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ORIGINAL RESEARCH

Anxiety and depression in patients with Philadelphia-negative myeloproliferative neoplasms: a nationwide population-based survey in Denmark

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Objective: We sought to determine the prevalence and severity of anxiety and depression among patients with Philadelphia-negative myeloproliferative neoplasms (MPNs) and respective associations of anxiety and depression with demographic and lifestyle factors, comorbidity burden, duration of MPN disease, financial difficulties, and health-related quality of life (QoL).

Methods: This study used data from a nationwide, population-based, cross-sectional survey of health-related QoL in MPN patients in Denmark called the MPNhealthSurvey. Individuals with a diagnosis of MPN in the National Patient Register were invited. The Hospital Anxiety and Depression Scale was used to assess the prevalence and severity of anxiety and depression. The associations of anxiety and depression with age, sex, education, body mass index (BMI), smoking, alcohol intake, physical activity, comorbidity burden, duration of MPN disease, financial difficulties, symptom burden, sexual problems, fatigue, functioning, and global health/QoL were examined.

Results: In total, 2,029 patients completed the Hospital Anxiety and Depression Scale. The prevalence of anxiety, depression, and both was 21%, 12%, and 8%, respectively. Many participants who reported anxiety or depression exhibited mild symptoms. Middle-aged and elderly participants had lower odds of experiencing anxiety and depression when compared to younger participants, and females had higher odds of anxiety compared to males. Participants with higher education had lower odds of anxiety compared to those with lower education. Current smokers and ex-smokers had higher odds of anxiety and depression compared to those who had never smoked, and sedentary participants and participants with a lower level of physical activity had higher odds of anxiety and depression compared to participants who performed hard training several times a week. Higher comorbidity burden increased the odds of depression, and greater financial difficulties increased the odds of anxiety and depression. Higher total symptom burden and fatigue burden and higher level of sexual problems increased the odds of anxiety and depression. Finally, lower functional level and global health/quality of life increased the odds of anxiety and depression. BMI, alcohol intake, comorbidity burden, and duration of disease were not substantially associated with anxiety, whereas sex, educational level, and duration of MPN disease were not substantially associated with depression.

Conclusion: There may be an unmet need in handling psychological distress in MPN patients. Future research might explore the utility of screening for psychological distress and the effectiveness of lifestyle interventions, rehabilitation, and MPN-symptom reduction in preventing and treating psychological distress.

Keywords: myeloproliferative neoplasm, anxiety, depression, health-related quality of life, patient-reported outcomes

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Introduction

The classical Philadelphia-negative myeloproliferative neoplasms (MPNs) include three diseases: essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF). In addition, some Philadelphia-negative MPNs are unclassifiable (MPN-U).[1,2] Bone-marrow transplantation can cure MPN, but very few patients are eligible for this treatment.[3] As such, MPNs are chronic diseases for the vast majority of patients. However, MPNs may develop into acute myeloid leukemia.[1]

For many MPN patients, living with one of these diseases entails burdensome symptoms, sexual concerns, financial difficulties, limited functioning in everyday life, and a reduced life span.[4–11] Struggling with health issues in everyday life and the prospect of possible symptom burden worsening, as well as reduced life span, may be psychologically challenging and cause psychological distress (here defined as symptoms of anxiety and/or depression).

Understanding the prevalence of anxiety and depression in MPN patients is crucial in determining how attentive health-care professionals must be in monitoring for the signs of these conditions. Moreover, knowledge of factors associated with anxiety and depression in MPN patients can help health-care professionals identify who might be particularly vulnerable patients, prevent development of anxiety and depression, and elucidate explanations for the presence of psychological distress in individual cases. However, to our knowledge, only two previous studies have explored anxiety and depression in MPN patients, both of them in patients with different disease duration. In an American single-center study from 2015, the prevalence of anxiety and depression was 31% and 13%, respectively, measured by the Hospital Anxiety and Depression Scale (HADS), in an MPN population consisting of 117 ET, PV, and MF patients.[12] In an international survey from 2014, the prevalence of depression was 23%, measured by the Patient Health Questionnaire 2, in 1,676 ET, PV, and MF patients.[6] In the latter study, associations were found between depression and younger age, lower educational level, high fatigue and total symptom burden, and impaired quality of life (QoL), while no association was found between depression and MPN subtype.

