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ORIGINAL ARTICLE

The association between education and risk of major cardiovascular events among prostate cancer patients: a study from the Diet, Cancer and Health study

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ABSTRACT

Background: High socioeconomic position is associated with better prognosis in prostate cancer patients but it is unknown if part of this association may be explained by socioeconomic differences in severe late effects. We investigated the association between education as an indicator for socioeconomic position and cardiovascular events after prostate cancer and if such associations were mediated by differences in lifestyle, cardiovascular risk factors and prostate cancer treatment.

Material and methods: We identified 1980 men diagnosed with prostate cancer from 1993 to 2014 among participants in the Danish Diet, Cancer and Health study. Individual level information on education, lifestyle, cardiovascular risk factors and prostate cancer clinical information were obtained from questionnaires, registries and medical records. The Cox proportional hazards models were used to evaluate the risk of incident acute myocardial infarction, ischemic stroke and heart failure during up to 18 years of follow-up for men with short (<9 years) or medium (9–12 years) compared with long education (>12 years).

Results: Compared to men with long education, we found an increased risk of acute myocardial infarction in men with medium and short education (HR 3.14, 95% CI 1.53–6.47 and HR 2.14, 95% CI 0.82–5.58, respectively). Adjusting for stage, first-line treatment, lifestyle and cardiovascular risk factors did not change the HRs substantially (adjusted HRs 3.04, 95% CI 1.47–6.31 and 2.07, 95% CI 0.78–5.53, respectively). There were no educational differences in risk for ischemic stroke or heart failure.

Conclusions: The risk of acute myocardial infarction was increased in prostate cancer patients with short or medium education compared with long education. Although the educational inequality did not seem to be explained by differences in treatment, lifestyle or cardiovascular risk factors, monitoring of cardiovascular health and health promotion should involve all prostate cancer patients regardless of social position to ensure best prognosis for all.

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Introduction

Lower socioeconomic position is associated with higher mortality in prostate cancer patients despite a higher incidence of the disease in men with higher socioeconomic position [1]. This may be due to differences in stage at diagnosis, access to treatment, quality of life and lifestyle by socioeconomic group [2–4]. Furthermore, preexisting comorbidities and development of late treatment effects might play a role in the socioeconomic differences in overall mortality after a prostate cancer diagnosis [5]. Cardiovascular diseases are some of the most common comorbidities and causes of death among prostate cancer patients [6–8]. Extensive evidence shows an increased risk of cardiovascular events in patients treated with androgen deprivation therapy (ADT) compared to those receiving other kinds of treatment or surveillance [9,10]. A large population-based Swedish study found a two-fold increased risk of cardiovascular diseases in prostate cancer patients receiving ADT compared to cancer-free controls during the first 6 months post treatment [11]. We have shown similar findings in a Danish setting, finding a two-fold higher rate of both stroke and heart failure in men assigned to palliative care as first-line treatment compared with cancer-free men [12].

The distribution of cardiovascular diseases is unequally distributed between socioeconomic groups in the general population [13]; however, we do not know if socioeconomic position is associated with risk of cardiovascular events after prostate cancer diagnosis.

We investigated the risk of cardiovascular events in men with prostate cancer according to socioeconomic position measured by education. Further, we analyzed if lifestyle,

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cardiovascular risk factors and first-line treatment mediated differences across educational groups.

Material and methods

The study population was part of a population-based cohort including 26,944 men participating in the Diet, Cancer and Health study established in Denmark from 1993 to 1997. All men were cancer-free and aged 50–65 years at time of enrollment. Each participant responded to an extensive questionnaire regarding lifestyle, diet and other health-related factors, while anthropometric measures along with blood samples were obtained by the staff. The cohort has been described in detail elsewhere [14]. The Diet, Cancer and Health study was approved by the regional ethical committees in Copenhagen and Aarhus ((KF)11-037/01) and the present study by the Danish Data Protection Agency (2013-41-4232).

