml^2 may represent a better a threshold, having the greatest Youden's index with a sensitivity and specificity of 72.9% (69.0-76.4%) and 77.9% (75.5-80.3%), respectively.

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When grouped by decade of life, csPCa patients in each group 50-79 had significantly greater PSA-D than patients with no cancer or Gleason 3+3 disease ($P < 0.0001$ for each), reflected by a higher PSA and lower PV. However, there was no significant difference in those with and without csPCa within the 40-49 group ($P = 0.14$), though this may be accounted for by the relative lack of data points in this group (**Figure 3**).

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Discussion

This study analysed how both age, and severity of disease affect three prostate-related measurements: PV, PSA and PSA-D. We demonstrated that the healthy prostate undergoes a non-linear increase in volume with age. In the symptomatic groups, we also found PV increased with age, with significant differences when stratified by disease severity. Additionally, for symptomatic patients, PSA increased with age regardless of whether clinically significant disease was present, however csPCa patients had consistently higher PSA. PSA-D only demonstrated a statistically significant increase for the csPCa group, and for all ages, the PSA-Ds for this group were above the NICE recommended PSA-D threshold.

To date, few physiological studies have mapped how the prostate volume changes across the lifespan of asymptomatic patients, but that which exists, agrees with our asymptomatic prostate volume results (13–19). Our study of disease-free patients benefited from a high sample size, analysis of all ages across the adult lifetime, and use of the highest clinical standard of MRI for more accurate measurements(20–22). The majority of prior studies employed transrectal US for volume measurements(14–19,22), and investigated men over 40 years(14,15,17–19), and of the few that did study younger males, the sample size was comparatively small(13,16,23). Notably, in the existing literature there is differing opinion as to whether prostate volume changes are linear(13), or better modelled with high-degree polynomials(14). We applied a cross-validated machine learning approach to derive our quadratic model, which, by avoiding overfitting, produced a higher quality of fit for our model of asymptomatic prostate volume compared to the non-validated approaches, thus our findings should be applicable to future patient cohorts.

The symptomatic, non-cancer group had the highest mean prostate volume, with the demonstrated increases in PV with age consistent with the existing literature (24,25). Patients developing BPH are more likely to present to primary care with lower urinary tract symptoms, leading to a raised PSA test and urological referral. Conversely, in patients with csPCa, as the Gleason score increases, prostate volume tended to decrease. This is in line with the limited prior studies in patient cohorts, with csPCa being associated with smaller gland volumes(26,27). However, mean prostate volumes in men with csPCa do not decrease below those of disease free, asymptomatic men, thus distinction between the models remains preserved.

Given the known relationship of PSA with gland volume, the dynamic changes in PV with age across all the cohorts would be broadly supportive of setting age-related PSA thresholds. We found PSA to increase with age, with the most marked increase between consecutive age groups being 60-69 to 70-79, both for those with and without csPCa. However, it is notable that the median PSA per decade in our symptomatic cohort was consistently greater than the age-stratified thresholds recommended by NICE(7). This may be heavily influenced by selection bias, as a threshold limit of at least 3.0 ng/ml is typically applied at the time of referral, reducing the potential number of patients with lower PSA levels in this study.

Conversely, we found that PSA-density does not significantly increase between consecutive age groups, thus a static threshold could be employed. PSA-D was significantly elevated in all age groups 50-79 for csPCa patients, consistent with previous studies(28,29). This reflects the significantly higher PSA and smaller volume prostates in these patients. Our results show that for PSA-D, the currently employed clinical threshold of 0.15 ng/ml² is supported, although the more conservative value of <0.13ng/ml² demonstrated a better statistical cut-off for benign disease.

Our study has some limitations, including the retrospective and cross-sectional design; ideally the same cohorts of men would be followed-up in a longitudinal study, with multiple repeat MRIs to map the changes across individuals. We cannot fully exclude the presence of undetected prostate cancer in the disease-free asymptomatic cohort, however, we reviewed the medical notes and excluded patients with a prior PSA test, or urological referral. Likewise, the presence of prostate cancer cannot be excluded in MRI-negative patients not undergoing biopsy, however, clinical follow-up has been employed for this purpose in other studies(24,30,31). Furthermore, any biopsy procedure is prone to sampling error and may have under- or over-estimated the presence of clinically significant prostate cancer in some patients. This was not a formal screening study, therefore patients referred to urology were highly likely to have symptoms, and/or a raised PSA above a threshold of 3.0 ng/ml, leading to higher median PSA levels than may have been expected across this cohort. MRI may under-estimate prostate volume compared to the gold standard of prostatectomy; however, it is known to outperform abdominal or transrectal ultrasound or CT and represents the best clinical reference standard(20). Our study additionally benefits from the large sample size and mix of patients across age-groups and disease states.

