Symptom burden profiles in men with advanced prostate cancer undergoing androgen deprivation therapy

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Abstract To identify symptom burden profiles among men with advanced prostate cancer undergoing androgen-deprivation therapy and examine their association with baseline sociodemographic and medical characteristics and psychosocial outcomes over time. Latent profile analysis was employed to identify distinct groups based on the Expanded Prostate Index Composite and the McGill Pain Questionnaire at baseline. Psychosocial outcomes were assessed at baseline, 6- and 12-month follow-ups. Three profiles emerged: "high symptom burden," "high sexual bother," and "low symptom burden." Men with "high symptom burden" were younger and exhibited higher baseline levels of depression, stress, cancer-specific distress, and anxiety than men in the other two groups. However, men with "high symptom burden" also demonstrated improvement in these psychosocial outcomes over time. Men with advanced prostate cancer who experience multiple co-occurring symptoms demonstrate worse psychosocial adjustment. Patients with substantial symptom burden, and specifically young men, may benefit from prompt referral to supportive care services.

Keywords Androgen deprivation therapy · Latent profile analysis · Prostate cancer · Psychosocial well-being · Quality of life · Symptom burden

Prostate cancer is the most frequently diagnosed cancer and the second leading cause of cancer death among men in the United States (Surveillance Epidemiology and End Results (SEER) Program, 2019). Although prostate cancer is most commonly diagnosed as localized disease (76%), the annual incidence of metastatic prostate cancer increased 72% between 2007 and 2013 (Weiner et al., 2016) and is expected to increase another 42% by 2025 (Kelly et al., 2018). Due to the developments in life-prolonging and palliative treatments, many men now live with advanced disease

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(either regional involvement or metastatic) for several years. The estimated 5-year survival rate for men with regionally-advanced prostate cancer is nearly 100% and 31% for men diagnosed with metastatic prostate cancer (Surveillance Epidemiology and End Results (SEER) Program, 2019). Therefore, understanding the specific needs of this increasing population is crucial in order to offer adequate supportive services tailored to their needs.

Men with advanced prostate cancer face unique challenges as they cope with a life-limiting illness and arduous treatments. These challenges include fear of death, losing hope, managing pain caused by the spread of cancer, non-curative treatment goals, feeling like a burden to others, impaired interpersonal relationships, and financial toxicity (Taylor-Ford, 2014). Compared to men with localized disease, men with advanced prostate cancer experience greater pain and fatigue, higher levels of psychosocial distress, increased risk of suicide, and poorer health-related quality of life (HRQOL; Bill-Axelson et al., 2010; Holm et al., 2018; Zajdlewicz et al., 2017). In addition, androgen-deprivation therapy (ADT), a key component of treatment for advanced prostate cancer (Litwin & Tan, 2017), has been associated with deleterious physical and psychosocial effects such as gynecomastia, sexual dysfunction, decreased bone mineral density, muscle loss, cardiovascular events, emotional lability, and cognitive impairment, which further exacerbate poor HRQOL (Donovan et al., 2015, 2018; Nguyen et al., 2015).

Although cancer-related symptoms have frequently been studied in isolation (Cleeland, 2007), patients with cancer often experience multiple co-occurring symptoms. Previous research suggests that the co-occurrence of symptoms may have a synergistic effect on patients' HRQOL, functional status, and prognosis (Fan et al., 2007). For example, one study of cancer survivors demonstrated that concurrent symptoms have significant direct associations with functional performance, in addition to the direct single associations between specific symptoms like insomnia, fatigue, and depression with functional performance (Oh et al., 2012). A growing body of research has examined the co-occurrence of symptoms in men with prostate cancer and their impact on health outcomes. Notably, most of these studies have been conducted in men with early-stage prostate cancer who were undergoing active treatment. (Dirksen et al., 2016; Lemanska et al., 2018; Maliski et al., 2008; Reeve et al., 2018). To our knowledge, only two studies have examined concurrent symptoms in men with advanced prostate cancer (Lee et al., 2015; Vayne-Bossert et al., 2017). Lee et al. (2015) identified six groups of concurrent symptoms using clinician reported adverse event data from a pharmacological randomized clinical trial; however, the impact of concurrent symptoms on health outcomes were not examined. Vayne-Bossert et al. (2017) identified two groups of concurrent

symptoms in men with metastatic prostate cancer; however, this analysis was conducted with a small sample size ($N = 37$). Furthermore, these studies used a variable-centered approach to examine relations between variables. A person-centered approach identifies subgroups of individuals based on their similarities on a set of variables. Latent profile analysis presents an opportunity to identify different groups of individuals within a given population that have similar response patterns across multiple observed characteristics (Oberski, 2016b). The identification of groups of advanced prostate cancer patients with similar symptom experiences has the potential to enhance patient care by informing symptom management and future intervention design. Given that the most frequently reported symptoms by men with advanced prostate cancer are fatigue, sexual dysfunction, urinary symptoms, and bone pain (Drudge-Coates et al., 2018), this study aimed to identify symptom burden profiles among men with advanced prostate cancer by conducting a latent profile analysis with the Expanded Prostate Cancer Index Composite (EPIC) and the McGill Pain Questionnaire. We also examined sociodemographic and medical characteristics associated with symptom burden profiles and evaluated the relationships among symptom burden profiles and psychosocial outcomes over time.

