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Body mass index in relation to serum prostate-specific antigen levels and prostate cancer risk

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High Body mass index (BMI) has been directly associated with risk of aggressive or fatal prostate cancer. One possible explanation may be an effect of BMI on serum levels of prostate-specific antigen (PSA). To study the association between BMI and serum PSA as well as prostate cancer risk, a large cohort of men without prostate cancer at baseline was followed prospectively for prostate cancer diagnoses until 2015. Serum PSA and BMI were assessed among 15,827 men at baseline in 2010–2012. During follow-up, 735 men were diagnosed with prostate cancer with 282 (38.4%) classified as high-grade cancers. Multivariable linear regression models and natural cubic linear regression splines were fitted for analyses of BMI and log-PSA. For risk analysis, Cox proportional hazards regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) and natural cubic Cox regression splines producing standardized cancer-free probabilities were fitted. Results showed that baseline Serum PSA decreased by 1.6% (95% CI: −2.1 to −1.1) with every one unit increase in BMI. Statistically significant decreases of 3.7, 11.7 and 32.3% were seen for increasing BMI-categories of 25 < 30, 30 < 35 and ≥35 kg/m^2, respectively, compared to the reference (18.5 < 25 kg/m^2). No statistically significant associations were seen between BMI and prostate cancer risk although results were indicative of a positive association to incidence rates of high-grade disease and an inverse association to incidence of low-grade disease. However, findings regarding risk are limited by the short follow-up time. In conclusion, BMI was inversely associated to PSA-levels. BMI should be taken into consideration when referring men to a prostate biopsy based on serum PSA-levels.

Prostate cancer was the most commonly diagnosed cancer among men in the developed world in 2012.[1] While incidence rates have increased, partly because of the widespread use of prostate-specific antigen (PSA) testing as a diagnostic tool, during previous decades, they have stabilized at a high level over the past 10 years.[2] Co-occurring with the increasing prostate cancer incidence is an increased prevalence of overweight and obesity.

The relationship between overweight/obesity, often defined by body mass index (BMI, kg/m^2), and prostate cancer is not yet fully established. While some studies have shown no association between BMI and the overall risk, others have shown a positive association between BMI and aggressive or fatal disease.[3] A recent report from the World Cancer Research Fund International[4] concluded that results from published studies constituted strong evidence for an increased risk of advanced prostate cancer among overweight and obese men. A dual effect of obesity on prostate cancer risk has also been suggested in a meta-analysis that showed increased risks of more advanced or aggressive disease and decreased risks of early stage and less aggressive cancers with increasing BMI.[5]

One possible explanation behind an association between BMI and prostate cancer risk may be an effect of BMI on serum PSA-levels. An inverse association between BMI and serum PSA has been shown in several studies.[6–13] Suggested mechanisms for this effect are decreased testosterone levels,[14] and hemodilution.[7] Increased prostate volume seen with higher BMI, making it harder to biopsy the prostate may be another explanation to the association seen between BMI and prostate cancer risk.[12,15,16] Since most cancers in developed countries today are detected by a biopsy following a PSA-test, it is important to determine which factors might influence serum PSA. Although not implemented as a national screening program in Sweden, PSA-testing is common and its use has increased during the past decade with >65% of men 60–69 years of age without a previous prostate cancer diagnosis having had a test in 2011.[17]

We aim to study the association between BMI and serum PSA in a large cohort of >15,000 men without prostate

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What's new?
High body mass index (BMI) has been associated with risk of aggressive or fatal prostate cancer. One possible explanation may be an effect on serum prostate-specific antigen (PSA) levels. Here, the authors assessed the association between BMI and serum PSA level and prostate cancer risk in a large prospective cohort study. While no statistically significant associations were found between BMI and overall risk of prostate cancer, increasing BMI was associated with decreased serum PSA levels among men with no previous prostate cancer diagnosis. BMI should be taken into consideration when referring men to a prostate biopsy based on PSA-test results.

cancer at baseline and prospectively follow them to investigate the association between BMI and prostate cancer risk.