Identification of men with prostate cancer and prostate cancer information

We used personal identification numbers to link the 26,944 men with records in the Danish Cancer Registry that holds information on all cancers diagnosed in Denmark [15]. A total of 2352 men were diagnosed with incident prostate cancer (ICD-10: C619) between study enrollment and 31 December 2014. From medical records, we obtained clinical information on stage, Gleason score, prostate-specific antigen (PSA) level at time of diagnosis and assigned first-line treatment. We evaluated stage of the disease based on the TNM classification system in the medical records. If stage was missing in the medical record, it was substituted with information from the Danish Cancer Registry. To include stage in prostate cancer cases recorded prior to the introduction of TNM into the Registry in 2003, we merged the two stage classifications into two stage categories ('localized disease' and 'non-localized disease'), which were used in the statistical analyses (for further details on algorithm, see Appendix). The Gleason score and PSA level at time of diagnosis were included as continuous covariates in the statistical models. Assigned first-line treatment was coded as 'no active treatment' (active surveillance, watchful waiting), 'intended curative' (radical prostatectomy, radiotherapy or brachytherapy) or 'palliative treatment' (primarily ADT).

Educational level and cohabitation status

Educational level of the year prior to diagnosis and cohabitation status at time of diagnosis were obtained from The Danish education [16] and Danish social registers [17], respectively. We categorized education as 'short' (basic school only; <7 years), 'medium' (high school or vocational; 7–12 years) or 'long' (higher education; >12 years). Cohabitation status was coded as 'cohabitating' or 'living alone'.

Cardiovascular events and vital status

The outcomes of interest were incident acute myocardial infarction, ischemic stroke and heart failure, collectively referred to as cardiovascular events. We obtained date of each incident cardiovascular event from the Danish National Patient Registry [18] where all in-patient hospital admissions since 1977 and outpatient contacts since 1995 are registered. Further, we retrieved information on cardiovascular events from the Danish Cause of Death Registry to include fatal incident cardiovascular events [19]. From the National Patient Registry, we also obtained information on diabetes present at baseline (yes/no) and three additional cardiovascular precursor diseases: angina pectoris, transitional cerebral ischemia and cardiomyopathy. The precursors were coded into a combined yes/no covariate with yes indicating presence of one or more precursor diseases at baseline (see definition in Appendix). We obtained vital status and emigration information from the Central Population Register. A total of 340 men diagnosed with one of the primary outcomes of interest prior to or on the date of the prostate cancer diagnosis were excluded, hence analyses included 1980 men.

Covariates obtained from questionnaires

Smoking status was defined as 'never', 'former' or 'current'. Alcohol intake in gram/day was included as a continuous covariate. We calculated metabolic equivalent of task (MET) in kcal/kg/hour from an average of summer and winter physical activity multiplied by number of hours per week to capture physical activity (also included as a continuous covariate). Body mass index (BMI) was included categorically as 'normal' (<25), 'overweight' (>25–30) or 'obese' (>30). Diastolic and systolic blood pressure (mmHg) and serum cholesterol (mmol/L) measured at time of enrollment in the cohort were included as continuous covariates (are referred to as cardiovascular risk factors onwards).

Statistical methods

To estimate cause-specific hazard ratios (HRs) for cardiovascular events in men with prostate cancer, we used the Cox proportional hazards models with time since diagnosis as underlying time scale. All men were followed from date of diagnosis to date of cardiovascular outcome of interest or date of diagnosis of a competing cardiovascular event (for acute myocardial infarction: ischemic stroke and heart failure and so forth), emigration, non-cardiovascular death or end of study (31 December 2014), whichever occurred first. We made stepwise adjustments for covariates to analyze if lifestyle, anthropometry and cardiovascular risk factors/precursors affected the estimated HRs. The first model was adjusted for confounders (age at time of diagnosis, time since enrollment into the Diet, Cancer and Health study, period of diagnosis and cohabitation status). Second model further adjusted for stage and assigned first-line treatment. In the third model, smoking, alcohol intake and physical activity were added. Finally, we adjusted for cardiovascular

precursor disease and/or diabetes present at entry. Models 2–4 aimed to evaluate any potential mediation between education and cardiovascular events. Men with missing information on educational level were excluded ($n = 32$). The continuous covariates BMI, alcohol intake, MET-score, diastolic and systolic blood pressure and serum cholesterol were included in the models as cubic splines. Other covariates with missing information were handled by multiple imputation with the assumption that missing values were missing at random. Ten imputations were conducted using all the variables in the final model and included the Gleason score and PSA level at time of diagnosis, as these covariates were considered to add information in order to predict stage and assigned first-line treatment when missing. Estimates from the analysis based on the imputed datasets were compared with the estimates based on analysis of complete cases.