Methods

Participants and procedures

The present study is a secondary analysis of a randomized controlled trial aimed at establishing the efficacy of a Cognitive Behavioral Stress Management (CBSM) intervention for improving HRQOL and reducing symptom burden in men with advanced prostate cancer. The study population and primary study results have been described in detail elsewhere (Penedo et al., 2020). Briefly, eligible men were at least 50 years old, initially diagnosed with stage III or IV prostate cancer, had received ADT and experienced an ADT-related symptom within the 12 months before study enrollment, and were fluent in English at the 6th grade level or higher. Participants were excluded if they received treatment for any cancer other than prostate cancer, had prior inpatient psychiatric treatment or current cognitive impairment, reported active substance or alcohol dependence problems, were diagnosed with an immunocompromising condition, or had a life expectancy < 12 months. After providing informed consent, participants ($n = 192$) were randomly assigned (1:1) to receive the 10-week CSBM intervention or a 10-week health promotion (HP) program. Both conditions were group-based and delivered via videoconference. The CBSM intervention included 90-min weekly sessions and its

content was adapted for men with advanced prostate cancer to provide knowledge and training on cognitive-behavioral stress- and self-management skills as well as relaxation skills (e.g., deep breathing, effective coping skills). The HP program included 60-min weekly sessions and presented general health information as well as information relevant to men with advanced prostate cancer (e.g., maintaining a healthy lifestyle, the importance of follow-up care). Participants completed in-person assessments at baseline, 6 months post-baseline (T2), and 12 months post-baseline (T3). Men in both groups showed improvements in cancer-related anxiety, cancer-related distress, and sexual functioning over time.

Measures

Sociodemographic and medical characteristics

Participants self-reported age, race-ethnicity, marital status, income, education, and occupation status. Data on cancer stage, metastatic status, prior treatments (e.g., surgery, radiotherapy), and body mass index (BMI) were extracted from their electronic medical records.

Symptom burden

The Expanded Prostate Cancer Index Composite (EPIC) was used to assess specific symptoms related to prostate cancer (Wei et al., 2000). This instrument has been widely used to assess symptom burden among men with prostate cancer undergoing ADT. This is a 50-item 4- to 5-point Likert scale questionnaire that evaluates patient functioning (symptom severity) and bother (the degree to which symptoms are problematic) after prostate cancer treatment and assesses four domains (hormonal, sexual, bowel, and urinary). The present analyses included the hormonal, sexual, and urinary domains. The hormonal domain considers symptoms associated with ADT such as hot flashes, lack of energy, and breast tenderness. The sexual domain assesses erectile dysfunction, level of sexual desire, and the ability to reach orgasm. The urinary domain includes symptoms related to urinary incontinence and dysuria. Scores were linearly transformed to a 0–100 scale and averaged to yield subscale scores, with higher scores representing less symptom burden. The domains had good internal consistency, with Cronbach's α coefficients ranging from 0.71 (hormonal) to 0.85 (sexual). The bowel domain was not included in the current analysis because participants reported very low levels of baseline bowel symptom burden (Mean Bowel Functioning $\pm$ SE $= 88.8 \pm 1.1$; Mean Bowel Bother $\pm$ SE $= 89.8 \pm 0.8$) and men with scores greater than 80 are less likely to experience problems with bowel function (Laviana et al., 2019). In addition, we used the short version of the McGill Pain Questionnaire to assess participants' pain experience (Melzack,

1987). This 15-item measure evaluates the sensory and affective components of pain on an intensity scale ranging from "none" to "severe." Scores were summed to yield a total pain score, with higher scores indicating more pain (Cronbach's $\alpha = 0.89$).

Psychosocial measures

The Memorial Anxiety Scale for Prostate Cancer (MAX-PC) was used to assess anxiety specific to prostate cancer (Roth et al., 2003). It consists of 18 items divided into three subscales: General Prostate Cancer Anxiety, Prostate-Specific Antigen (PSA) Anxiety, and Fear of Recurrence. All items are rated on a 4-point Likert scale. The total score ranges from 0 to 54, with higher scores indicating more anxiety. For this study, we report the General Prostate Cancer Anxiety subscale (Cronbach's $\alpha = 0.93$). Stress was measured with the Perceived Stress Scale (PSS) (Cohen et al., 1983). It consists of 14 items, with seven positive items and seven negative items rated on a 5-point Likert scale. Positive items were reverse coded prior to scoring and all items were then summed to generate a total score, with higher scores indicating greater stress (Cronbach's $\alpha = 0.82$). In addition, we assessed depression with the Patient-Reported Outcome Measurement Information System (PROMIS) Depression Item Bank computer adaptive test (Ader, 2007). PROMIS assessments are *t* scored so that a mean score of 50 with a standard deviation of 10 represents the average U.S. population score. Higher scores indicate more symptoms of depression. The Impact of Event Scale-Revised (IES-R) was used to evaluate cancer-specific distress (Weiss et al., 1997). This 22-item instrument was developed to assess symptoms of post-traumatic stress disorder (i.e., intrusion, avoidance, and hyperarousal) associated with a life-threatening event. Higher scores indicate greater distress. The subscales had good internal consistency, with Cronbach's α coefficients ranging from 0.81 (hyperarousal) to 0.85 (intrusion). The Functional Assessment of Cancer Therapy-General (FACT-G) scale was used to assess HRQOL (Cella et al., 1993). This 5-point Likert scale instrument includes 27 items and yields four subscales (physical, social, emotional, and functional well-being) and a total score, with higher scores indicate better HRQOL. For this study, we report the social ($\alpha = 0.76$) and emotional ($\alpha = 0.85$) subscales.

