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Mortality Risks Associated with Depression in Men with Prostate Cancer

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Abstract

Background: Men diagnosed with prostate cancer (PC) have an increased risk of depression; however, it is unclear to what extent depression affects long-term survival. A better understanding of such effects is needed to improve long-term care and outcomes for men with PC.

Objective: To determine the associations between major depression and mortality in a national cohort of men with PC.

Design, setting, and participants: A national cohort study was conducted of all 180 189 men diagnosed with PC in Sweden during 1998–2017. Subsequent diagnoses of major depression were ascertained from nationwide outpatient and inpatient records through 2018.

Outcome measurements and statistical analysis: Deaths were identified from nationwide records through 2018. Cox regression was used to compute hazard ratios (HRs) for all-cause mortality associated with major depression, adjusting for sociodemographic factors and comorbidities. Subanalyses assessed differences by PC treatment during 2005–2017. PC-specific mortality was examined using competing risks models.

Results and limitations: In 1.3 million person-years of follow-up, 16 134 (9%) men with PC were diagnosed with major depression and 65 643 (36%) men died. After adjusting for sociodemographic factors and comorbidities, major depression was associated with significantly higher all-cause mortality in men with high-risk PC (HR, 1.50; 95% confidence interval [CI], 1.44–1.55) or low- or intermediate-risk PC (1.64; 1.56–1.71). These risks were elevated regardless of PC treatment or age at PC diagnosis, except for youngest men (<55 yr) in whom the risks were nonsignificant. Major depression was also associated with increased PC-specific mortality in men with either high-risk PC (HR, 1.35; 95% CI, 1.28–1.43) or low- or intermediate-risk PC (1.42; 1.27–1.59). This study was limited to Sweden and will need replication in other countries when feasible.

Conclusions: In this national cohort of men with PC, major depression was associated with ~50% higher all-cause mortality. Men with PC need timely detection and treatment of depression to support their long-term outcomes and survival.

Patient summary: In this report, we examined the effects of depression on survival in men with prostate cancer. We found that among all men with prostate cancer, those

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who developed depression had a 50% higher risk of dying than those without depression. Men with prostate cancer need close monitoring for the detection and treatment of depression to improve their long-term health outcomes.

1. Introduction

Prostate cancer (PC) is the most commonly diagnosed cancer among men in the USA, Europe, and most countries worldwide, with over 1.2 million new diagnoses globally each year [1,2]. Men with PC may experience psychosocial distress from the diagnosis, physical symptoms, or treatment side effects [3,4], and are at a higher risk of depression [5,6]. Depression may potentially worsen long-term health outcomes by adversely affecting self-care, receipt of treatment, or clinical follow-up. However, little is known about the impacts of depression on survival in men with PC. A better understanding of such impacts is needed to improve long-term clinical care and outcomes for men with PC.

We recently reported that the risk of major depression was elevated 1.8-fold in men with high-risk PC and 1.2-fold in men with low- or intermediate-risk PC, compared with population-based control men without PC [5]. Depression has been associated with premature mortality in general populations [7–9], but its influence on mortality has seldom been examined in men with PC. The few prior studies have suggested that depression is associated with moderately higher all-cause mortality in men with PC, with most relative risks in the 1.2–1.4 range [10–12]. However, those studies were based on selected patient samples that may not represent all men with PC and had limited ability to assess potential differences by age, PC treatment, or other factors. To our knowledge, no studies have examined mortality risks associated with depression in a large population-based cohort of men with PC.

We sought to address these knowledge gaps using nationwide data for >180 000 men with PC in Sweden. Our goals were to determine mortality risks associated with major depression and whether such risks vary by PC risk group, age at PC diagnosis, or PC treatment. We hypothesized that major depression is independently associated with higher mortality in men of all ages with high-risk PC or low- or intermediate-risk PC.

2. Patients and methods

2.1. Study population and PC ascertainment

In the National Prostate Cancer Register (NPCR) of Sweden, we identified 183 495 men who were diagnosed with PC during 1998–2017 [5,13]. The NPCR captures 98% of all incident PC cases since 1998 compared with the Swedish National Cancer Register to which reporting is mandated by law [14]. The NPCR contains data on cancer characteristics including tumor grade according to Gleason score; disease stage according to the tumor, nodes, metastasis (TNM) classification; and prostate-specific antigen (PSA) level at diagnosis, with the primary aim of analyzing adherence to national guidelines [15,16]. We excluded 3306 (2%) men who had missing data for any of these characteristics, leaving 180 189 (98%) men for the analysis [5,13].