Conclusions

Our study maps the increases in prostate volume with age across symptomatic and asymptomatic men and demonstrate how the presence and grade of disease can affect volume. We provide evidence for the use of age-related PSA thresholds and establish that a static PSA-density threshold can be applied across age groups to help differentiate presence of clinically significant prostate cancer from benign, low-grade, or the absence of prostate cancer.

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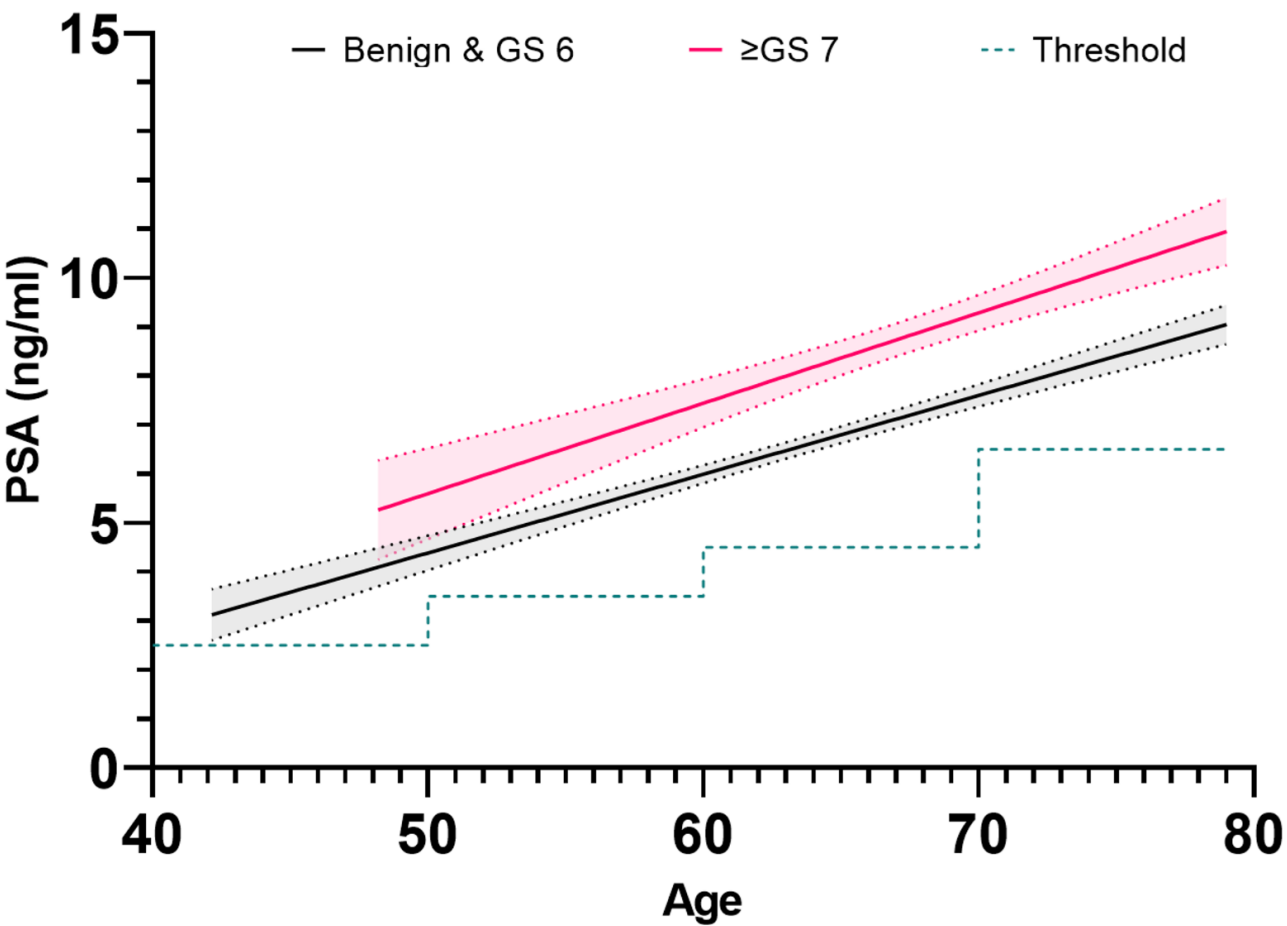