Statistical analysis

Model building and evaluation

We conducted a latent profile analysis (LPA) to identify different symptom profiles based on the sexual bother, sexual function, hormonal bother, hormonal function, urinary incontinence, urinary irritative/obstructive EPIC

sub-domains and the McGill total score pain. LPA is a particular kind of mixture modeling where the observed variables are continuous (Oberski, 2016a). Several models were built by estimating models with an increasing number of profiles (i.e., estimating 2- to 5-profile models). A combination of fit indices were used to determine the optimal number of profiles: Akaike Information Criteria (AIC), sample-size adjusted Bayesian Information Criteria (sBIC), Entropy, Vuong–Lo–Mendell–Rubin likelihood ratio test (VLMR), and Bootstrapped likelihood ratio test (BLRT). Better model fit is indicated by lower values for the AIC and sBIC. Significant VLMR and BLRT p values indicate that the k profile model fit is significantly improved compared to the k-1 profile model (e.g., that the 3-profile model fits better than the 2-profile model). Entropy is measured on a zero to one scale with higher values indicating greater classification accuracy (Clark & Muthén, 2009). Class size was also considered when determining the optimal number of profiles and profiles containing less than 5% of the sample were considered spurious (Hipp & Bauer, 2006).

Examining differences among profiles

After determining the number of profiles, we examined whether there were significant differences regarding demographic and medical characteristics at baseline. We applied the modified Bolck-Croon-Hagennars (BCH) method to evaluate significant differences on continuous and categorical variables across profiles. The BCH method is the recommended method for examining relationships among profiles and auxiliary variables (Asparouhov & Muthén, 2020; Bakk & Vermunt, 2016). Auxiliary variables are covariates or predictors of group membership as well as distal outcomes (observed variables predicted by the latent class variable). The inclusion of these variables as auxiliary variables ensures that they do not play a role in the LPA model and do not affect the original latent profile solution (Asparouhov & Muthén, 2020). Analysis was performed in Mplus version 8.4. The sample size used for this analysis was 192; of note, 88.5% ($n = 170$) and 80.2% ($n = 154$) of the total sample completed study assessments at 6 months

and 12 months, respectively. Little's MCAR test was not significant, suggesting that missing data were completely at random ($\chi^2(672) = 715.28$, $p = 0.131$). Maximum likelihood with robust standard errors estimation was used for this analysis.

We conducted latent growth models with the repeated measures of psychosocial outcomes (i.e., prostate cancer anxiety, depression, perceived stress, cancer-related distress, emotional well-being, and social well-being). In each growth model, we examined whether the associations between initial level and slope were negative, which referred to as the regression to the mean phenomenon (Marsh & Hau, 2002). Then, the resulting profiles were used in separate multilevel models to assess change in the psychosocial measures over time. Analyses were performed in SAS version 9.4 using the PROC MIXED procedure. Time was included as a continuous level 1 predictor (coded as 0, 1, 2) and the symptom burden profiles were included as a level 2 categorical predictor. Continuous covariates (i.e., age, comorbidity index) were grand mean centered and categorial covariates were dummy coded (i.e., marital status, metastatic disease, intervention arm). All models included a cross-level two-way interaction term (time-by-group interaction). We used contrast and estimate statements within the mixed procedure to test for the group differences. Due to the multiple comparisons, a Bonferroni-adjusted significance level of 0.017 was calculated to account for the increased possibility of type-I error.

Results

Symptom burden profiles

Fit indices for the models with two through five profiles are shown in Table 1. The statistical criteria indicated that the four-profile model had a better fit compared to the three-profile model (LMR, $p = 0.0466$). However, one of the estimated profiles had only 10 individuals. Therefore, the three-profile solution was selected. The fit indices indicated that the three-profile model had a better fit compared to the two-profile

Table 1 Indicators of model fit across all latent profile analysis models

No. of profiles	AIC	sBIC	LMRT *p*-value	BLRT *p*-value	Entropy	Sample size per class
2	11,007.88	11,009.85	0.0184	< 0.001	0.944	C1 = 24; C2 = 168
3	10,930.64	10,933.34	0.0300	< 0.001	0.903	C1 = 21; C2 = 95; C3 = 76
4	10,878.23	10,881.64	0.0466	< 0.001	0.905	C1 = 76; C2 = 85; C3 = 21; C4 = 10
5	10,826.65	10,830.78	0.2042	< 0.001	0.902	C1 = 20; C2 = 51; C3 = 85; C4 = 26; C5 = 10

AIC Akaike Information Criterion; *sBIC* Sample-Size Adjusted Bayesian Information Criterion; *LMRT* Lo-Mendell-Rubin Likelihood Ratio Test; *BLRT* Bootstrap Likelihood Ratio Test

model (LMR, $p = 0.0300$). The entropy was 0.904 which indicates clear profile separation.