PC risk groups were defined at the time of diagnosis based on a modification of the criteria from the National Comprehensive Cancer Network practice guidelines [14,17]. Low-risk PC was defined by clinical local stage T1–T2, Gleason score 2–6, and PSA <10 ng/ml, and intermediate-risk PC was defined by T1–T2 with Gleason score 7 and/or PSA 10–<20 ng/ml. High-risk PC was defined by clinical stage T3 or T4, Gleason score $\geq$8, and/or PSA $\geq$20 ng/ml at the time of diagnosis, and was further stratified as locally advanced (stage T3 and PSA 20–<50 ng/ml), very advanced/regionally metastatic (stage T4 and/or N1 and/or PSA 50–<100 ng/ml in the absence of distant metastases [M0 or Mx]), or distant metastases (stage M1 and/or PSA $\geq$100 ng/ml) [14,17].

Primary treatment within 6 mo after diagnosis was identified from the NPCR. Androgen deprivation therapy (ADT) was further identified using Anatomical Therapeutic Chemical codes L02AE (gonadotropin-releasing hormone [GnRH] analogs), L02BB (antiandrogens), and L02BX (other hormone antagonists) in the Swedish Prescribed Drug Register, which contains all medication prescriptions dispensed nationwide since July 1, 2005. This study was approved by the Regional Ethical Review Board in Lund, Sweden (no. 2012/795 and later amendments). Participant consent was not required because this study used only pseudonymized registry-based secondary data.

2.2. Major depression ascertainment

The exposure of interest was the earliest diagnosis of major depression, which was ascertained from the date of PC diagnosis through December 31, 2018, and modeled as a time-dependent variable. Major depression was identified using *International Classification of Diseases, tenth revision* (ICD-10) codes F32-F33 in the Swedish In-Patient and Out-Patient Registers and primary care records. The In-Patient Register contains all primary and secondary hospital discharge diagnoses, with 86% coverage of the Swedish population starting in 1973 and 100% coverage since 1987 [18]. Psychiatric diagnoses in this register have been found to be highly reliable, with most positive predictive values in the 85–95% range [18]. In addition, the Swedish Out-Patient Register contains all diagnoses from specialty clinics nationwide, with approximately 87% nationwide coverage starting in 2001 [19]. Primary care diagnoses collected previously by our group [20] were available for 20% of the Swedish population starting in 1998, 45% starting in 2001, and 90% starting in 2008 and onward. Previous studies have suggested that major depression diagnoses in these com-

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bined sources have high validity based on their prevalence, sex ratio, and sibling and twin correlations [20,21].

2.3. Mortality ascertainment

The primary outcome was all-cause mortality, which was ascertained from the PC diagnosis date through December 31, 2018. Date and cause of death were obtained from the Swedish Cause of Death Register, which includes the date of death and ICD codes for the cause of death among all persons registered in Sweden since 1960, with compulsory reporting nationwide. PC-specific mortality was examined as a secondary outcome and was identified based on all deaths attributed to PC (ICD-10 code C61) as the primary cause of death.

2.4. Covariates

Other characteristics that may be associated with depression and mortality were identified using Swedish national census and health registry data, which were linked using a pseudonymous serial number. Covariates included age at PC diagnosis (modeled simultaneously as a continuous variable and a categorical variable with 10-yr intervals), birth country (Sweden/other), marital status (married/not married), education level ($\leq$9, 10–12, and >12 yr), income (quartiles), region (large cities, other/Southern, other/Northern, and unknown), Charlson Comorbidity Index (CCI) score (0, 1, and $\geq$2) [22], and prior diagnosis of bipolar disorder, schizophrenia, anxiety disorder, or major depression at the PC diagnosis date (each modeled as a separate covariate). The CCI was included because comorbidities are associated with higher risks of mental health problems [23] and mortality. Prior diagnoses of mental disorders were ascertained from the Swedish In-Patient and Out-Patient Registers and primary care records using ICD-10 codes (bipolar disorder: F31, schizophrenia: F20, anxiety disorder: F40-F42, and major depression: F32-F33). All covariates were >99% complete. Missing data were modeled as a separate category and had little effect on risk estimates because of their rarity.

2.5. Statistical analysis

Cox regression was used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality associated with major depression. PC-specific mortality was examined using competing risk models [24] to account for other causes of death. The observation period for each man began at the PC diagnosis date and ended on December 31, 2018. Major depression was modeled as a time-dependent exposure based on the earliest diagnosis after the PC diagnosis date. Men were censored at emigration, as determined by the absence of a residential address in census data (n = 458). All analyses were adjusted for covariates (as defined above). The proportional hazard assumption was tested by examining log-log plots and was satisfied in each model.