Given the scantiness of research on this topic, we saw a need for a robust survey investigating the prevalence and severity of anxiety and depression and factors associated with these conditions in a large population of MPN patients. The results from such a survey could help guide health-care professionals on how to detect, prevent, and treat anxiety and depression in these patients. In Denmark, MPN patients attend public hospitals. The health-care system is financed by taxes, and covers the treatment expenses for all hematological diseases. Diagnoses are recorded at hospitals and forwarded to the National Patient Register (NPR).[13,14] Furthermore, every resident in Denmark has a Civil Personal Register (CPR) number, which is linked to personal and demographic information in the CPR.[13,15] As a result of these practices, we were able to undertake a nationwide, population-based survey of anxiety and depression and factors associated with these conditions in MPN patients who had equal, cost-free access to the best available treatment for their hematological disease.

The present study aims to show the prevalence and severity of anxiety and depression in Philadelphia-negative MPN patients, based on the results of a nationwide, population-based, cross-sectional survey on health-related QoL conducted in Denmark called the MPNhealthSurvey. Furthermore, we sought to determine potential associations of anxiety and depression with demographic and lifestyle factors, comorbidity burden, duration of disease, financial difficulties, and health-related QoL in these participants.

Methods

The methods of the MPNhealthSurvey have been described in detail in a previously published article.[16] Here, we describe only the methods relevant to the investigation of anxiety and depression.

Participants

We identified individuals diagnosed with ET, PV, MF, or MPN-U based on the International Classification of Diseases (ICD) codes recorded in the NPR in Denmark between 1977 (when the NPR was created) and March 31, 2013, and who were alive on September 4, 2013, when the survey population was formed. The following MPN ICD-diagnosis codes were used: ICD8 287.29 and ICD10 D47.3 for ET, ICD8 208.99 and ICD10 D45 for PV, ICD8 209 and ICD10 D47.4 for MF, and ICD10 D47.1 for chronic myeloproliferative disease. The diagnosis of MPN had to be recorded at least once at a department of hematology or internal medicine that handles or had previously handled MPN patients. The ICD-diagnosis codes for inpatients have been registered in the NPR since its creation in 1977, while those for outpatients have been recorded from 1995.[14]

All individuals who met the aforementioned inclusion criteria were invited to participate in the survey, except those who were registered as protected from being contacted to participate in research or from having to disclose their address information. Patients' addresses were found in the CPR.[15] On September 11, 2013, a survey booklet, an envelope with a stamp, a code for logging into the online survey, and a cover letter were sent to all MPN patients who met the inclusion

criteria. Individuals were asked to complete and return the survey booklet or complete the same survey online. A reminder letter was dispatched to invited patients who had not responded to the survey before October 25. The survey period ended on December 31, 2013. All Philadelphia-negative participants in the MPNhealthSurvey who had not developed acute myeloid leukemia or undergone bone-marrow transplantation and who had completed the HADS questionnaire constitutes the population under study here.

Participant characteristics

Information on age and sex was retrieved from the CPR. Participants themselves provided information about their educational level and lifestyle, including smoking habits, weekly alcohol intake, and physical activity.[17–20] Participants were also asked to write down height and weight for the calculation of their body mass index (BMI). Comorbid diagnoses included all diagnoses registered in the NPR in the 5 years before September 4, 2013 and that are included in the Charlson Comorbidity Index (CCI).[21] MPN diagnoses were excluded when evaluating the comorbidity burden. The duration of disease was established as the time span between the date of the first registration of an MPN disease in the NPR and September 4, 2013.