To label the profiles, mean scores for all items within each profile were examined. It should be noted that men scored low in the sexual function EPIC subdomain across all three profiles (Fig. 1 and Table 2). The first group was labeled "high symptom burden" and included 11% of participants ($n = 21$). Men in this group reported worse symptoms of hormone deprivation and urinary dysfunction (lower scores in the hormonal and urinary domains),

a higher degree of sexual bother (lower score), and greater levels of pain (higher score) compared to the other profiles. The second group was labeled "high sexual bother" and included 40% of the sample ($n = 76$). Men in this group reported a higher degree of sexual bother (lower score), fewer symptoms of hormone deprivation and urinary dysfunction (higher scores in the hormonal and urinary domains), and lower levels of pain (low score). The third group was labeled "low symptom burden" and included 49% of the sample ($n = 95$). Men in this group reported fewer symptoms related to hormonal, urinary, and sexual domains (higher scores in the hormonal, urinary
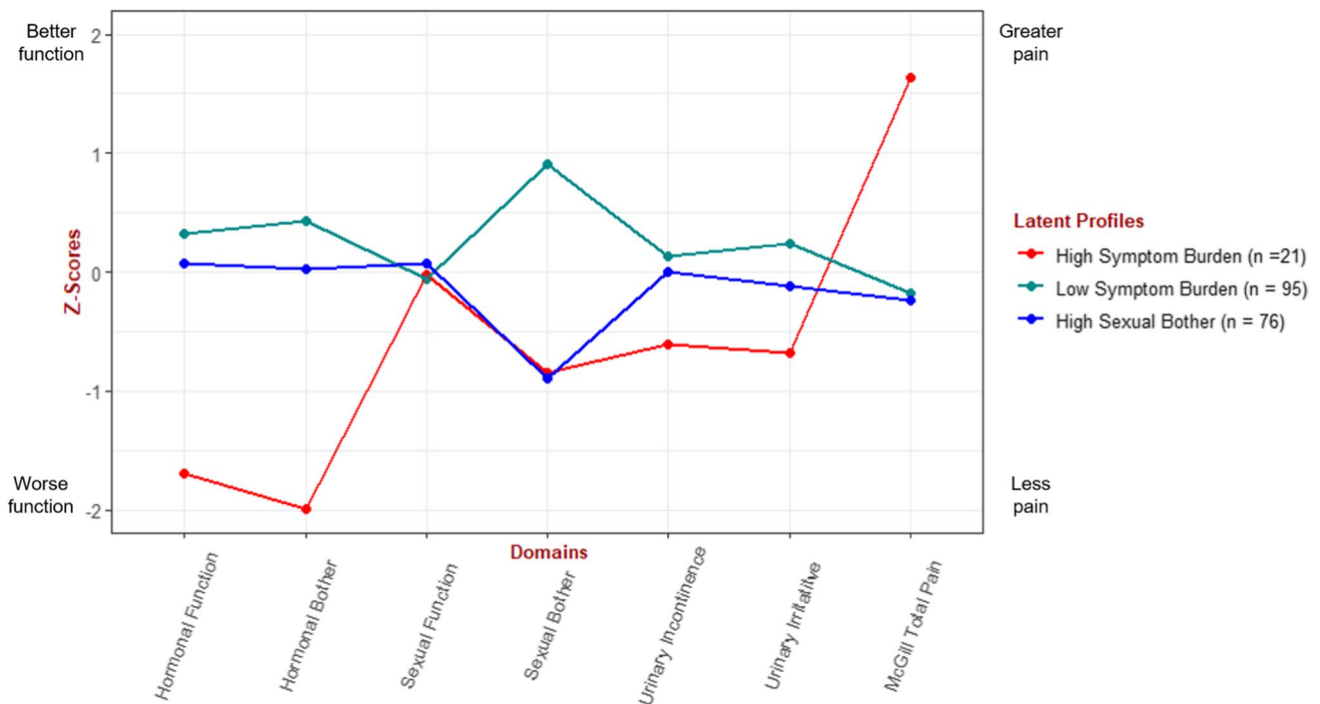

Fig. 1 Standardized conditional response means (z-scores) for symptom burden profiles

Table 2 Sample means and profile conditional response means

	Total ($n = 192$) M (se)	High symptom burden ($n = 21$) M (se)	High sexual bother ($n = 76$) M (se)	Low symptom burden ($n = 95$) M (se)
Expanded prostate index composite				
Hormonal function	68.66 (1.38)	36.85 (5.81)	70.08 (1.72)	74.81 (1.64)
Hormonal bother	84.81 (1.03)	56.45 (3.90)	85.09 (1.33)	90.88 (0.93)
Sexual function	12.44 (1.31)	11.99 (2.99)	13.78 (1.88)	11.45 (2.18)
Sexual bother	55.30 (2.91)	22.44 (6.41)	20.50 (2.50)	90.58 (1.80)
Urinary incontinence	73.79 (1.96)	57.37 (6.63)	73.93 (3.62)	77.24 (2.48)
Urinary irritative/obstructive	82.18 (0.96)	73.01 (3.34)	80.57 (1.58)	85.38 (1.40)
McGill total pain score	5.84 (0.54)	18.03 (2.47)	4.04 (0.67)	4.55 (0.60)

M mean; *SE* standard error

and sexual domains), and lower levels of pain (low score). We used the "low symptom burden" profile as the reference group.

Differences in demographic and medical characteristics

Overall, participants had a mean age of 68.7 ± 0.6 years. The majority were married (67%), non-Hispanic white (56%), and retired (57%). Almost 40% had completed some college or obtained further education and 46% reported an annual income less than $50,000 (Table 3). Regarding the medical characteristics, almost 40% had metastatic disease, 51% had a history of prostatectomy, 20% had received radiation therapy, and only 3% had received chemotherapy within the 6 months before the study. The majority were overweight or obese (78%) with a mean BMI of 28.8 ± 0.4 kg/m². Men with "high symptom burden" were younger (Mean Age $\pm$ SE $= 61.8 \pm 1.4$ years) compared to men with "high sexual bother" or "low symptom burden" (Table 2). Compared to men with "low symptom burden," men with "high symptom burden" and "high sexual bother" were more likely to have received radiation in the past 6 months. No other differences in sociodemographic or medical characteristics among symptom profiles were observed.