Material and Methods

The population-based STHLM-2 cohort comprises men who were referred to a PSA-test in laboratories in Stockholm County, Sweden, between the years 2010 and 2012. Study participants were invited to STHLM-2 during the blood sampling visit at which baseline serum PSA were measured. Men who accepted inclusion donated additional blood and urine samples and were asked to respond to a questionnaire assessing lifestyle factors. A total of 24,966 men were included at baseline. The STHLM-2 cohort, including the biological sample collections, has been described in detail elsewhere.[18,19]

Information regarding incident prostate cancers was obtained from the National Cancer Registry (NCR).[20] Additional information of clinical variables relating to the cancer was obtained through the National Prostate Cancer Registry (NPCR).[21] The study has been approved by the local ethics committee at Karolinska Institutet, Stockholm, Sweden.

BMI at baseline was calculated based on self-reported current weight and height. Men were categorized by BMI as normal weight ($18.5 < 25$ kg/m^2), overweight ($25 < 30$ kg/m^2) or obese level I ($30 < 35$ kg/m^2) and obese level II (>35 kg/m^2) as defined by the National Institute of Health.[22] Additional lifestyle factors that were assessed and considered potential confounding factors were: age at study inclusion (continuous, based on date of birth), education level (<9, 9–12, >12 years, and "other"), smoking status ("current," "former" and "never"), level of stress ("never," "sometimes," "often" and "always"), family history of prostate cancer ("yes", "no", and "don't know") and physical activity (continuous, daily time spent on moderate-to-vigorous physical activity level).

For present analysis, the following exclusions were made in consecutive order: men with missing date of inclusion to the study ($n = 34$) or missing information on date of birth ($n = 88$), men who had not responded to the questionnaire ($n = 4{,}491$), men with a prostate cancer diagnosis prior to study inclusion ($n = 4{,}251$), men for whom information on BMI ($n = 108$) or PSA ($n = 64$) was missing, men with a reported BMI <18.5 ($n = 61$) or >50 kg/m^2 ($n = 42$). In total, 15,827 men were included in the final analysis of BMI and serum PSA. For analysis of prostate cancer risk, all men diagnosed with prostate cancer within 6 months of inclusion in STHLM-2 were excluded ($n = 501$) to reduce the risk of reverse causation. The final risk analysis included a total of 15,326 men of whom 735 were diagnosed with prostate cancer during the follow-up. The mean follow-up time for all men was 3.5 (±0.6) years.

Statistical analysis

Characteristic variables are described as distributions (n and %) and means (±SD). One-way ANOVA and χ^2 tests were used to study differences in distributions of continuous and categorical variables, respectively, across BMI categories.

The association between BMI and serum PSA was studied using multivariable linear regression. Because of the skewed distribution of serum PSA-values, this outcome variable was logarithmically transformed before analysis. Results from linear regression models are therefore interpreted as percent change in serum PSA with increasing BMI. BMI was analyzed both as a continuous and a categorical exposure. To illustrate the dose-response relationship between serum PSA and BMI, natural (cubic) linear regression splines were fitted with one knot at BMI = 25 and one knot at BMI = 30 kg/m^2.[23] To summarize the fitted spline models, regression standardization was used, in which the predicted means obtained from the adjusted (for confounders) spline function were standardized to the confounder distribution in the sample.[24] In all models, the association between BMI and serum PSA was studied separately for all men, men diagnosed with prostate cancer during the follow-up, and men without a diagnosis during follow-up. Complete case-analysis was performed and men with missing data for any covariates included in models were excluded. All men ($n = 15{,}827$) were included in unadjusted and age-adjusted models while only men with complete information for all covariates ($n = 14{,}490$) were included in multivariable models.