Anxiety and depression assessment

Participants completed the HADS.[22,23] The HADS is a symptom-specific questionnaire originally developed to detect and examine the severity of symptoms of anxiety and depression in hospital outpatients; however, subsequent use has shown it to be a reliable questionnaire for measuring anxiety and depression in cancer settings.[24] It contains 14 items, with separate scales for anxiety and depression. Scores range from 0 to 21. A score <8 is interpreted as no anxiety/depression, 8–10 as mild anxiety/depression, 11–14 as moderate anxiety/depression, and 15–21 as severe anxiety/depression.[23]

Prevalence and severity of anxiety and depression

The prevalence of anxiety and depression was assessed for all participants who completed the HADS in the MPNhealthSurvey and for each subgroup of participants by MPN subtype. Furthermore, the prevalence of both anxiety and depression was assessed for both the total population and the MPN subgroups. Differences in prevalence between MPN subgroups were determined. The presence and severity of anxiety and depression, respectively, were explored using the aforementioned divisions of the two conditions into not present, mild, moderate, and severe as prescribed in the HADS manual.[23]

Factors associated with anxiety and depression

Examination of factors potentially associated with anxiety and depression was done on the total study population. To examine these associations, we used a HADS cutoff score of 8 to indicate anxiety and depression. Age, sex, education, lifestyle factors, comorbidity burden, duration of disease, financial difficulties, symptom burden, sexual problems, fatigue, functioning, and global health/QoL were investigated for potential associations with anxiety and depression. The presence of typical MPN symptoms was measured by the disease-specific MPN questionnaire called the MPN Symptom Assessment Form (MPN-SAF).[9] This tool was developed for use in combination with the Brief Fatigue Inventory, which measures fatigue related to cancer and the impact of this fatigue on daily living.[25] A total symptom score (TSS) was calculated based on certain prevalent symptoms measured by the MPN-SAF and Brief Fatigue Inventory, according to the MPN-SAF TSS manual.[26] Specifically, the MPN-SAF TSS was calculated from the following symptoms: worst level of fatigue during the last 24 hours, early satiety, abdominal discomfort, inactivity, concentration problems, night sweats, itching, bone pain, fever, and weight loss. The MPN-SAF TSS ranges from 0 to 100. A high score indicates a high symptom burden. Sexual problems were investigated using a single item in the MPN-SAF. This item score ranges from 0 to 10. A high number indicates a high level of sexual problems. Financial difficulties, fatigue, functioning, and global health/QoL were measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30):[27] functioning was subdivided into physical, role, cognitive, emotional, and social functioning according to the questionnaire manual. EORTC QLQ-C30 scores range from 0 to 100. A high score on the fatigue scale indicates a high fatigue burden. A high score on a functioning scale and the global health/QoL scale indicates better functioning and global health/QoL, respectively. Participants' symptom burden, sexual problems, fatigue, functioning, and global health/QoL scores are presented as quartiles.[28] Social functioning score is divided into three levels.

Confounders

Age, sex, and comorbidity were considered important confounders for anxiety and depression. Therefore, these were adjusted for when examining the associations of different factors with anxiety and depression in the MPN study population. MPN diagnoses were excluded when calculating the comorbidity burden, because in this study we wanted to

adjust for comorbid diseases when examining the factors associated with anxiety and depression related to the MPN.

Statistics

Frequency distributions and percentages for the different demographic and lifestyle factors, CCI, and disease duration were calculated for the total study population and for each MPN subgroup. In analyses of factors associated with anxiety and depression, the effects of age, sex, and CCI on anxiety and depression were tested in a multivariate model including all three covariates simultaneously, while the effects of the other factors on anxiety and depression were tested using separate logistic regression models, each adjusted for age, sex, and CCI. In analyses of the associations of anxiety and depression with symptom burden, sexual problems, fatigue, functioning, and global health/QoL, 25th quartile, median, and 75th quartile were used to divide the scores into different levels. Social functioning score was divided into three levels, because half the population had a score of 100. Odds ratios tend to overestimate proportion-ratios when events are rather frequent like anxiety and depression in this study. We therefore tried to carry out log-binomial regressions to estimate relative risks in place of odds ratios. However, the procedure for estimating relative risks in a log-binomial regression is more prone to numerical instability or lack of convergence, and we found that only in about half of our models we were able to get estimates and associated hessian matrices. Thus, while it might be preferable to use relative risks in lieu of odds ratios, we kept the odds ratios for consistency. R software 3.4.3 was employed for all statistical analyses.