Differences in psychosocial measures

At baseline, men with "high symptom burden" reported higher levels of anxiety, stress, depression, cancer-specific distress, and lower levels of emotional well-being compared

Table 3 Demographic and clinical characteristics

	Total ($n=192$)	High symptom burden ($n=21$)	High sexual bother ($n=76$)	Low symptom burden ($n=95$)	p (overall test)
Study conditions, n (%)					0.908
HP	97 (50.50)	10 (48.60)	40 (52.70)	47 (49.30)	
CBSM	95 (49.50)	11 (51.40)	36 (47.30)	48 (50.70)	
Demographic characteristics					
Age, mean (SE)	68.71 (0.64)	61.82 (1.38)	67.77 (1.12)	70.98 (0.89)	**< .001**[a,b]
Race/ethnicity, n (%)					0.254
Non-Hispanic White	108 (56.25)	11 (52.38)	42 (55.26)	55 (57.89)	
Non-Hispanic Black	69 (35.94)	9 (42.86)	27 (35.53)	33 (34.74)	
Non-Hispanic-Other	8 (4.17)	1 (4.76)	2 (2.63)	5 (5.26)	
Hispanic/Latino	6 (3.13)	–	5 (6.58)	1 (1.05)	
Marital status, n (%)					0.527
Married or equivalent	128 (66.67)	12 (57.14)	51 (67.11)	65 (68.42)	
Education, n (%)					0.724
High school or less	60 (31.25)	9 (42.86)	22 (28.95)	29 (30.53)	
Some or completed college	75 (39.06)	8 (38.10)	29 (38.16)	38 (40.00)	
Graduate school	53 (27.60)	4 (19.05)	24 (31.58)	25 (26.32)	
Annual income, n (%)					0.361
Less than $50,000	89 (46.35)	13 (61.90)	31 (40.79)	45 (47.37)	
Occupation, n (%)					0.271
Working full/part time	74 (38.54)	7 (33.33)	31 (40.79)	36 (37.89)	
Unemployed	7 (3.65)	4 (19.05)	2 (2.63)	1 (1.05)	
Retired	110 (57.29)	10 (47.62)	43 (56.58)	57 (60.00)	
Medical characteristics					
Charlson Comorbidity Index, mean (SE)	1.39 (0.10)	2.00 (0.46)	1.29 (0.14)	1.33 (0.13)	0.317
BMI, mean (SE)	28.82 (0.37)	31.25 (1.34)	29.18 (0.60)	28.02 (0.53)	0.054
Metastatic disease, n (%)	74 (38.54)	7 (33.33)	23 (30.26)	44 (46.32)	0.070[c]
History of prostatectomy, n (%)	98 (51.04)	10 (47.62)	44 (57.89)	44 (46.32)	0.339
Received chemotherapy within past 6 months, n (%)	6 (3.13)	–	1 (1.32)	5 (5.26)	0.042
Received radiotherapy within past 6 months, n (%)	39 (20.31)	6 (28.57)	22 (28.95)	11 (11.58)	**0.001**[c]

Bold values denote statistical significance

BMI body mass index; *CBSM* Cognitive-Behavioral Stress Management intervention; *HP* health promotion program. Statistically significant p values between profiles ($p < .017$): a = High Symptom Burden group vs. High Sexual Bother group; b = High Symptom Burden group vs. Low Symptom Burden group; c = Low Symptom Burden group vs. High Sexual Bother group

to men with "high sexual bother" or "low symptom burden." In addition, men with "high symptom burden" reported higher levels of cognitive avoidance and lower levels of social well-being compared to men with "low symptom burden." Men with "high sexual bother" reported higher levels of anxiety, depression, and cognitive avoidance and lower levels of social well-being compared to men with "low symptom burden" (Table 4).

Six months after baseline, men with "high symptom burden" reported higher levels of anxiety, stress, depression, and cancer-specific distress as well as lower levels of emotional well-being compared to men with "high sexual

Table 4 Means and standard errors for psychosocial measures as a function of symptom burden profiles