We checked for temporal variation in HRs by splitting the time scale into three intervals according to time since diagnosis. Thus, we analyzed if HRs for the first year, one to five years and beyond five years post diagnosis were significantly different for men with basic and vocational education compared to those with long education.

We tested the proportional hazards assumption in all analyses by inspecting p values and plots of each covariate in all models based on Schoenfeld's residuals. We stratified all analyses by age group due to continuous violation of the assumption. In some models, cohabitation and MET-score also violated the assumption; however, stratifying on these covariates did not affect the HRs for the exposures of interest. Cumulative incidences were calculated for each cardiovascular outcome and death from other causes as a competing event. Gray's test was used to evaluate hypotheses of equality of cause-specific cumulative incidence functions between educational groups.

The analyses were done with R version 3.3.3. Descriptive analyses were done using packages 'plyr' and 'TableOne'. The Cox proportional hazards models, check for proportional hazards, cumulative incidence plots and multiple imputation were carried out with packages 'survival', 'timereg', 'mitools', 'prodlim' and 'smcfcs' (see Appendix for R package references).

Results

Among the 1980 men with prostate cancer, 11% experienced a cardiovascular event during a median follow-up of 4.6 years (interquartile range (IQR) 2.1–7.3 years); cardiovascular events occurred in 14%, 12% and 8% of men with short, medium and long education, respectively. Men with short or medium education were more often living alone, obese and current smokers compared to men with long education. Although only minor differences were found regarding tumor spread, men with short education were more likely to undergo palliative care than men with long education (Table 1).

The cumulative incidence of acute myocardial infarction was increased in men with short and medium education compared with men with long education. Five years after diagnosis about 3% of prostate cancer patients with medium education had an acute myocardial infarction compared with less than 1% of men with long education (Figure 1(a)). The cumulative incidence of ischemic stroke was highest among those with short education (Figure 1(b)). The cumulative incidence for heart failure was similar across educational levels (Figure 1(c)).

Compared to men with the longest education, we found an increased HR of acute myocardial infarction of 3.14 (95% CI 1.53–6.47) and 2.14 (95% CI 0.82–5.58) in men with medium and short education, respectively (Table 2). For men with medium education, estimates from stepwise adjustment for clinical factors, lifestyle and cardiovascular risk factors, respectively, did not differ substantially from the result of the initial model (adjusted HR 3.04, 95% CI 1.47–6.31). The rates of ischemic stroke and heart failure were higher for shorter education across models; however, the estimates did not reach statistical significance in any model. We found no educational differences in death from other causes than acute myocardial infarction, ischemic stroke or heart failure (Table 1, Appendix).

We found no substantial difference between the estimates based on all observations (multiple imputation) and the estimates based on the complete cases (data not shown).

Discussion

Using education as an indicator for socioeconomic position, we found an inequality in the risk of acute myocardial infarction after a prostate cancer diagnosis. This difference in risk by education did not seem to be attributable to differences in lifestyle, cardiovascular risk profile or assigned cancer treatment in the study population at hand. After full adjustment, a three-fold increased rate for acute myocardial infarction was observed in men with medium education compared with those with long education. Previous research has focused on the association between prostate cancer treatment and risk of cardiovascular disease; to our knowledge, we are the first to investigate educational differences in the rate of cardiovascular disease after prostate cancer.

The present study had several strengths such as the prospective cohort design and unique precancer information on lifestyle and cardiovascular risk factors. The prospective design allowed us to identify a cardiovascular disease-naïve study population and incident cases of prostate cancer that we were able to follow up for up to 18 years with no loss to follow up. Information on cardiovascular outcomes was collected independently of exposure status and was obtained from the National Danish Patient Registry, containing high quality, validated data [20–22]. We included unique self-reported information on lifestyle factors known to be associated with both level of educational level and risk of cardiovascular events. The available objective measures of blood pressure and cholesterol made it possible to account for cardiovascular health in the years before prostate cancer diagnosis. Such pre-cancer information provided us with an opportunity to explore mediating effects of lifestyle in social

Table 1. Distribution of characteristics according to educational level among 1980 men diagnosed with prostate cancer in the Danish prospective Diet, Cancer and Health study.