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515 **Figure 1. PSA change with age in the cohort.** Best fit lines represent absence (benign and Gleason 6) or presence ($\geq$ Gleason
516 7) of clinically significant prostate cancer. Threshold plotted shows NICE thresholds for suspecting PCa. Shaded areas
517 represent 95% confidence intervals. GS = Gleason score.
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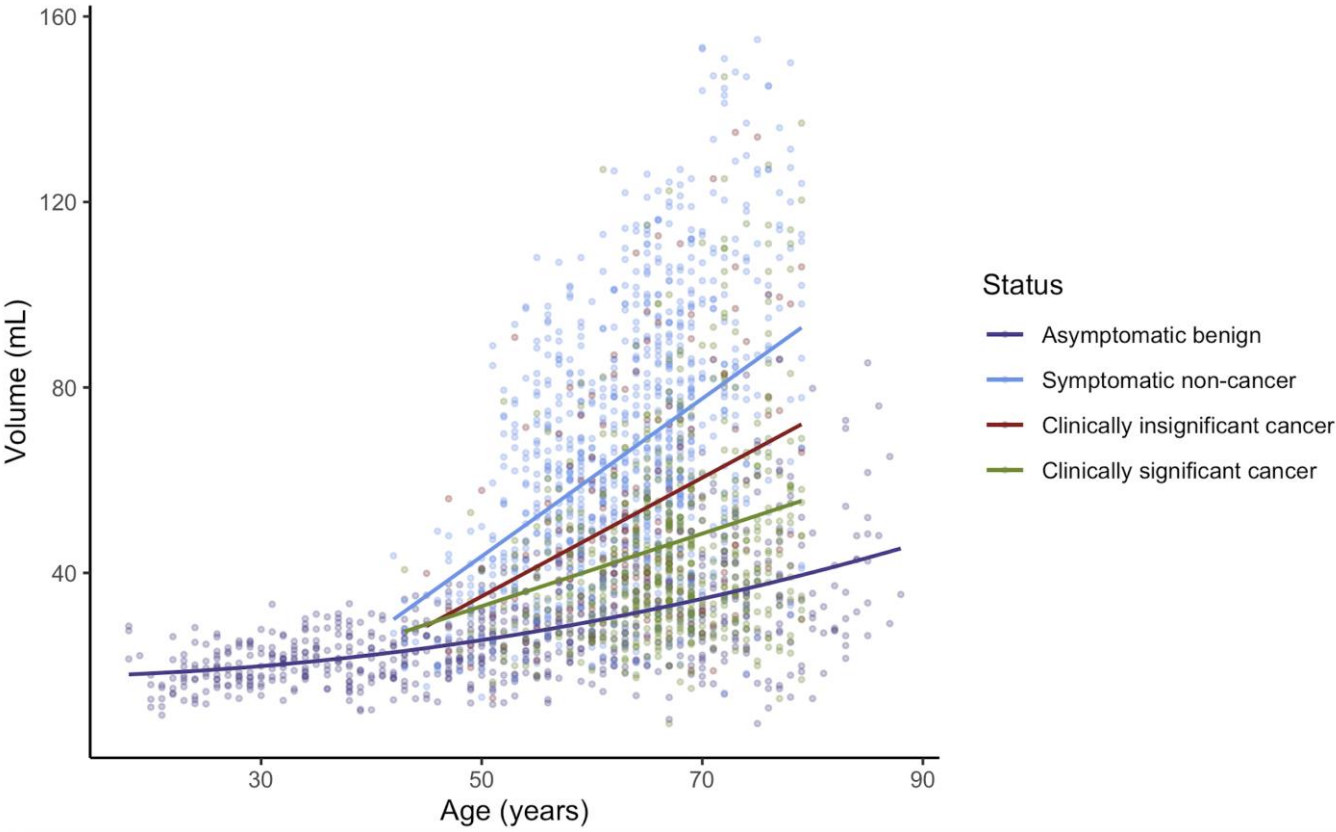


Figure 2. Prostate volumes as a function of age. The optimal regression models overlaid are defined by individual repeated k-fold cross validations for each clinical group.