	Symptom burden profiles	Baseline	Mean score	
			6 months after baseline	12 months after baseline
MAS: prostate cancer anxiety	High symptom burden	16.50 (2.02)	6.38 (1.74)	6.91 (1.97)
	High sexual bother	7.02 (0.98)	6.28 (0.97)	5.55 (1.06)
	Low symptom burden	3.78 (0.44)	4.23 (0.59)	3.42 (0.53)
	p (overall test)	**<.001**[a,b,c]	0.147[a,b]	0.068
PROMIS depression	High symptom burden	57.79 (1.55)	51.92 (2.32)	50.62 (2.52)
	High sexual bother	46.98 (0.89)	46.25 (0.99)	45.65 (1.03)
	Low symptom burden	43.51 (0.72)	44.58 (0.81)	45.08 (0.92)
	p (overall test)	**<.001**[a,b,c]	**0.009**[a,b]	0.118
Perceived stress scale	High symptom burden	24.21 (1.61)	20.08 (1.55)	20.25 (1.76)
	High sexual bother	16.77 (0.75)	16.15 (1.02)	14.74 (0.97)
	Low symptom burden	15.22 (0.71)	14.51 (0.75)	15.17 (0.79)
	p (overall test)	**<.001**[a,b]	**0.005**[a,b]	0.019[a,b]
FACT-G: social well-being	High symptom burden	18.27 (0.97)	20.73 (0.92)	20.26 (1.32)
	High sexual bother	19.97 (0.54)	20.48 (0.54)	20.90 (0.59)
	Low symptom burden	21.62 (0.44)	22.37 (0.52)	22.29 (0.48)
	p (overall test)	**0.002**[b c]	0.039[b,c]	0.114[c]
FACT-G: emotional well-being	High symptom burden	15.14 (1.42)	18.11 (1.31)	19.10 (1.36)
	High sexual bother	20.20 (0.45)	20.22 (0.50)	20.25 (0.61)
	Low symptom burden	21.38 (0.28)	21.42 (0.34)	20.99 (0.36)
	p (overall test)	**<.001**[a,b]	**<.015**[a,b]	0.277[b]
IES-R intrusions	High symptom burden	1.56 (0.16)	0.80 (0.13)	0.83 (0.17)
	High sexual bother	0.52 (0.06)	0.50 (0.08)	0.49 (0.08)
	Low symptom burden	0.32 (0.04)	0.31 (0.04)	0.28 (0.04)
	p (overall test)	**<.001**[a,b]	**0.001**[a,b,c]	**<.001**[b]
IES-R avoidance	High symptom burden	1.23 (0.20)	0.97 (0.16)	1.38 (0.25)
	High sexual bother	0.68 (0.07)	0.67 (0.10)	0.62 (0.11)
	Low symptom burden	0.52 (0.06)	0.51 (0.08)	0.49 (0.07)
	p (overall test)	**0.002**[b]	0.038[a,b]	**0.002**[a,b]
IES-R hyperarousal	High symptom burden	1.29 (0.20)	0.73 (0.15)	0.56 (0.14)
	High sexual bother	0.36 (0.05)	0.34 (0.05)	0.30 (0.06)
	Low symptom burden	0.20 (0.03)	0.20 (0.04)	0.19 (0.04)
	p (overall test)	**<.001**[a,b]	**<.001**[a,b,c]	0.021[b]
IES-R total score	High symptom burden	30.08 (3.45)	18.49 (2.64)	21.08 (3.48)
	High sexual bother	11.82 (1.29)	11.34 (1.52)	10.69 (1.56)
	Low symptom burden	7.86 (0.80)	7.78 (1.02)	7.25 (0.98)
	p (overall test)	**<.001**[a,b,c]	**<.001**[a,b,c]	**<.001**[a,b]

Bold values denote statistical significance

MAS Memorial Anxiety Scale; *PROMIS* Patient-Reported Outcome Measurement Information System; *FACT-G* Functional Assessment of Cancer Therapy-General; *IES-R* The Impact of Event Scale-Revised. Statistically significant *p* values between profiles (Bonferroni-adjusted $p < .017$): a = High Symptom Burden group vs. High Sexual Bother group; b = High Symptom Burden group vs. Low Symptom Burden group; c = Low Symptom Burden group vs. High Sexual Bother group

bother" and "low symptom burden" (Table 4). Moreover, men with "high symptom burden" and "high sexual bother" reported lower levels of social well-being compared to men with "low symptom burden."

Twelve months after baseline, men with "high symptom burden" reported higher levels of stress and cancer-specific distress compared to men with "high sexual bother" and "low symptom burden" (Table 4). Furthermore, men with "high symptom burden" reported lower levels of emotional well-being compared to men with "low symptom burden." Men with "high sexual bother" reported lower levels of social well-being compared to men with "low symptom burden."

Results from the latent growth models showed positive, but not significant associations of initial level and slopes across all target outcomes. Thus, our longitudinal data did not support the regression to the mean phenomenon. There were significant group-by-time interactions for the "high symptom burden" group on changes in anxiety, depression, emotional well-being, and cancer-specific distress scores after controlling for age, marital status, comorbidities, metastatic disease, and intervention group. (Table 5). Compared to men with "low symptom burden," men with "high symptom burden" demonstrated significant reductions in anxiety, depression, and cancer-specific distress as well as increases in emotional well-being over time. There were no significant group-by-time interactions among men with "high sexual bother" on psychosocial outcomes.

Discussion

Symptom burden has been understudied in men with advanced prostate cancer undergoing ADT. This study

Table 5 Multilevel modeling regression coefficients for each of the psychosocial outcomes