	Educational level[a]					
	Long (>12 years)		Medium (9–12 years)		Short (<9 years)	
Characteristics						
Men included, *N* (%)	662	33	1037	52	281	14
Person-years at risk, *N*	3549	–	5175	–	1362	–
Calendar period of diagnosis, *N* (%)						
1993–2000	49	(7.4)	79	(7.6)	28	(10.0)
2001–2005	150	(22.7)	215	(20.7)	61	(21.7)
2006–2010	272	(41.1)	449	(43.3)	119	(42.5)
2011–2014	191	(28.9)	294	(28.4)	73	(26.0)
Number of events and deaths, *N* (%)						
Acute myocardial infarction	7	(1.4)	38	(3.7)	8	(2.5)
Ischemic stroke	27	(3.8)	49	(4.2)	19	(6.0)
Heart failure	22	(3.3)	43	(4.1)	15	(5.3)
Death from other causes	117	(17.7)	226	(23.3)	69	(24.6)
SES characteristics[b]						
Age at diagnosis (IQR)						
Median, years	68	(65–72)	69	(65–72)	70	(66–73)
Cohabiting status, *N* (%)						
Cohabiting	552	(83.4)	848	(81.8)	205	(73.0)
Living alone	110	(16.6)	189	(18.2)	76	(17.0)
Clinical characteristics[b]						
Tumor spread, *N* (%)						
Localized	430	(65.0)	671	(64.6)	186	(66.2)
Non-localized	181	(27.3)	294	(28.3)	80	(28.5)
Missing	51	(7.7)	73	(7.0)	15	(5.3)
Assigned first-line treatment, *N* (%)						
No active treatment	136	(20.5)	221	(21.3)	60	(21.4)
Curative intent	256	(38.7)	354	(34.1)	88	(31.3)
Palliative care	143	(21.6)	263	(25.3)	85	(30.2)
Missing	127	(19.2)	199	(19.2)	48	(17.1)
Lifestyle characteristics[c]						
Physical activity (MET-score)						
Median (IQR)	59	(37–73)	57	(37–84)	52	(36–94)
Missing (*N*)	<5	(<1)	<5	(<1)	<5	(<1)
Body mass index[b], *N* (%)						
Normal (<25 kg/m)	282	(42.6)	371	(35.8)	76	(27.0)
Overweight (25–30 kg/m)	315	(47.6)	543	(52.4)	147	(52.3)
Obese (>30 kg/m)	65	(9.8)	123	(11.9)	58	(20.6)
Alcohol intake[b], *N* (%)						
0 g/day	<15	(<5)	<40	(<5)	<30	(<10)
<36 g/day	516	(77.9)	828	(79.8)	210	(74.7)
>36 g/day	127	(19.2)	169	(16.3)	44	(15.7)
Missing	5	(<1)	<5	(<1)	<5	(<1)
Smoking[b], *N* (%)						
Never	220	(33.2)	<320	(<35)	<80	(<30)
Former	268	(40.5)	357	(34.4)	83	(29.5)
Current	<180	(<30)	364	(35.1)	120	(42.7)
Missing	<5	(<1)	<5	(<1)	<5	(<1)

Information obtained at [a]one year before date of diagnosis, [b]time of diagnosis, [c]time of enrollment in the Diet, Cancer and Health study (1993–1997).

inequality in health consequences after cancer diagnosis. Information from medical records allowed us to consider key clinical factors such as first-line treatment that differs by socioeconomic position [3,4] and may affect the risk of subsequent cardiovascular events in men with prostate cancer [3,4,10].

The study is, however, not without limitations. Participation in the Diet, Cancer and Health study is characterized by an overrepresentation of men with long compared to short education, with only 14% of men having short education [23]; this selection is reflected in a lower mortality rate among men in the overall cohort than the background population of men [4,23]. Although in principle this should not affect internal validity, a selection of more healthy participants in each educational stratum may reduce the variance in lifestyle and other factors affecting cardiovascular health by education. A reduced difference in cardiovascular risk may despite a considerable sample size result in low statistical power in our study to detect differences between men with long and short education. Further, we did not have information on actual treatment, but only on assigned first line treatment, which may result in some misclassification of the treatment groups as some men in active surveillance or watchful waiting would later be assigned to either curative treatment or palliative treatment. This misclassification may have led to an underestimation of the rate of cardiovascular events among men in palliative care and overestimation among men in active surveillance, watchful