Age-specific differences were assessed by stratifying on age at the time of PC diagnosis (<55, 55–64, 65–74, 75–84, and $\geq$85 yr) while adjusting for age as a continuous variable within each stratum. Secondary analyses were also stratified by primary PC treatment modality (ADT only, radical prostatectomy, radiation with or without adjuvant ADT, or both radical prostatectomy and radiation) using treatment data available during 2005–2017. Subanalyses of ADT examined treatment with GnRH analogs versus monotherapy with antiandrogens separately. Interactions between major depression and either age or PC treatment were tested formally using a likelihood ratio test.

In exploratory analyses, we also assessed for interactions between major depression and other covariates, which could potentially reveal other subgroups of men with PC who are more susceptible to adverse effects of depression on survival. In addition, we explored whether associations between major depression and mortality varied according to whether antidepressant medications were used (identified by code N06A in the Prescribed Drug Register). All statistical tests were two sided and used a significance level of 0.05. All analyses were conducted using Stata version 16.1.

3. Results

Among 180 189 men with PC, 56% had low- or intermediate-risk disease and 44% had high-risk disease. Men with low- or intermediate-risk disease had a median age of 67 yr (interquartile range [IQR], 62–73) at PC diagnosis and a median follow-up time of 7 yr (IQR, 4–11). Men with high-risk disease had a median age of 75 yr (IQR, 68–81) at PC diagnosis and a median follow-up time of 4 yr (IQR, 2–8).

In 1.3 million person-years of follow-up, 16 134 (9%) men were diagnosed with major depression, and 65 643 (36%) men died. Of all deaths, 30 071 (46%) were attributed to PC as the primary cause and 338 (0.2%) were by suicide. The median ages at diagnosis of major depression and at death were, respectively, 73 and 81 yr for men with low- or intermediate-risk PC, and 79 and 82 yr for men with high-risk PC.

Table 1 shows the characteristics of men with high-risk PC, those with low- or intermediate-risk PC, and all men diagnosed with major depression or who died. Men with high-risk PC had lower education or income levels than men with low- or intermediate-risk PC. Men diagnosed with major depression were more likely to have previous psychiatric diagnoses, and those who died were more likely to have multiple comorbidities at baseline.

3.1. Major depression and mortality

In men with high-risk PC, major depression was associated with 1.5-fold higher all-cause mortality after adjusting for sociodemographic factors and comorbidities (HR, 1.50; 95% CI, 1.44–1.55; Table 2). This risk was slightly higher in men with locally advanced disease (adjusted HR, 1.57; 95% CI, 1.50–1.65) than in those with very advanced/regionally metastatic disease (1.39; 1.29–1.50) or distant metastases (1.44; 1.32–1.58; p for heterogeneity = 0.02). In men with low- or intermediate-risk PC, the corresponding HR was 1.64 (95% CI, 1.56–1.71; Table 2). Figure 1 shows the probability of survival in men with either high-risk PC or

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Table 1 – Characteristics of study participants, 1998–2018, Sweden