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) in analysis of prostate cancer risk using time from inclusion to STHLM-2 as the underlying time-scale. End points were either date of diagnosis or date of last registry linkage (April 24th, 2015), whichever came first. BMI was analyzed both as a continuous and a categorical exposure. Natural (cubic) Cox regression splines were fitted, with one knot at BMI = 25 and one knot at BMI = 30 kg/m^2, and summarized

Table 1. Characteristics of study participants STHLM-2

	All ($n = 15,827$)		BMI (kg/m^2) category								
			<25 ($n = 5,990$)		25 < 30 ($n = 7,688$)		30 < 35 ($n = 1,788$)		≥35 ($n = 361$)		p
Age, mean (SD)	65.2	(10.1)	66.2	(10.7)	64.9	(9.7)	63.9	(9.2)	62.4	(9.5)	0.000
PSA (ng/ml), mean (SD)	4.34	(55.5)	5.23	(73.1)	3.40	(12.7)	5.63	(92.7)	3.05	(14.3)	0.178
Total leisure MVPA hours/day, mean (SD)	1.24	(1.3)	1.33	(1.3)	1.23	(1.3)	1.01	(1.2)	0.93	(1.3)	0.000
Education, *n* (%)											0.000
<9 years	3,005	(19.0)	914	(15.3)	1,547	(20.1)	447	(25.0)	97	(26.9)	
9–12 years	4,534	(28.7)	1,598	(26.7)	2,258	(29.4)	558	(31.2)	120	(33.2)	
>12 years	6,511	(41.1)	2,792	(46.6)	3,038	(39.5)	573	(32.1)	108	(29.9)	
Other	1,525	(9.6)	592	(9.9)	722	(9.4)	177	(9.9)	34	(9.4)	
Missing information	252	(1.6)	94	(1.6)	123	(1.6)	33	(1.9)	2	(0.6)	
Smoking status, *n* (%)											0.000
Current	1,923	(12.2)	707	(11.8)	919	(12.0)	240	(13.4)	57	(15.8)	
Former	7,428	(46.9)	2,513	(42.0)	3,792	(49.3)	934	(52.2)	189	(52.4)	
Never	6,253	(39.5)	2,680	(44.7)	2,874	(37.4)	589	(32.9)	110	(30.5)	
Missing information	223	(1.4)	90	(1.5)	103	(1.3)	25	(1.4)	5	(1.4)	
Stress, *n* (%)											0.000
Never	2,633	(16.6)	1,037	(17.3)	1,229	(16.0)	305	(17.1)	62	(17.2)	
Sometimes	7,389	(46.7)	2,884	(48.2)	3,621	(47.1)	749	(41.9)	135	(37.4)	
Often	4,173	(26.4)	1,528	(25.5)	2,047	(26.6)	495	(27.7)	103	(28.5)	
Always	894	(5.7)	259	(4.3)	450	(5.9)	144	(8.1)	41	(11.4)	
Missing information	738	(4.7)	282	(4.7)	341	(4.4)	95	(5.3)	20	(5.5)	
Family history of prostate cancer, *n* (%)											0.036
Yes	2,341	(14.8)	928	(15.5)	1,118	(14.5)	246	(13.8)	49	(13.6)	
No	11,232	(71.0)	4,227	(70.6)	5,491	(71.4)	1,273	(71.2)	241	(66.8)	
Do not know	1,724	(10.9)	649	(10.8)	814	(10.6)	205	(11.5)	56	(15.5)	
Missing information	530	(3.4)	186	(3.1)	265	(3.5)	64	(3.6)	15	(4.2)	
Prostate cancer cases[1], *n* (%)	735	(3.0)	260	(2.8)	378	(3.0)	83	(2.8)	14	(4.2)	0.440
Gleason score, *n* (%)											0.106
<7	256	(34.8)	95	(36.5)	138	(36.5)	19	(22.9)	4	(28.6)	
≥7	282	(38.4)	101	(38.9)	136	(36.0)	38	(45.8)	7	(50.0)	
Missing information	197	(26.8)	64	(24.6)	104	(27.5)	26	(31.3)	3	(21.4)	
Tumor stage, *n* (%)											0.000
TX	9	(1.2)	3	(1.2)	3	(0.8)	0	(0)	3	(21.4)	
T1	325	(44.2)	116	(44.6)	172	(45.5)	30	(36.1)	7	(50.0)	
T2	94	(12.8)	40	(15.4)	42	(11.1)	11	(13.3)	1	(7.1)	
T3/T4	16	(2.2)	4	(1.5)	8	(2.1)	3	(3.6)	1	(7.1)	
Missing information	291	(39.6)	97	(37.3)	153	(40.5)	39	(47.0)	2	(14.3)	
N-Classification, *n* (%)											0.062
NX	336	(45.7)	122	(46.9)	168	(44.4)	36	(43.4)	10	(71.4)	
N0	97	(13.2)	39	(15.0)	51	(13.5)	6	(7.2)	1	(7.1)	
N1	6	(0.8)	2	(0.8)	1	(0.3)	2	(2.4)	1	(7.1)	
Missing information	296	(40.3)	97	(37.3)	158	(41.8)	39	(47.0)	2	(14.3)	
M-Classification, *n* (%)											0.199
M0	427	(58.1)	161	(61.9)	213	(56.4)	41	(49.4	12	(85.7)	