Ethics

The Danish Data Protection Agency approved the survey (SJ-RO-02). Approval from the Committee on Health Research Ethics was not obligatory, and informed consent from the participants was not required (Committee Act section 14.2; National Committee on Health Research Ethics [Denmark] guidelines).[29]

Results

Response rate and participant characteristics

The MPNhealthSurvey had a response rate of 60% of the total population of patients with Philadelphia-negative MPN in Denmark registered in the NPR and eligible for participation. Of these participants, 2,029 (95%) completed the HADS, including 695 ET, 870 PV, 67 MF, and 397 MPN-U patients (Table 1). Participants' mean age was 68 years. More females than males completed the questionnaire (56% females, 44% males), and more participants were middle-aged than young or elderly (8% females and 7% males <50 years, 58% females and 60% males 50–75 years, and 34% females and 33% males >75 years). More participants had completed upper secondary/vocational school than either basic school or higher education (19% had completed basic school, 39% upper secondary/vocational school, 20% higher education, and 22% had not completed the answers to educational level). Many participants had a relatively healthy lifestyle. Half the participants had no or low comorbidity burden (50% had a CCI score of 0, 37% 1–2, and 13% ≥3). The majority of participants were not newly diagnosed with MPN: of note, patients diagnosed within half a year prior to the survey were not invited to participate (7% had been diagnosed for <1 year, 36% 1–4 years, and 57% ≥5 years).

Prevalence and severity of anxiety and depression

Anxiety was more prevalent than was depression (21% of the total population had anxiety, 12% depression, and 8% both; Table 2). The prevalence of anxiety was highest among participants with ET and lowest among those with MF (23% ET, 21% MPN-U, 19% PV, and 15% of MF participants reported anxiety). The prevalence of depression was highest among participants with ET and MPN-U and lowest among MF participants (13% ET, 13% MPN-U, 12% PV, and 6% MF participants reported depression). Most participants with anxiety reported mild anxiety (13% mild, 7% moderate, and 1% severe anxiety). A similar pattern was seen for depression (8% mild, 3% moderate, and 1% severe depression).

Factors associated with anxiety

Middle-aged and elderly participants had lower odds of anxiety compared to younger patients, while females had higher odds of anxiety compared to males (Table 3). Participants with higher education had lower odds of anxiety compared to those with lower education. Current smokers and ex-smokers had higher odds of anxiety compared to participants who had never smoked. Participants who were sedentary or less physically active had increased odds of anxiety compared to participants who reported performing hard training several times a week. Greater financial difficulties were associated with higher odds of anxiety. Higher total symptom burden and fatigue burden, and higher level of sexual problems, increased the odds of anxiety. Indeed, high symptom burden and high fatigue burden were strongly associated with anxiety. Generally, lower levels of functioning and lower global health/QoL