	High-risk PC [a] N = 78 951 n (%)	Low- or intermediate-risk PC [b] N = 101 238 n (%)	Major depression N = 16 134 n (%)	Death N = 65 643 n (%)
Age at PC diagnosis (yr)				
<55	1372 (2)	5728 (6)	792 (5)	754 (1)
55–64	10 791 (14)	32 406 (32)	3905 (24)	6909 (11)
65–74	27 258 (35)	45 054 (45)	6264 (39)	21 017 (32)
75–84	30 272 (38)	16 356 (16)	4410 (27)	28 464 (43)
≥85	9258 (12)	1694 (2)	763 (5)	8499 (13)
Sweden born	72 846 (92)	92 334 (91)	14 724 (91)	60 936 (93)
Marital status				
Married	54 933 (70)	72 080 (71)	11 205 (69)	45 703 (70)
Not married	24 018 (30)	29 158 (29)	4929 (31)	19 940 (30)
Education (yr)				
≤9	37 659 (48)	32 615 (32)	6229 (39)	34 814 (53)
10–12	27 165 (34)	40 885 (40)	6261 (39)	21 277 (32)
>12	14 117 (18)	27 727 (27)	3664 (23)	9552 (15)
Unknown	10 (<0.1)	11 (<0.1)	0 (0)	0 (0)
Income (quartile)				
1st (highest)	15 832 (20)	39 920 (39)	3949 (24)	7136 (11)
2nd	21 091 (27)	28 529 (28)	4721 (29)	14 488 (22)
3rd	22 291 (28)	20 252 (20)	4514 (28)	21 964 (33)
4th (lowest)	19 694 (25)	12 481 (12)	2942 (18)	22 033 (34)
Unknown	43 (0.1)	56 (0.1)	8 (<0.1)	22 (<0.1)
Region				
Large cities	34 100 (43)	53 073 (52)	9297 (58)	29 704 (45)
Other/southern	29 884 (38)	33 257 (33)	4734 (29)	24 002 (37)
Other/northern	14 957 (19)	14 899 (15)	2102 (13)	11 929 (18)
Unknown	10 (<0.1)	9 (<0.1)	1 (<0.1)	8 (<0.1)
Charlson Comorbidity Index				
0	54 987 (70)	77 632 (77)	11 778 (73)	3939 (6)
1	9210 (12)	12 953 (13)	2097 (13)	20 349 (31)
≥2	14 754 (19)	10 653 (11)	2259 (14)	41 355 (63)
Prior diagnoses				
Bipolar disorder	346 (0.4)	626 (0.6)	384 (2.4)	305 (0.5)
Schizophrenia	247 (0.3)	235 (0.2)	70 (0.4)	227 (0.4)
Anxiety disorder	2814 (4)	4370 (4)	2019 (12)	1913 (3)
Major depression	3167 (4)	5108 (5)	3361 (21)	2153 (3)

PC = prostate cancer; PSA = prostate-specific antigen.
[a] High-risk PC was defined by clinical stage T3–T4, Gleason score ≥8, or PSA ≥20 ng/ml at the time of diagnosis.
[b] Low-risk PC was defined by clinical stage T1–T2, Gleason score 2–6, and PSA <10 ng/ml, and intermediate-risk PC was defined by clinical stage T1–T2, with Gleason score 7 or PSA 10–<20 ng/ml.

Table 2 – All-cause mortality through 2018 in men with PC (1998–2017) who were diagnosed with major depression compared with those who were not, stratified by PC treatment

	Men with PC	Major depression		All-cause mortality		Adjusted model [a]		Interaction with treatment
	n (%)	No. of cases	Cum. inc. (%)	No. of deaths	Cum. inc. (%)	HR (95% CI)	p value	p value
High-risk PC [b]	78 951	6490	8	46 050	58	1.50 (1.44, 1.55)	<0.001	
Treatment (2005–2017) [c]	43 255 (100)							0.16
ADT only	27 367 (63)	2346	9	11 860	43	1.56 (1.45, 1.67)	<0.001	
RP	2251 (5)	241	11	994	44	1.63 (1.30, 2.05)	<0.001	
Radiation	12 433 (29)	1051	8	5012	40	1.40 (1.25, 1.58)	<0.001	
RP and radiation	1204 (3)	130	11	471	39	1.49 (1.07, 2.08)	0.02	
Low- or intermediate-risk PC [d]	101 238	9644	10	19 593	19	1.64 (1.56, 1.71)	<0.001	
Treatment (2005–2017) [c]	78 468 (100)							0.008
Deferred treatment [e]	48 718 (62)	3618	7	3739	8	1.67 (1.48, 1.88)	<0.001	
ADT only	9489 (12)	1133	12	1979	21	1.82 (1.58, 2.09)	<0.001	
RP	6976 (9)	657	9	774	11	2.10 (1.63, 2.70)	<0.001	
Radiation	11 438 (15)	1142	10	1616	14	1.40 (1.16, 1.68)	<0.001	
RP and radiation	1847 (2)	187	10	368	20	1.27 (0.82, 1.96)	0.29	

ADT = androgen deprivation therapy; CI = confidence interval; Cum. inc.= cumulative incidence; HR = hazard ratio; PC = prostate cancer; PSA = prostate-specific antigen; RP = radical prostatectomy.
[a] Adjusted for age, birth country, marital status, education, income, region, Charlson Comorbidity Index, and pre-existing psychiatric disorders (bipolar disorder, schizophrenia, anxiety disorder, major depression) at PC diagnosis.
[b] High-risk PC was defined by clinical stage T3–T4, Gleason score ≥8, or PSA ≥20 ng/ml at the time of diagnosis.
[c] Subanalyses for men diagnosed with PC in 2005–2017 when treatment data were available.
[d] Low-risk PC was defined by clinical stage T1–T2, Gleason score 2–6, and PSA <10 ng/ml, and intermediate-risk PC was defined by clinical stage T1–T2, with Gleason score 7 or PSA 10–<20 ng/ml.
[e] Includes active surveillance or watchful waiting.