	MAS: prostate cancer anxiety b (se)	PROMIS depression b (se)	Perceived stress scale b (se)	FACT-G: social well-being b (se)	FACT-G: emotional well-being b (se)	IES-R intrusions b (se)	IES-R avoidance b (se)	IES-R hyper-arousal b (se)	IES-R: total score b (se)
Intercept	**3.90 (1.16)**	**42.79 (4.49)**	**13.16 (4.17)**	**23.27 (2.36)**	**18.51 (2.36)**	**0.91 (0.29)**	0.81 (0.41)	0.42 (0.25)	**16.42 (6.17)**
High symptom Burden group	**9.81 (1.68)**	**13.18 (1.92)**	**8.50 (1.76)**	**−3.26 (1.05)**	**−5.54 (0.98)**	**1.02 (0.13)**	**0.56 (0.18)**	**0.97 (0.11)**	**18.54 (2.64)**
High sexual bother group	**2.63 (1.04)**	**3.44 (1.20)**	1.79 (1.10)	**−2.22 (0.66)**	−1.30 (0.61)	0.19 (0.08)	0.18 (0.11)	0.16 (0.07)	**3.96 (1.65)**
Time	−0.12 (0.29)	**0.98 (0.40)**	0.06 (0.36)	0.26 (0.25)	−0.17 (0.17)	−0.02 (0.03)	−0.01 (0.04)	−0.01 (0.02)	−0.19 (0.55)
Time*high symptom burden	**−3.92 (0.71)**	**−4.11 (0.96)**	−1.45 (0.87)	0.45 (0.61)	**1.23 (0.41)**	**−0.33 (0.07)**	0.10 (0.09)	**−0.29 (0.06)**	**−3.47 (1.33)**
Time*high sexual bother	−0.58 (0.44)	−1.38 (0.59)	−0.89 (0.54)	0.18 (0.37)	0.08 (0.25)	−0.003 (0.04)	−0.03 (0.06)	−0.01 (0.04)	−0.33 (0.82)
CBSM intervention	1.55 (0.89)	0.41 (0.99)	0.60 (0.91)	**−1.28 (0.52)**	−0.50 (0.52)	0.07 (0.06)	0.11 (0.09)	0.04 (0.06)	1.72 (1.36)
Age	**−0.14 (0.06)**	−0.02 (0.06)	0.01 (0.06)	−0.02 (0.03)	0.07 (0.03)	**−0.01 (0.004)**	−0.01 (0.01)	−0.004 (0.003)	−0.16 (0.09)
Marital status	0.12 (0.96)	1.55 (1.06)	1.21 (0.98)	**1.70 (0.56)**	−1.01 (0.56)	−0.01 (0.07)	0.04 (0.10)	−0.02 (0.06)	0.18 (1.46)
Charlson Comorbidity Index	0.41 (0.34)	0.70 (0.37)	0.46 (0.34)	−0.15 (0.20)	−0.39 (0.20)	**0.06 (0.02)**	0.05 (0.03)	**0.05 (0.02)**	**1.26 (0.51)**
Metastatic disease	−1.21 (0.93)	−0.60 (1.04)	−1.00 (0.96)	−0.44 (0.55)	−0.60 (0.55)	−0.01 (0.07)	0.01 (0.09)	0.10 (0.06)	0.67 (1.43)

MAS Memorial Anxiety Scale; *PROMIS* Patient-Reported Outcome Measurement Information System; *FACT-G* Functional Assessment of Cancer Therapy-General; *IES-R* The Impact of Event Scale-Revised. Bold values indicate statistically significant regression coefficients (Bonferroni-adjusted $p < .017$). Reference group: "Low symptom burden." Age and Charlson Comorbidity Index were grand mean centered. Time was coded as 0, baseline; 1, 6 months after baseline; 2, 12 months after baseline; CBSM Intervention was coded as 1, received CBSM Intervention; 0, received HP; Marital Status was coded as 1, married or living equivalently; 0, not married; Metastatic Disease was coded as 1, metastatic disease; 0, non-metastatic disease

aimed to identify symptom burden profiles among men with advanced prostate cancer based on their EPIC scores for sexual, hormonal, and urinary symptoms, and their McGill Pain Questionnaire total score. We identified three symptom burden profiles: "high symptom burden", "high sexual bother" and "low symptom burden." Men with high symptom burden were younger and more likely to have received radiation in the past six months. They also exhibited higher baseline levels of anxiety, stress, depression, and cancer-specific distress as well as lower levels of emotional well-being when compared to men with high sexual bother and low symptom burden. In addition, men with high symptom burden demonstrated significant reductions in anxiety, depression, and cancer-specific distress as well as increases in emotional well-being over time.

Although ADT is associated with numerous deleterious physical and psychosocial effects, almost half of the men in this study reported low symptom burden. A possible explanation for this might be that men who have better physical functioning and were relatively healthier participated in the study. Previous studies examining factors associated with non-participation and dropout rates in clinical trials have shown that cancer survivors who are older adults with advanced cancer, poor general health status, poor social support, poor quality of life, low education and socioeconomic status are less willing to participate in research studies (Gebert et al., 2021; Roick et al., 2018). Other possible explanations are that these men had greater social support and self-efficacy which are associated with better symptom management (Paterson et al., 2015; Shelby et al., 2014; Zhou et al., 2010). Our study suggests that men with advanced prostate cancer who experience multiple co-occurring symptoms have worse psychosocial well-being. Greater prostate cancer- and treatment-related symptom burden may diminish men's ability to perform daily activities, restrict their participation in leisure activities and social interactions, affect their efficiency and productivity at work (or increase their odds of unemployment), and act as a constant reminder of their cancer diagnosis, which could lead to greater depression, anxiety, stress, and cancer-related distress (Wu & Harden, 2015). In addition, symptoms that are not well-managed may cause other serious adverse consequences, including non-compliance with treatment, increased health care utilization, and poor treatment satisfaction (Nipp et al., 2017; Numico et al., 2015). Therefore, identifying men with high symptom burden is crucial. Promising strategies to increase their identification include the integration of patient-reported outcomes into routine follow-up visits, improving patient-provider communication by prompting patients to communicate their symptoms, and promoting routine symptom monitoring (Gilbert et al., 2015).