Table 1 Participant characteristics

	ET + PV + MF + MPN-U	ET	PV	MF	MPN-U
Total (n)	2,029	695	870	67	397
Age, years, mean (SD)	68.90 (12.37)	67.24 (13.30)	69.56 (11.52)	71.32 (12.74)	69.96 (12.15)
Sex, n (%)					
Female	1,146 (56)	441 (63)	435 (50)	34 (51)	236 (59)
Male	883 (44)	254 (37)	435 (50)	33 (49)	161 (41)
Female, n (%)					
<50	95 (8)	48 (11)	24 (6)	2 (6)	21 (9)
50–75	668 (58)	254 (58)	271 (62)	16 (47)	127 (54)
>75	383 (34)	139 (31)	140 (32)	16 (47)	88 (37)
Male, n (%)					
<50	64 (7)	26 (10)	29 (7)	2 (6)	7 (4)
50–75	528 (60)	156 (62)	257 (59)	20 (61)	95 (59)
>75	291 (33)	72 (28)	149 (34)	11 (33)	59 (37)
Education, n (%)					
Basic school	383 (19)	138 (20)	158 (18)	5 (8)	82 (21)
Upper secondary/vocational school	796 (39)	254 (37)	340 (39)	33 (49)	169 (43)
Higher education	412 (20)	142 (20)	175 (20)	18 (27)	77 (19)
Missing	438 (22)	161 (23)	197 (23)	11 (16)	69 (17)
BMI, n (%)					
<18.5	52 (3)	14 (2)	23 (3)	2 (3)	13 (3)
≤18.5–<25.0	1,034 (51)	370 (53)	431 (49)	33 (49)	200 (50)
≤25.0–<30.0	615 (30)	208 (30)	270 (31)	20 (30)	117 (30)
≥30	261 (13)	78 (11)	119 (14)	10 (15)	54 (14)
Missing	67 (3)	25 (4)	27 (3)	2 (3)	13 (3)
Smoking, n (%)					
Yes	360 (18)	125 (18)	149 (17)	9 (13)	77 (19)
Ex-smoker	895 (44)	295 (42)	398 (46)	30 (45)	172 (43)
No	722 (36)	262 (38)	298 (34)	25 (37)	137 (35)
Missing	52 (2)	13 (2)	25 (3)	3 (5)	11 (3)
Alcohol, units, n (%)					
≤7	1,379 (68)	464 (67)	575 (66)	44 (66)	296 (74)
≤8–≤14	353 (17)	136 (19)	155 (18)	12 (18)	50 (13)
≤15–≤21	148 (7)	53 (8)	65 (7)	4 (6)	26 (7)
≤22	141 (7)	37 (5)	73 (8)	6 (9)	25 (6)
Missing	8 (1)	5 (1)	2 (1)	1 (1)	0
Physical activity, n (%)					
Hard training and competitive sports several times a week	106 (5)	51 (7)	37 (4)	2 (3)	16 (4)
Training, heavy garden work, or similar ≥4 times a week	403 (20)	150 (22)	177 (20)	12 (18)	64 (16)
Walking, cycling, light garden work, or similar ≥4 times a week	946 (47)	326 (47)	409 (47)	22 (33)	189 (48)
Reading, watching tv, or other sedentary work	472 (23)	142 (20)	200 (23)	24 (36)	106 (27)
Missing	102 (5)	26 (4)	47 (6)	7 (10)	22 (5)
Comorbidity, CCI score					
Mean (SD)	1.10 (1.67)	0.94 (1.54)	1.16 (1.68)	1.39 (2.17)	1.17 (1.77)
0, n (%)	1,016 (50)	379 (54)	416 (48)	35 (52)	186 (47)
1–2, n (%)	742 (37)	241 (35)	321 (37)	18 (27)	162 (41)
≥3, n (%)	271 (13)	75 (11)	133 (15)	14 (21)	49 (12)
Duration of disease, n (%)					
<1 year	150 (7)	48 (7)	45 (5)	26 (39)	31 (8)
1–4 years	729 (36)	250 (36)	274 (32)	28 (42)	177 (44)
≥5 years	1,150 (57)	397 (57)	551 (63)	13 (19)	189 (48)

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; ET, essential thrombocythemia; MF, myelofibrosis; MPN-U, myeloproliferative neoplasm – unclassifiable; PV, polycythemia vera.

were associated with higher odds of anxiety. BMI, alcohol intake, comorbidity burden, and duration of disease were not substantially associated with anxiety.