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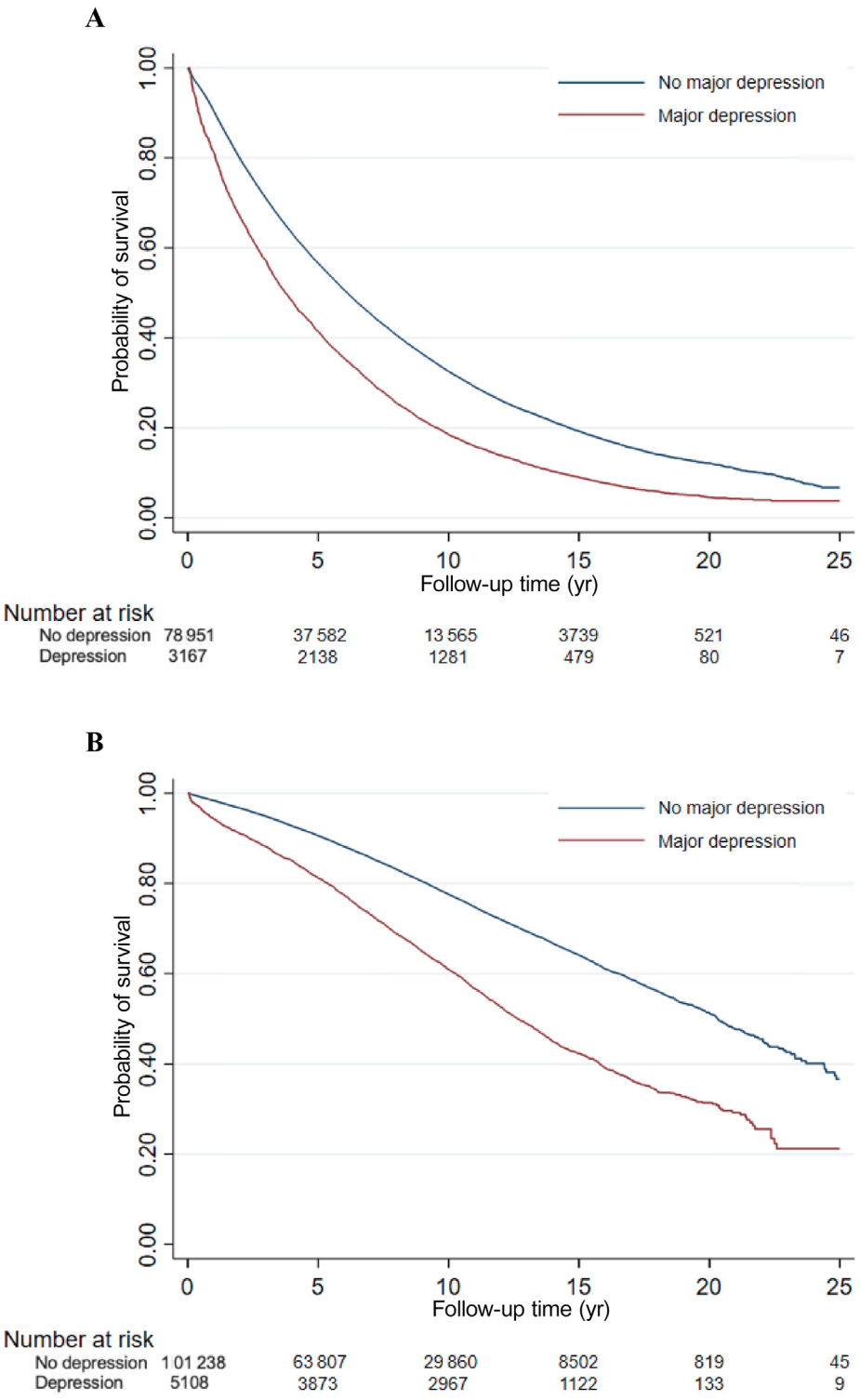

Fig. 1 – Probability of survival in men with (A) high-risk PC or (B) low- to intermediate-risk PC by time since PC diagnosis, stratified by major depression status. PC = prostate cancer.

low- or intermediate-risk PC by time since PC diagnosis, stratified by major depression status.