Table 1. Characteristics of study participants STHLM-2 (Continued)

	All ($n = 15,827$)		BMI (kg/m^2) category <25 ($n = 5,990$)		25 < 30 ($n = 7,688$)		30 < 35 ($n = 1,788$)		≥35 ($n = 361$)		p
M1	12	(1.6)	2	(0.8)	7	(1.9)	3	(3.6)	0	(0)	
Missing information	296	(40.3)	97	(37.3)	158	(41.8)	39	(47.0)	2	(14.3)	

[1]Men diagnosed with prostate cancer within 6 months of inclusion to the study have been excluded.

Table 2. Results from crude, age-adjusted and multivariable adjusted multiple linear regression models of BMI in association to baseline PSA

Exposure		Crude % change (95% CI)	Age-adjusted % change (95% CI)	Multivariable adjusted[1] % change (95% CI)
All men		($n = 15,827$)	($n = 15,827$)	($n = 14,490$)
BMI continuous		**−2.74 (−3.20 to −2.28)**	**−1.84 (−2.28 to −1.40)**	**−1.61 (−2.07 to −1.14)**
BMI	<25	1.00	1.00	1.00
	25 < 30	**−9.68 (−13.19 to −6.18)**	**−5.46 (−8.79 to −2.13)**	**−3.71 (−7.18 to −0.24)**
	30 < 35	**−21.88 (−27.37 to −16.40)**	**−14.38 (−19.59 to −9.16)**	**−11.65 (−17.14 to −6.17)**
	≥35	**−45.08 (−56.10 to −34.05)**	**−32.74 (−43.22 to −22.27)**	**−32.30 (−43.21 to −21.38)**
Global *p* values		0.000	0.000	0.000
No PC diagnosis[2]		(n=14,591)	(n=14,591)	(n=13,341)
BMI continuous		**−2.75 (−3.20 to −2.30)**	**−1.87 (−2.30 to −1.43)**	**−1.65 (−2.11 to −1.19)**
BMI	<25	1.00	1.00	1.00
	25 < 30	**−9.36 (−12.83 to −5.89)**	**−5.36 (−8.65 to −2.06)**	**−3.55 (−7.00 to −0.11)**
	30 < 35	**−23.03 (−28.46 to −17.61)**	**−15.75 (−20.90 to −10.60)**	**−13.67 (−19.12 to −8.22)**
	≥35	**−43.52 (−54.31 to −32.72)**	**−31.21(−41.45 to −20.97)**	**−28.78 (−39.42 to −18.42)**
Global *p* values		0.000	0.000	0.000
PC diagnosis[2]		($n = 1,236$)	($n = 1,236$)	($n = 1,149$)
BMI continuous		−0.91 (−2.49 to 0.67)	−0.43 (−1.94 to 1.09)	0.18 (−1.38 to 1.74)
BMI	<25	1.00	1.00	1.00
	25 < 30	−6.79 (−18.47 to 4.89)	−2.26 (−13.50 to 8.99)	−0.20 (−11.56 to 11.16)
	30 < 35	−1.86 (−20.27 to 16.55)	4.07 (−13.64 to 21.77)	6.82 (−10.82 to 24.47)
	≥35	−17.02 (−60.58 to 26.53)	−17.70 (−59.50 to 24.11)	−16.75 (−65.01 to 31.50)
Global *p* values		0.632	0.751	0.752