Factors associated with depression

Middle-aged and elderly participants had lower odds of depression compared to younger patients (Table 4). Lifestyle

Table 2 Prevalence and severity of anxiety and depression

HADS	Total, n=2,029	ET, n=695	PV, n=870	MF, n=67	MPN-U, n=397
Anxiety, n (%)					
Not present (score 0–7)	1,603 (79)	533 (77)	701 (81)	57 (85)	312 (79)
Present (score 8–21)	426 (21)	162 (23)	169 (19)	10 (15)	85 (21)
Mild (score 8–10)	264 (13)	108 (16)	92 (11)	9 (13)	55 (14)
Moderate (score 11–14)	134 (7)	44 (6)	65 (7)	0	25 (6)
Severe (score 15–21)	28 (1)	10 (1)	12 (1)	1 (2)	5 (1)
Depression, n (%)					
Not present (score 0–7)	1,781 (88)	606 (87)	765 (88)	63 (94)	347 (87)
Present (score 8–21)	248 (12)	89 (13)	105 (12)	4 (6)	50 (13)
Mild (score 8-10)	164 (8)	69 (10)	68 (8)	2 (3)	25 (7)
Moderate (score 11–14)	67 (3)	15 (2)	29 (3)	2 (3)	21 (5)
Severe (score 15–21)	17 (1)	5 (1)	8 (1)	0	4 (1)
Both anxiety and depression, n (%)					
Not present (score 0–7)	1,863 (92)	634 (91)	798 (92)	66 (99)	365 (92)
Present (score 8–21)	166 (8)	61 (9)	72 (8)	1 (1)	32 (8)

Abbreviations: ET, essential thrombocythemia; HADS, Hospital Anxiety and Depression Scale; MF, myelofibrosis; MPN-U, myeloproliferative neoplasm – unclassifiable; PV, polycythemia vera.

factors were associated with depression: current smokers had higher odds of depression compared to participants who had never smoked, and a similar tendency was seen for ex-smokers; sedentary participants had higher odds of depression compared to those who were physically active; excessive alcohol intake (≥22 units per week) was associated with higher odds of depression compared to a lower intake, but moderate to high alcohol intake (8–21 units per week) was associated with lower odds of depression compared to low alcohol intake (≤7 units per week). BMI was not significantly associated with depression. Higher comorbidity burden increased the odds of depression, as did greater financial difficulties. Higher total symptom burden, higher level of sexual problems, and higher fatigue burden increased the odds of depression compared to lower symptom burden, lower level of sexual problems, and lower fatigue burden. Of these, high symptom burden and high fatigue burden had particularly strong associations with depression. Lower levels of functioning in general were associated with higher odds of depression compared to higher levels of functioning: the lower the functioning level, the higher the odds of depression. Low global health/QoL was remarkably strongly associated with depression compared to high global health/QoL. Sex, educational level, and duration of MPN disease were not substantially associated with depression.

Discussion

In this nationwide, population-based, cross-sectional survey, 2,029 participants with Philadelphia-negative MPNs completed the HADS, and self-reported prevalence of anxiety and depression was 21% and 12%, respectively. Mild forms of these conditions were far more prevalent than moderate or severe forms. When prevalence by MPN subgroup was compared, ET participants reported the highest and MF participants the lowest prevalence of anxiety, whereas ET and MPN-U participants reported the highest and MF participants the lowest prevalence of depression. However, differences between the MPN subgroups were minor. Middle-aged and elderly participants had lower odds of anxiety and depression than younger participants. Female sex was associated with higher odds of anxiety compared to male sex. Participants with higher education had lower odds of anxiety compared to those with lower education. Current smokers and ex-smokers had higher odds of anxiety and depression compared to those who never smoked, participants who were sedentary or less physically active had increased odds of anxiety and depression, and excessive alcohol intake was associated with higher odds of depression, whereas a moderate to high alcohol intake was actually associated with lower odds of depression. Higher comorbidity burden was associated with higher odds of depression, and greater financial difficulties increased the odds of anxiety and depression. Higher total symptom burden, higher level of sexual problems, and higher fatigue burden were associated with higher odds of anxiety and depression. Notably, high symptom burden and fatigue burden were very strongly associated with depression. Generally, lower level of functioning and lower global health/QoL were associated with higher odds of anxiety and depression. BMI, alcohol intake, comorbidity burden, and duration of disease were not substantially associated with anxiety, whereas sex, educational level, and duration of MPN disease were not substantially associated with depression.