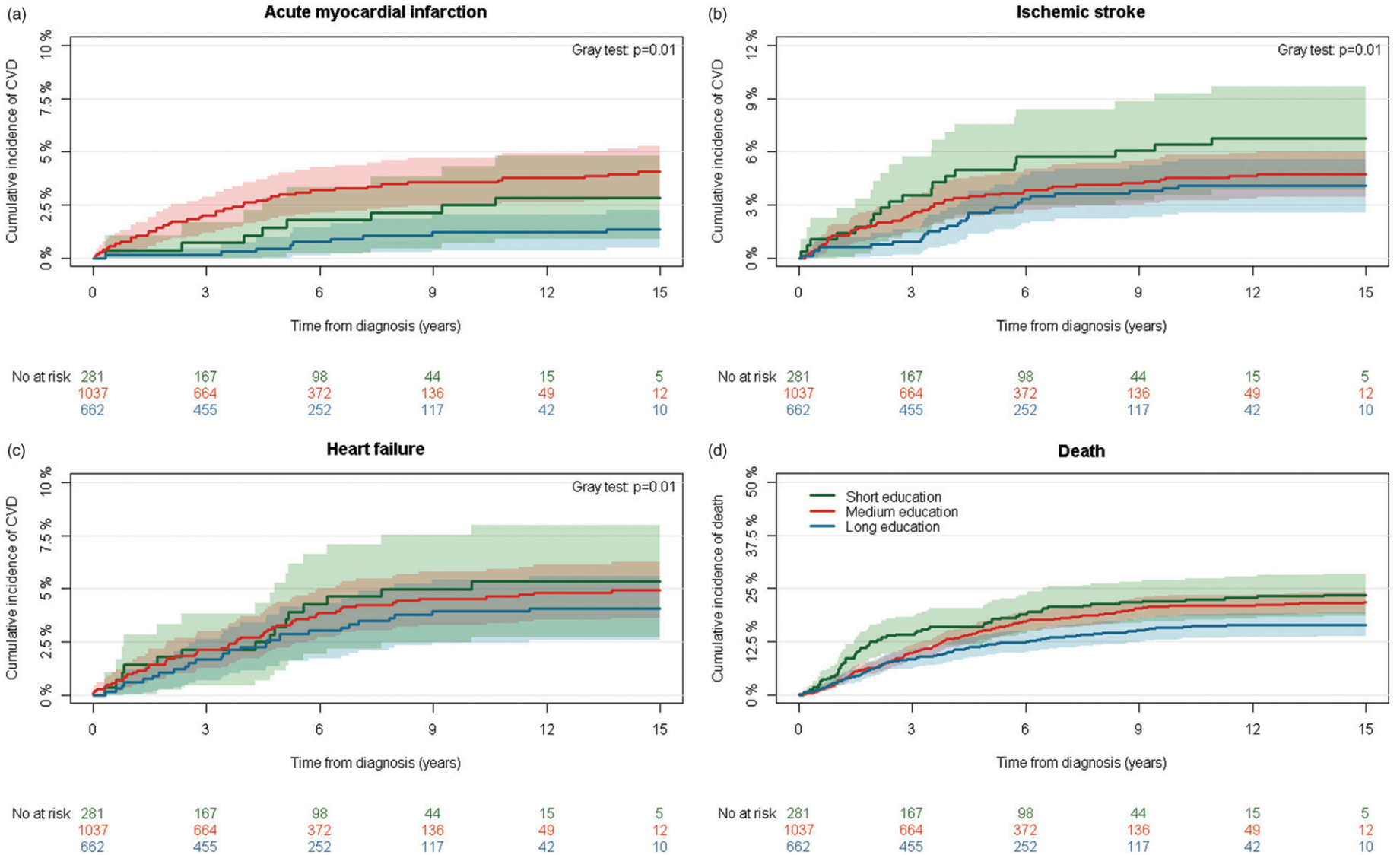

Figure 1. (a–d) Cumulative incidences of myocardial infarction, ischemic stroke, heart failure and death following prostate cancer diagnosis, stratified on educational level. The study population includes 1980 men diagnosed with prostate cancer among participants in the Danish prospective Diet, Cancer and Health Study from 1993 to 2014.