[1]Multivariable adjusted for age, time spent at moderate-to-vigorous physical activity level (h/day), education, smoking status, stress, family history of prostate cancer.
[2]During study follow-up.

through regression standardization. This analysis produces standardized "survival" (*i.e.*, cancer-free) probabilities, as a function of time since inclusion in the study. In all models, the association between BMI and prostate cancer risk was studied separately for all, low-grade, and high-grade cancers. Cancers with a Gleason score <7 or ≥7 were defined as low- and high-grade, respectively.

Potential confounding by other factors was assessed by testing if the variables were statistically associated with both the exposure (BMI) and the outcome (PSA or prostate cancer incidence) as well as assessed through subject matter knowledge. Covariates included in the final multivariable-adjusted models were age, education level, smoking status, level of stress, family history of prostate cancer and physical activity. The standard linear and Cox regression models were fitted unadjusted, age-adjusted and multivariable-adjusted. The spline linear and Cox regression models were only fitted multivariable-adjusted. Complete case-analysis was performed. All men ($n = 15,326$) were included in unadjusted and age-adjusted models while only men with complete information for all covariates ($n = 14,027$) were included in multivariable models. The level of significance was set to $\alpha = 0.05$. The splines and regression standardization analyses were performed with the statistical software R,[25] while all other analyses were performed with STATA 13.0 (STATA Corporation, College Station, TX).

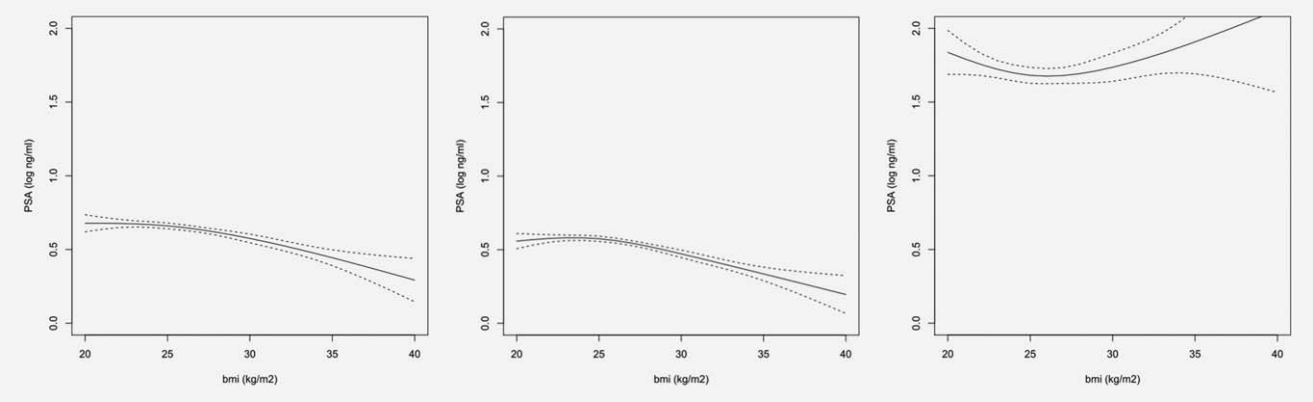

Figure 1. Standardized mean serum log PSA level obtained from multivariable adjusted linear regression splines (solid lines), as a function of BMI, together with point wise 95% CIs.(dashed lines). (*a*) All men included in the study ($n = 14{,}359$), (*b*) men not diagnosed with prostate cancer during the follow-up ($n = 13{,}213$), and (*c*) men diagnosed with prostate cancer during the follow-up ($n = 1{,}146$).