In secondary analyses, major depression was also associated with higher PC-specific mortality in men with either high-risk PC (adjusted HR, 1.35; 95% CI, 1.28–1.43) or low- or intermediate-risk PC (1.42; 1.27–1.59; Supplementary Table 1), but with slightly lower HRs than for all-cause mortality.

3.2. *Age-specific differences*

In men with high-risk PC, major depression was associated with significantly increased all-cause mortality at all ages

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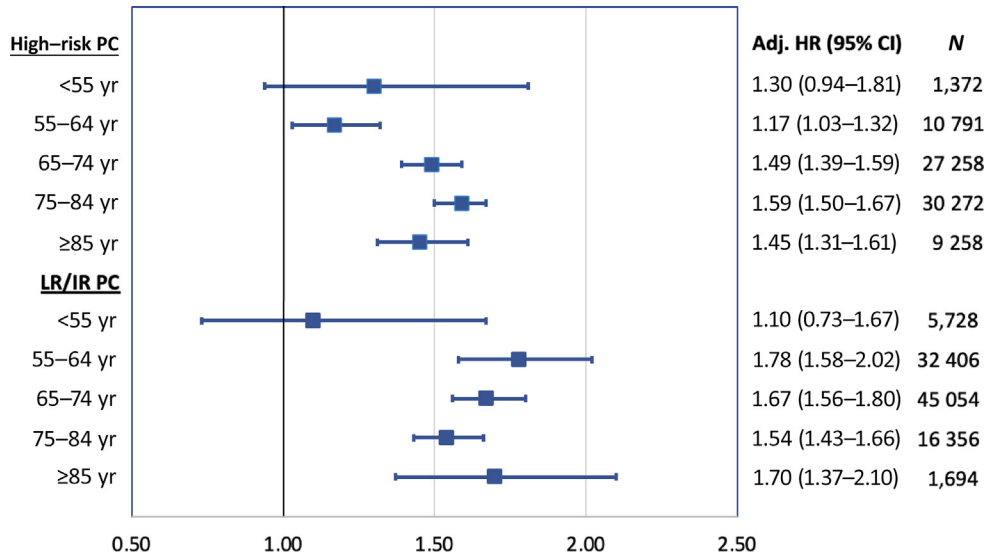

Fig. 2 – Adjusted hazard ratios and 95% confidence intervals for all-cause mortality through 2018 in men with PC who were diagnosed with major depression compared with those who were not, stratified by age at PC diagnosis (1998–2017). Adj. HR = adjusted hazard ratio; CI = confidence interval; IR = intermediate risk; LR = low risk; PC = prostate cancer.

≥55 yr at PC diagnosis, but not in younger men (Fig. 2 and Supplementary Table 2). Only 2% of men with high-risk PC were diagnosed at ages <55 yr, resulting in wide CIs for that subgroup. Significant heterogeneity was found by age ($p < 0.001$), with strongest associations (1.5- to 1.6-fold) in men aged ≥65 yr at PC diagnosis. A similar pattern was found in men with low- or intermediate-risk PC: significant heterogeneity was found by age ($p = 0.01$), with significantly increased risks (1.5- to 1.8-fold) in all age groups ≥55 yr at PC diagnosis, but not in younger men.

In contrast, secondary analyses of PC-specific mortality showed that men with high-risk PC had significant heterogeneity by age ($p < 0.001$) but with strongest associations (1.3- to 1.5-fold) in men aged <65 yr at PC diagnosis (Supplementary Table 3). In men with low- or intermediate-risk PC, no heterogeneity was found by age ($p = 0.87$).

3.3. Differences by PC treatment

In men with high-risk PC, major depression was associated with higher all-cause mortality regardless of PC treatment, without significant heterogeneity (p for interaction = 0.16; Table 2). The association between major depression and all-cause mortality was also similar among men treated with GnRH analogs (adjusted HR, 1.52; 95% CI, 1.41–1.64) or antiandrogen monotherapy (1.75; 1.42–2.15; $p = 0.21$ for difference in HRs).

In men with low- or intermediate-risk PC, major depression was associated with increased mortality in all PC treatment groups except for men treated with both radical prostatectomy and radiation (Table 2). However, there was significant heterogeneity by PC treatment (p for interaction = 0.008), with stronger associations among those treated with radical prostatectomy (adjusted HR, 2.10; 95% CI, 1.63–2.70, based on 657 depression diagnoses and 774 deaths among 6976 men) or ADT only (1.82; 1.58–2.09; Table 2). The association between major depression and all-cause mortality also was stronger among those treated with antiandrogen monotherapy (adjusted HR, 2.50; 95% CI, 1.91–3.28) than among those treated with GnRH analogs (1.64; 1.39–1.94; $p = 0.009$ for difference in HRs).