Table 2. Hazard ratios for acute myocardial infarction, ischemic stroke or heart failure by educational level among 1980 prostate cancer patients participating in the Danish prospective Diet, Cancer and Health study.

	Model 1[a]			Model 2[b]			Model 3[c]			Model 4[d]		
	MI	IS	HF	MI	IS	HF	MI	IS	HF	MI	IS	HF
Educational level		HR (95% CI)			HR (95% CI)			HR (95% CI)			HR (95% CI)	
Long (>12 years)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Medium (9–12 years)	3.14 (1.53–6.47)	1.17 (0.73–1.87)	1.16 (0.73–1.86)	3.09 (1.50–6.38)	1.14 (0.71–1.83)	1.14 (0.71–1.83)	3.02 (1.46–6.26)	1.09 (0.68–1.77)	1.07 (0.66–1.72)	3.04 (1.47–6.31)	1.09 (0.67–1.76)	1.00 (0.62–1.62)
Short (≤7 years)	2.14 (0.82–5.58)	1.55 (0.85–2.80)	1.15 (0.61–2.17)	2.18 (0.83–5.71)	1.52 (0.83–2.76)	1.15 (0.60–2.17)	2.07 (0.78–5.52)	1.39 (0.75–2.58)	0.96 (0.49–1.86)	2.07 (0.78–5.53)	1.38 (0.75–2.56)	0.90 (0.46–1.75)

MI: acute myocardial infarction; IS: ischemic stroke; HF: heart failure.
[a]Model 1 is adjusted for age, time since entry, calendar period of diagnosis and cohabitation status.
[b]Model 2 is further adjusted for stage* and assigned first-line treatment (conservative treatment, curative treatment or palliative care).
[c]Model 3 is further adjusted for lifestyle factors (body mass index, metabolic equivalent of task-score, smoking status and alcohol intake).
[d]Model 4 is further adjusted for cardiovascular risk factors (systolic and diastolic blood pressure and serum cholesterol) at entry, diabetes at time of diagnosis and cardiovascular precursors (transient cerebral ischemia, cardio myopathy or angina pectoris) at time of diagnosis.
*Information on stage and primary treatment was imputated using Gleason score and prostate-specific antigen level at baseline as auxiliary variables.

waiting and curative treatment group and if differential by education may have introduced bias in our results.

Our results align partly with a recent study of educational inequality in the development of cardiovascular disease over a period of 24 years, including all individuals in the Danish population aged 35–84 years. Authors showed educational inequalities in several cardiovascular diagnoses with the most pronounced disparities in ischemic heart disease, acute myocardial infarction, heart failure and stroke [13].

In the prostate cancer setting, men with low socioeconomic position have a higher prostate cancer mortality than men with high socioeconomic position [1,23] possibly because socioeconomic position is associated with PSA-screening [24,25], timing of diagnosis [26] and choice of treatment [3, 26] favoring those with high versus low socioeconomic position. Although systematic screening with PSA has never been recommended in Denmark, a previous study in the Diet, Cancer and Health study showed that prostate cancer patients with long education were more likely to be diagnosed based on PSA testing without any clinical indication [27].

In the present study, we likewise showed that men with medium and short education, were less likely to be assigned to curative treatment than men with long education, thus potentially being at higher risk for treatment related cardiovascular events. Surprisingly, the associations observed were largely unaffected by the adjustments for lifestyle, cardiovascular risk factors and precursors or treatment, that we hypothesized might mediate the educational inequality in acute myocardial infarction. Although changes in lifestyle and cardiovascular risk factors over time may be different by socioeconomic position; residual confounding or mediation may additionally explain why men with medium and short education are more prone to acute myocardial infarction than men with a long education.

Our study is the first to document an educational difference in acute myocardial infarction among men with prostate cancer. We thus extend the evidence of social inequality in prostate cancer to include indications of socioeconomic inequality in cardiovascular late effects despite the universal access to health care in Denmark.

In conclusion, we demonstrate social inequality in risk of acute myocardial infarction following a prostate cancer diagnosis, even when differences in lifestyle, cardiovascular risk factors, precursors and first-line treatment are taken into account. Working towards closing the socioeconomic gap in mortality after prostate cancer we must include monitoring of cardiovascular health and health promotion regardless of education, income and cohabitation status in order to secure the best outcome for all patients on equal terms.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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