Table 3. Results from crude, age-adjusted and multivariable adjusted multiple Cox regression models of BMI (kg/m^2) and prostate cancer risk divided by low- and high-grade cancer

Exposure		No. of cases	Crude HR (95% CI)	Age-adjusted HR (95% CI)	Multivariable adjusted[1] HR(95% CI)
All prostate cancer cases			($n = 15{,}326$)	($n = 15{,}326$)	($n = 14{,}027$)
BMI continuous		735	1.01 (0.99–1.03)	1.01 (0.99–1.03)	1.01 (0.99–1.03)
BMI	<25	260	1.00	1.00	1.00
	25 < 30	378	1.13 (0.96–1.32)	1.15 (0.98–1.34)	1.14 (0.97–1.34)
	30 < 35	83	1.06 (0.83–1.36)	1.10 (0.85–1.40)	1.14 (0.88–1.48)
	≥35	14	0.89 (0.52–1.52)	0.94 (0.55–1.61)	0.72 (0.38–1.36)
Global *p* values			0.444	0.368	0.235
Low–grade prostate cancer[2]					
BMI continuous		256	0.99 (0.95–1.03)	0.99 (0.95–1.02)	0.99 (0.96–1.03)
BMI	<25	95	1.00	1.00	1.00
	25 < 30	138	1.12 (0.87–1.46)	1.12 (0.86–1.45)	1.12 (0.85–1.47)
	30 < 35	19	0.67 (0.41–1.09)	0.66 (0.40–1.08)	0.73 (0.44–1.20)
	≥35	4	0.69 (0.25–1.89)	0.68 (0.25–1.85)	0.72 (0.26–1.97)
Global *p* values			0.144	0.138	0.290
High-grade prostate cancer[3]					
BMI continuous		282	1.01 (0.98–1.05)	1.02 (0.99–1.06)	1.02 (0.98–1.05)
BMI	<25	101	1.00	1.00	1.00
	25 < 30	136	1.04 (0.81–1.35)	1.08 (0.84–1.40)	1.08 (0.83–1.41)
	30 < 35	38	1.25 (0.86–1.82)	1.34 (0.92–1.95)	1.36 (0.92–2.02)
	≥35	7	1.14 (0.53–2.45)	1.27 (0.59–2.74)	0.98 (0.40–2.43)
Global *p* values			0.692	0.472	0.489

[1]Multivariable adjusted for age, time spent at moderate-to-vigorous physical activity level (h/day), education, smoking status, stress, family history of PC.
[2]Gleason score <7.
[3]Gleason score ≥7.

Results

Characteristics of all study participants divided by BMI-categories are shown in Table 1. The mean age was 65.2 years. A higher BMI was associated with younger age, less time spent in moderate-to-vigorous physical activity, lower level of education and increased stress levels. Among men with a lower BMI, there were fewer current smokers and more never smokers compared to men in higher BMI categories. There were no differences in family history of prostate cancer, total number of prostate cancer cases, and