In secondary analyses, associations between major depression and PC-specific mortality had no significant heterogeneity by PC treatment in men with either high-risk PC ($p = 0.18$) or low- or intermediate-risk PC ($p = 0.36$; Supplementary Table 1).

3.4. Other interactions

In exploratory analyses of other interactions, major depression was more strongly associated with all-cause mortality among men with high-risk PC who had no prior history of depression at baseline (adjusted HR, 1.56; 95% CI, 1.50–1.62) than among those with such a history (1.18; 1.05–1.32; $p < 0.001$ for interaction; Supplementary Table 4). The same interaction ($p < 0.001$) also was found among men with low- or intermediate-risk PC (adjusted HRs, 1.70; 1.62–1.78, and 1.17; 1.00–1.37, respectively; Supplementary Table 5). The only other significant interaction was between major depression and CCI among men with high-risk PC, with a stronger association among men with comorbidities (CCI score 1: 1.58; 95% CI, 1.44–1.73; and CCI score ≥2: 1.46; 1.40–1.52) than among those without (CCI score 0: 1.10; 0.56–2.14; $p = 0.02$ for interaction).

Among men with PC who were diagnosed with major depression since 2005 (when pharmacy data became available), 94% were treated with antidepressant medications. In men with high-risk PC, all-cause mortality was higher among those with depression not treated with antidepressants (adjusted HR, 2.01; 95% CI, 1.67–2.43) than among those treated with antidepressants (1.52; 1.44–1.61), each compared with men without depression ($p = 0.005$ for difference in HRs). In men with low- or intermediate-risk PC, the corresponding HRs were 1.77 (95% CI, 1.36–2.31) among

those without antidepressant treatment and 1.66 (1.54–1.80) among those with such treatment (p = 0.65 for difference in HRs).

4. Discussion

In this national cohort, after adjusting for sociodemographic factors and comorbidities, major depression was associated with a 1.5-fold higher mortality in men with high-risk PC and a 1.6-fold higher mortality in men with low- or intermediate-risk PC. These risks were elevated regardless of PC treatment or age at PC diagnosis, except that these were nonsignificant among youngest men (<55 yr) who were a small subgroup. Major depression also was more strongly associated with mortality in men without a prior history of depression at baseline than in men with such a history.

To our knowledge, this is the first study to examine long-term mortality outcomes associated with major depression in a national cohort of men with PC. A study of 40 412 US military veterans with localized PC reported that those subsequently diagnosed with depression had nearly 1.3-fold higher all-cause mortality during a median follow-up of 9 yr [10]. A Surveillance, Epidemiology, and End Results study of 41 275 US men with localized PC reported that those with depression within 2 yr before PC diagnosis had elevated all-cause mortality during 2–6 yr of follow-up, with higher relative rates among those with low-risk PC (1.8-fold) than among those with intermediate- or high-risk PC (1.1- to 1.3-fold) [12]. A study of 1101 men newly diagnosed with PC in Taiwan also reported nearly 1.4-fold higher all-cause mortality in those with depression than in those without [11].

Our findings showed that men with either high-risk PC or low- or intermediate-risk PC who were subsequently diagnosed with major depression had substantially increased (1.5- to 1.6-fold) all-cause mortality. PC-specific mortality was also increased in such men, but with smaller risk estimates than all-cause mortality, possibly related to misclassification that is common in cause-of-death data [25–27]. Misattribution of PC-related death to other causes is likely to occur nondifferentially with respect to depression and therefore to influence results toward the null. In addition, major depression was more strongly associated with mortality in men without prior diagnoses of depression at baseline. Depression after PC diagnosis in such men is more likely to represent new depression related to their PC diagnosis or treatment, which may have more severe effects on outcomes than persistence or recurrence of pre-existing depression. We also found that men with high-risk PC and depression who did not receive antidepressant treatment had higher all-cause mortality than those with such treatment. Further elucidation of survival outcomes by specific treatment for depression may be useful in future studies of men with PC.