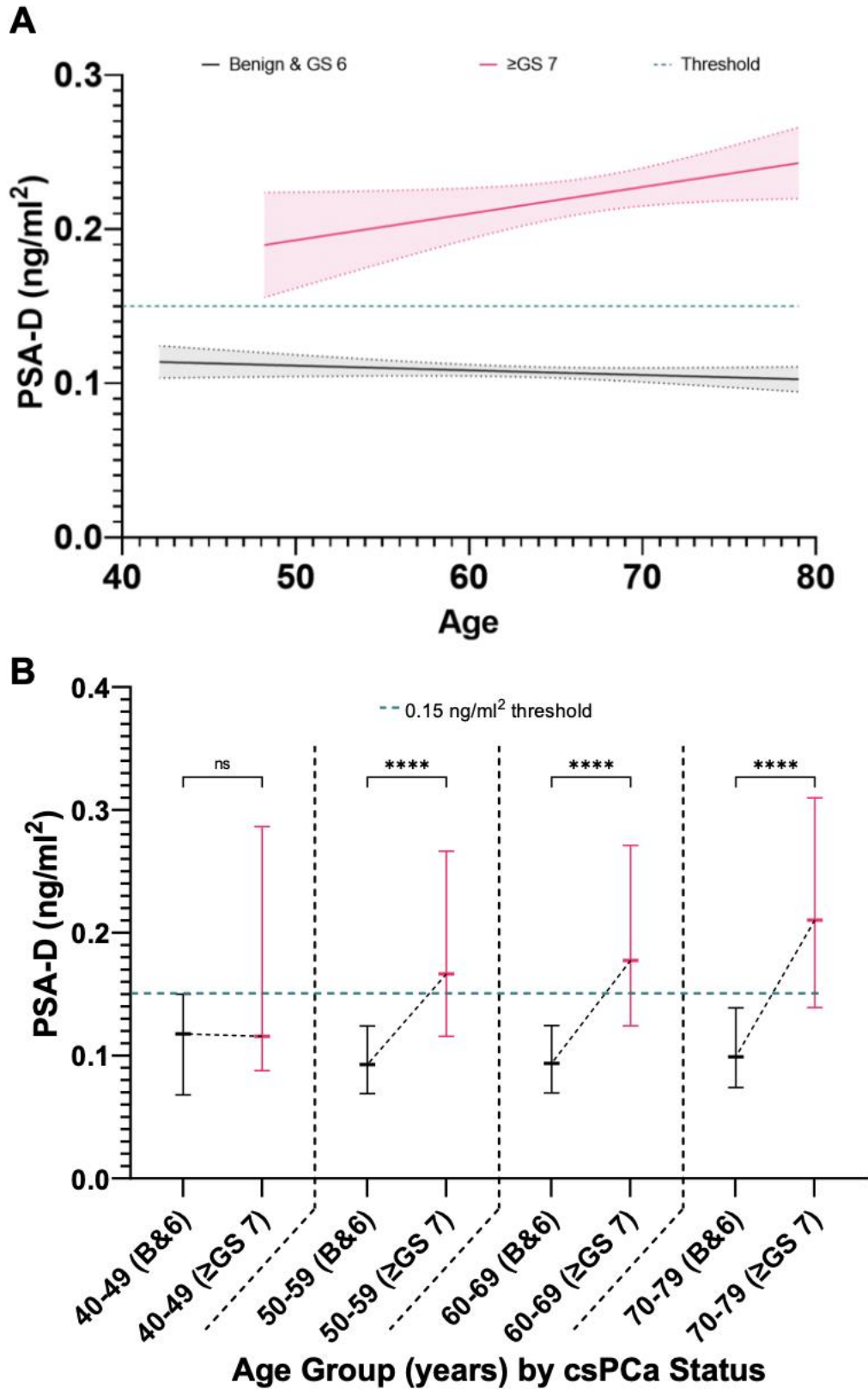


Figure 3. PSA-Density change with age in the cohort.

A: Best fit lines represent absence (benign and Gleason 6) or presence ($\geq$ Gleason 7) of clinically significant prostate cancer. Threshold represents the clinically recommended PSA-Density value of 0.15 ng/ml². Shaded areas represent 95% confidence intervals.

B: Comparisons of PSA-D medians with interquartile ranges within age groups segregated by csPCa status. Putative 0.15ng/ml² threshold is plotted. ns = not significant ($P > 0.05$); **** = $P \leq 0.0001$.