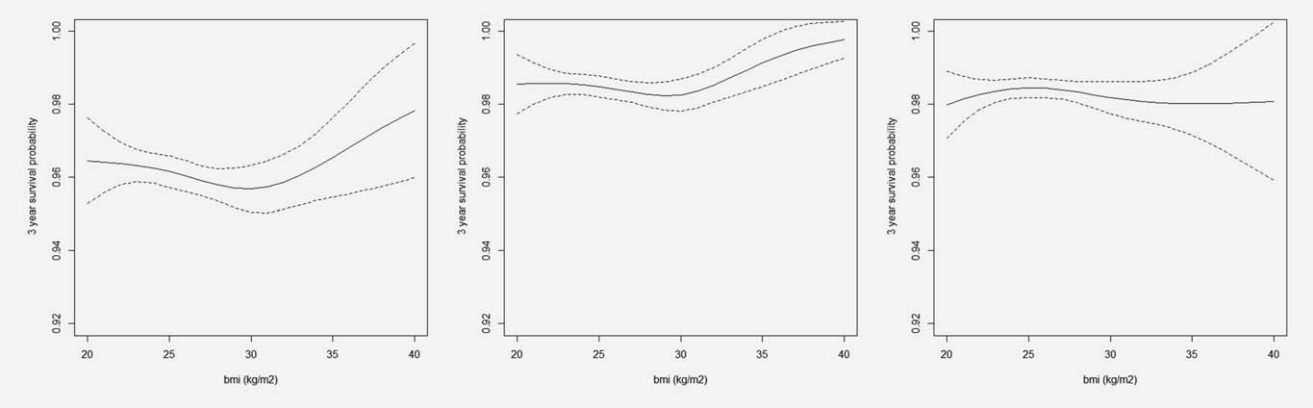

Figure 2. Standardized "survival" (*i.e.*, cancer-free) probabilities obtained from the multivariable adjusted Cox regression splines (solid lines), at 3 years after inclusion into the study, as a function of BMI, together with point wise 95% CIs (dashed lines). (*a*) All cancers, (*b*) low grade prostate cancer (*c*) high grade prostate cancer.

distribution of low- versus high-grade cancers, or serum PSA levels between BMI categories.

Linear regression models showed decreases in serum PSA with increasing BMI at baseline, Table 2. The association appeared to be mainly confounded by age. For all men, serum PSA levels decreased by 1.6% (95% CI: −2.1 to −1.1) with every one unit (kg/m^2) increase in BMI in multivariable adjusted models. Greater changes in serum PSA were seen for each increasing BMI category with decreases of 3.7% (95% CI: −7.2 to −0.2), 11.7% (95% CI: −17.1 to −6.2) and 32.3% (95% CI: −43.2 to −21.4) for men with a BMI of $25 < 30$, $30 < 35$ and ≥ 35 kg/m^2, respectively, compared to the reference group with a BMI of $18.5 < 25$ kg/m^2. Similar results were seen among men who were not diagnosed with prostate cancer during the follow-up. No significant changes in serum PSA by BMI were seen among men who were diagnosed with prostate cancer during the follow-up. Linear regression splines of the association between BMI and serum log-PSA confirmed results from regression models. Figures 1*a*–1*c* display the standardized mean serum log PSA level obtained from the linear regression splines, as a function of BMI, together with point wise 95% CIs. A clear trend of decreasing mean serum log-PSA with increasing BMI was seen for all men, with a steeper slope at higher BMIs, Figure 1*a*. Results were similar for men who were not diagnosed with prostate cancer during the follow-up, Figure 1*b*, while no clear trend was seen among men who were diagnosed during the follow-up, Figure 1*c*.

Results from Cox proportional hazards regression models showing hazard ratios (HRs) between baseline BMI and prostate cancer risk are shown in Table 3. No significant associations were seen in the multivariable-adjusted models for all, low- or high-grade prostate cancer. However, point estimates for low-grade cancer showed suggestive and borderline significant decreased rates among men with a BMI >30 kg/m^2 while point estimates for high-grade cancer indicate an increased rate among men with a BMI of $30 < 35$ kg/m^2. Figures 2*a*–2*c* display the standardized "survival" (*i.e.*, cancer-free) probabilities, obtained from the Cox regression splines, at 3 years after inclusion into the study, as a function of BMI, together with point wise 95% CIs. The cancer-free probability with respect to all cancers and low-grade cancers seems to have a U-shape, Figures 2*a* and 2*b*, while the cancer-free probability with respect to high-grade cancer seems be a slowly decreasing function of BMI, with an increase at the higher end of the BMI range, Figure 2*c*.

Discussion

Our results showed that serum PSA-levels decreased with increasing BMI among men with no previous prostate cancer diagnosis. This confirms results from earlier studies showing inverse associations between BMI and serum PSA. However, significant decreases in serum PSA were only seen for men who were not diagnosed with prostate cancer during the follow-up of the study. Moreover, suggestively, decreased risks of low-grade prostate cancer were seen for men with a BMI of $30 < 35$ kg/m^2 or ≥ 35 kg/m^2 while a suggestive increase in risk of high-grade prostate cancer was seen among men with a BMI of $30 < 35$ kg/m^2.