Table 3 Factors associated with anxiety

	OR (95% CI)*
Demographics	
Age, years	
<50	Reference
50–75	0.37 (0.26–0.53)
>75	0.31 (0.21–0.46)
Sex	
Male	Reference
Female	1.62 (1.29–2.03)
Education	
Basic school	Reference
Upper secondary/vocational school	0.62 (0.46–0.83)
Higher education	0.70 (0.50–0.98)
Lifestyle	
BMI	
<18.5	Reference
≤18.5–<25.0	1.15 (0.58–2.47)
≤25.0–<30.0	0.98 (0.49–2.14)
≥30.0	1.27 (0.62–2.84)
Smoking	
No	Reference
Ex-smoker	1.31 (1.01–1.70)
Yes	2.32 (1.72–3.14)
Alcohol, units	
≤7	Reference
≤8–≤14	0.91 (0.67–1.22)
≤15–≤21	0.92 (0.57–1.42)
≤22	1.03 (0.64–1.61)
Physical activity	
Hard training and competitive sports several times a week	Reference
Training, heavy garden work, or similar ≥4 times a week	1.69 (0.91-3.35)
Walking, cycling, light garden work, or similar ≥4 times a week	1.96 (1.09-3.81)
Reading, watching tv, or other sedentary work	3.15 (1.69-6.26)
Comorbidity	
CCI score 0	Reference
CCI score 1–2	1.04 (0.82–1.32)
CCI score ≥3	1.17 (0.82–1.63)
Duration of MPN disease	
<1 year	Reference
1–4 years	1.37 (0.87–2.24)
≥5 years	1.49 (0.96–2.42)
Financial difficulties (EORTC QLQ-C30)	
Not at all	Reference
A little	3.71 (2.74–5.00)
Quite a bit	4.43 (2.79–7.00)
Very much	6.45 (3.65–11.54)
Health-related quality of life	
Symptom burden (MPN-SAF TSS)	
Score 0–7	Reference
Score 8–17	4.68 (2.60–9.07)
Score 18–30	12.46 (7.14–23.60)
Score 31–100	36.24 (21.04–68.07)
Sexual problems (MPN-SAF)	
Score 0	Reference
Score 1–2	2.14 (1.44–3.16)
Score 3–7	3.02 (2.20–4.17)
Score 8–10	5.92 (4.31–8.19)
Fatigue (EORTC QLQ-C30)	
Score 0–11.11	Reference
Score 11.12–33.33	4.05 (2.46–7.04)
Score 33.34–55.56	15.13 (9.19–26.33)
Score 55.57–100	29.41 (17.82–51.34)
Physical functioning (EORTC QLQ-C30)	
Score 93.34–100	Reference
Score 80.01–93.33	1.72 (1.19–2.50)
Score 60.01–80.00	3.76 (2.66–5.36)
Score 0–60.00	7.20 (5.07–10.34)
Role functioning (EORTC QLQ-C30)	
Score 100	Reference
Score 83.34–99.99	2.29 (1.48–3.50)
Score 66.68–83.33	4.40 (3.15–6.17)
Score 0–66.67	9.64 (7.04–13.34)
Emotional functioning (EORTC QLQ-C30)	
Score 100	Reference
Score 83.34–99.99	3.20 (1.56–7.05)
Score 66.68–83.33	21.25 (11.52-43.86)
Score 0–66.67	144.89 (78.31–300.30)
Cognitive functioning (EORTC QLQ-C30)	
Score 100	Reference
Score 83.34–99.99	2.91 (2.00–4.28)
Score 66.68–83.33	8.42 (5.75–12.52)
Score 0–66.67	18.39 (12.66–27.18)
Social functioning (EORTC QLQ-C30)	
Score 100	Reference
Score 66.68–99.99	4.43 (3.35–5.89)
Score 0–66.67	13.43 (9.78–18.56)
Global health/quality of life (EORTC QLQ-C30)	
Score 83.33–100	Reference
Score 66.67–83.32	3.74 (2.48–5.70)
Score 50.00–66.66	9.59 (6.58–14.24)
Score 0–49.99	22.73 (15.54–33.93)