A notable finding from this study is that men with "high symptom burden" were younger, consistent with prior research in prostate cancer (Dirksen et al., 2016). A possible explanation for this might be that younger men have better urinary and sexual functional scores at diagnosis than older patients, and therefore, they have higher expectations and feel more bothered as these functions decline (Hampson et al., 2015). In addition to physical symptoms, younger men diagnosed with advanced prostate cancer may experience more psychosocial distress than older men because they face more work-related difficulties, disruptions in family or marital relationships, and insurance and financial issues (Naughton & Weaver, 2014). Young men with advanced prostate cancer may be well served by an active symptom surveillance and timely referral to supportive care services. To better understand the relationship between age and symptom burden, future studies should take into account other important variables such as negative affect, financial burden, and cognitive function.

Men with high symptom burden and high sexual bother were more likely to have received radiation in the past 6 months compared to men with low symptom burden. Radiation therapy has been associated with sexual dysfunction, urinary obstructive symptoms, and persistent bowel symptoms (Alemozaffar et al., 2011; Martin & D'Amico, 2014). Furthermore, the concomitant use of ADT is an established risk factor for acute and late effects of radiation (Budäus et al., 2012). However, the severity of the symptoms is mostly driven by baseline function scores (Chen et al., 2009). Given that older adults with prostate cancer are less often treated with curative intent than younger patients (Lunardi et al., 2017; Vernooij et al., 2019), it is also plausible that younger men may report more side effects and treatment complications than older men. Although we were not able to identify other demographic or medical predictors of group membership, future studies should explore these associations in other racial/ethnic groups (e.g., Hispanics) and minority groups (e.g., men who have sex with men).

Compared to men with low symptom burden, men with advanced prostate cancer who experienced high sexual bother also reported higher levels of anxiety, depression, and cancer-related distress and lower levels of social well-being. These results are in line with those observed in previous studies (Benedict et al., 2014; Wittmann et al., 2009). Sexual bother may affect men's psychological well-being by threatening their sense of masculinity and contributing to low self-esteem and relationship difficulties (Benedict et al., 2014). This study highlights the importance of assessing sexual bother as part of routine clinical practice. Creating an accepting environment for men who are living with high sexual bother may increase the likelihood that they will openly discuss their concerns and seek help. Addressing sexual bother through psychosocial interventions may improve their distress related to sexual dysfunction as well as other social well-being outcomes.

The results of this study also demonstrate that men with high symptom burden show reductions in depression, anxiety, and cancer-related distress and increases in emotional well-being over time. We conducted latent growth models with the repeated measures of psychosocial outcomes to determine if regression toward the mean is plausible. Our longitudinal data did not support the regression to the mean phenomenon (Marsh & Hau, 2002). However, this finding should be interpreted with caution as all men enrolled in this study were randomized to one of two psychosocial interventions. This finding may suggest that this population could benefit from psychosocial interventions targeting self-management, social support, and positive lifestyle behaviors. Furthermore, both CBSM and HP included online group sessions which may have increased perceived social support and connectedness, and prompted group bond, trust, and support. Thus, this could explain the limited effects of the CBSM intervention in improving HRQOL when compared to the HP intervention, as well as the small number of men with high symptom burden that participated in this trial. Future trials may benefit from including National Cancer Institute-recommended patient-reported outcomes measures (Chen et al., 2014) as part of screening, in order to identify and enroll only those patients experiencing high symptom burden. In addition, although several pharmacological, psychological, and behavioral therapies have been developed to reduce physical and psychosocial side effects that manifest during prostate cancer survivorship, most of the psychosocial interventions have been tested in White older men with localized prostate cancer who are receiving curative treatments (Parahoo et al., 2015). Therefore, interventions that meet the needs of the advanced prostate cancer population as well as those of younger men and underrepresented racial/ethnic groups should be tested and offered.

This study contributes to a deeper understanding of cancer-related symptom burden in men with advanced prostate cancer who are undergoing ADT, however several limitations should be noted. First, participants were predominantly married and well-educated, which limits the generalizability of the findings. Second, the sample size may be considered small for latent profile analysis (Tein et al., 2013), which could lead to insufficient power to detect rare classes, convergence issues, or unstable solutions (Nylund-Gibson & Choi, 2018). However, there is no well-established rule of thumb regarding a minimum sample size that is appropriate for LPA, and previous methodological studies have suggested that simple models with well-separated classes can be conducted with a sample size as small as 30 (Nylund-Gibson & Choi, 2018). Importantly, although the advanced prostate cancer population is difficult to recruit (Parahoo et al., 2015), our study team was able to recruit a diverse sample of participants (36% non-Hispanic Black, 7% Other race/ethnicity), enroll the target number of participants needed for the trial, and attain an acceptable retention rate. Third, the low number of men in one of the subgroups warrants the replication of our findings in future, larger studies. The validation in a new sample from the same population is considered the strongest type of validation, however, the inclusion of covariates and class-predicted outcomes in the analysis can also validate the interpretation of the latent classes (Lubke & Luningham, 2017). Finally, although only validated and well-established instruments were administered in the present study, the collected data might be affected by self-report response bias.

Conclusions

In summary, our study contributes to the body of literature on the interrelationship between symptom burden and psychosocial well-being among men with advanced prostate cancer. The routine assessment of cancer-related symptoms and quality of life should be part of routine clinical practice to identify men who are at risk of experiencing high symptom burden. Patients with substantial symptom burden, particularly young men, may benefit from prompt referral to supportive care services.

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