While some previous studies have not shown an association between BMI and serum PSA in men without prostate cancer,[16,26,27] our results are in line with the majority of studies that have found an inverse association.[6–13] The numbers of studies including men who have been diagnosed with prostate cancer are fewer and results inconclusive. While Bañez *et al.* found increased BMI to be associated with decreased levels of preoperative serum PSA among men who underwent radical prostatectomy in three different studies, Freedland *et al.* did not find any such association.[7,14] Our data did not show any statistically significant association between BMI and serum PSA among men who were diagnosed with prostate cancer later on during the follow-up period. This may indicate that while BMI indeed had an effect on PSA levels, this did not affect the likelihood of being diagnosed in this population.

There are several suggested explanations for the inverse association between BMI and serum PSA including hemodilution due to a larger plasma volume among men with a high BMI. Significant associations between BMI and plasma volumes as well as serum PSA-concentrations have been seen concomitant to nonsignificant differences in PSA-mass in several cohorts.[7,10] This supports the theory of hemodilution. Another explanation is decreased levels of circulating androgens, which are important for normal growth and differentiation of the prostate, seen with increasing BMI.[28]

High BMI has also been associated with increased prostate weight[15] and prostate volume[12,15,16] which affect cancer detection through biopsies. Many prostate cancers today are detected through a biopsy following a PSA-test indicating elevated levels of PSA in serum. If hemodilution due to a high BMI masks an increased PSA-mass caused by prostate cancer, this may delay detection of the cancer, both through a delayed biopsy because of the lower serum PSA and through the increased difficulty of detecting a cancer through biopsy due to increased prostate volume. This may also explain the increased risk of advanced or fatal prostate cancer as well as the decreased risk of localized disease seen among men with a high BMI.[5] In line with previous studies, while we did not find any statistically significant association between BMI and overall prostate cancer risk. Our results indicate an increased risk of high-grade prostate cancer among men with a BMI of $30 < 35$ kg/m^2, although this was not statistically significant. A suggestively decreased risk of low-grade cancer was also seen among men with a BMI of $30 < 35$ or ≥ 35 kg/m^2. However, the short follow-up time in our study is a major limitation and a longer follow-up of study participants would increase the number of men diagnosed and the power of the statistical analysis.

There are several further strengths and weaknesses of the present study that needs to be acknowledged. The main strengths include the large sample size and the population based and prospective design. Complete follow-up of prostate cancer diagnosis, including clinical variables, through the National Prostate Cancer Registry of Sweden is also a noteworthy strength. Nevertheless, missing clinical data on Gleason score among one fourth of participants is a limitation. Another limitation to the study is the lack of information on the indication for PSA-testing among men included in the study which may lead to selection bias. However, PSA-testing is common and more than two thirds of men 60–69 years of age without a previous prostate cancer diagnosis in Stockholm have undergone testing.[17] The lack of mortality information in also a limitation although the mean age in the cohort was 65 years and few deaths likely occurred during the follow up. The self-reported height and weight used to calculate subjects BMI at study baseline is another a limitation. Although self-reported weight and height have been shown to be highly correlated with measured ($r = 0.94$ and $r = 0.95$, respectively),[29] increased underestimations of weight have been seen among overweight and obese individuals.[30] The latter may attenuate any potential association between high BMI and prostate cancer risk.

Conclusions

In conclusion, we found increasing BMI to be associated with decreased serum PSA levels among men with no previous prostate cancer diagnosis. No statistically significant associations between BMI and overall risk of prostate cancer were seen. While our results indicated a positive association between BMI and high-grade prostate cancer and decreased rates of low-grade prostate cancer among men with a high BMI, these results were not statistically significant and should be interpreted with caution. BMI is a factor that should be taken into consideration when referring men to a prostate biopsy based on results from a PSA-test.

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