To our knowledge, this was the first study to assess whether the association between depression and mortality varies by PC treatment. We found positive associations for nearly all treatment groups. However, there was significant heterogeneity in men with low- or intermediate-risk PC, with depression having the strongest association with mortality (two-fold) among men treated with radical prostatectomy. This was an unexpected finding based on a small subgroup and will need confirmation in future studies. Men with low- or intermediate-risk PC who opt for prostatectomy are a selected group with high health awareness, little comorbidity, and higher survival than the background population [28,29]. We previously found that in men with either high-risk PC or low- or intermediate-risk PC, the risk of developing major depression was lower in those treated with radical prostatectomy or radiation than in those treated with ADT only [5]. In fact, men with high-risk PC treated with ADT only had the highest risk of major depression, which was even higher in those treated with GnRH analogs than in those treated with antiandrogen monotherapy (two- vs 1.5-fold, compared with population-based control men without PC) [5]. The present study found that major depression was associated with increased all-cause mortality, with a similar magnitude in these subgroups. Altogether, the evidence suggests that men with high-risk PC treated with ADT are at a particularly high risk of depression, which adversely affects survival, and thus they may benefit from additional psychosocial support early in the treatment course.

These findings add to prior evidence demonstrating the importance of addressing mental health in men with PC. In the same Swedish cohort as the present study, we previously found that men with high-risk PC had a 1.8-fold higher risk of major depression and a 2.4-fold higher risk of death by suicide, compared with population-based control men without PC [5]. Other studies have suggested that psychosocial distress may worsen quality of life [30] and long-term health outcomes [6,12,31–33] in PC survivors. Depression is not only a psychological burden but may also have other health consequences such as treatment nonadherence [34]. The American Cancer Society has previously recommended screening at least annually for psychosocial distress and depression in men with PC [34]. Our findings underscore the importance of such screening in all men with PC, in both urology and primary care clinics, followed by referral of men with positive screens for treatment. Routine screening and referral have been shown to reduce psychosocial distress in men or women with other common cancers [35], but need further study in men with PC. Validated instruments to assess mental health and social determinants of health are used increasingly in cancer patients [36,37] and can be deployed in urology clinics for men with PC.

4.1. Strengths and limitations

A key strength of this study was its large national cohort design, which provided high statistical power needed to examine major depression and mortality in men with PC and in high-risk subgroups, while controlling for multiple potential confounders. Clinical diagnoses from all health care settings, including primary care, allowed more complete ascertainment of major depression, thus enabling more valid risk estimates based on a national population.

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Previously reported incidence rates for depression are comparable between Sweden and the USA [20,38].

This study also had certain limitations. Major depression diagnoses were identified using nationwide ICD codes, whereas detailed clinical information needed to validate them was unavailable [5]. However, high validity of these diagnoses has previously been supported by their prevalence, sex ratio, sibling and twin correlations, and associations with well-documented psychosocial risk factors [20,21]. Depression is often undiagnosed, and such cases could not be identified in this study; the reported diagnoses may represent the most severe cases. However, the inclusion of diagnoses from primary care settings, where most depression is diagnosed and treated [20], enabled more complete capture than in prior studies. In addition, this study was limited to Sweden and will need replication in other countries when feasible, including assessment for potential racial/ethnic differences.

5. Conclusions

In this national cohort of men with PC, major depression was associated with ~50% higher mortality after adjusting for sociodemographic factors and comorbidities. This risk was elevated regardless of PC treatment and for nearly all ages at PC diagnosis. Moreover, men with depression who did not receive antidepressant treatment had higher mortality than those with such treatment. Men with PC need close clinical follow-up for the detection and treatment of depression to support their long-term health outcomes and survival.

***Author contributions*:** Jan Sundquist had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Crump, Stattin, Brooks, J. Sundquist, Sieh, K. Sundquist.
Acquisition of data: Stattin, J. Sundquist, K. Sundquist.
Analysis and interpretation of data: Crump, Stattin, Brooks, J. Sundquist, Sieh, K. Sundquist.
Drafting of the manuscript: Crump.
Critical revision of the manuscript for important intellectual content: Crump, Stattin, Brooks, J. Sundquist, Sieh, K. Sundquist.
Statistical analysis: J. Sundquist.
Obtaining funding: Crump, J. Sundquist, Sieh, K. Sundquist.
Administrative, technical, or material support: Stattin, J. Sundquist, K. Sundquist.
Supervision: Stattin, J. Sundquist, K. Sundquist.
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Data sharing statement: Owing to ethical concerns, supporting data cannot be made available openly. Further information about the data registries is available from the Swedish National Board of Health and Welfare: https://www.socialstyrelsen.se/en/statistics-and-data/registers/ .

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2024.03.012.

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