Notes: Symptom burden, sexual problems, fatigue, functioning, and global health/quality-of-life scores presented as quartiles; social functioning score divided into three levels, because half the population had a score of 100. *Adjusted for age, sex, and comorbidity.

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; MPN, myeloproliferative neoplasm; MPN-SAF: Myeloproliferative Neoplasm Symptom Assessment Form; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; OR, odds ratio.

Higher age might at least partly explain the lowest prevalence of psychological distress among MF participants compared to participants with other MPN subtypes.

In the American study by McFarland et al, the prevalence of anxiety was 31% in MPN patients, higher than in the

Table 4 Factors associated with depression

	OR (95% CI)*
Demographics	
Age, years	
<50	Reference
50–75	0.44 (0.29–0.68)
>75	0.41 (0.26–0.66)
Sex	
Male	Reference
Female	0.88 (0.67–1.15)
Education	
Basic school	Reference
Upper secondary/vocational school	0.75 (0.52–1.09)
Higher education	0.72 (0.47–1.10)
Lifestyle	
BMI	
<18.5	Reference
≤18.5–<25.0	0.99 (0.44–2.64)
≤25.0–<30.0	1.04 (0.45–2.80)
≥30.0	1.11 (0.47–3.08)
Smoking	
No	Reference
Yes	1.98 (1.37–2.86)
Ex-smoker	1.23 (0.89–1.71)
Alcohol, units	
≤7	Reference
≤8–≤14	0.65 (0.43–0.95)
≤15–≤21	0.42 (0.19–0.80)
≤22	1.16 (0.69–1.87)
Physical activity	
Hard training and competitive sports several times a week	Reference
Training, heavy garden work, or similar ≥4 times a week	0.91 (0.45–1.94)
Walking, cycling, light garden work or similar ≥4 times a week	1.10 (0.58–2.27)
Reading, watching tv, or other sedentary work	3.05 (1.58–6.43)
Comorbidity	
CCI score 0	Reference
CCI score 1–2	1.39 (1.03–1.86)
CCI score ≥3	1.55 (1.02–2.31)
Duration of MPN disease	
<1 year	Reference
1–4 years	0.82 (0.51–1.38)
≥5 years	0.75 (0.47–1.25)
Financial difficulties (EORTC QLQ-C30)	
Not at all	Reference
A little	3.02 (2.10–4.29)
Quite a bit	5.06 (3.06–8.20)
Very much	7.78 (4.31–13.89)
Health-related quality of life	
Symptom burden (MPN-SAF TSS)	
Score 0–7	Reference
Score 8–17	13.77 (4.09–85.75)
Score 18–30	40.40 (12.55–247.21)
Score 31–100	113.70 (35.89–691.24)
Sexual problems (MPN-SAF)	
Score 0	Reference
Score 1–2	1.10 (0.62–1.89)
Score 3–7	2.47 (1.67–3.68)
Score 8–10	4.73 (3.25–6.96)
Fatigue (EORTC QLQ-C30)	
Score 0–11.11	Reference
Score 11.12–33.33	12.09 (3.64–74.85)
Score 33.34–55.56	63.31 (19.65–387.48)
Score 55.57–100	170.69 (53.36–1042.0)
Physical functioning (EORTC QLQ-C30)	
Score 93.34–100	Reference
Score 80.01–93.33	5.20 (2.88–9.82)
Score 60.01–80.00	10.50 (6.00–19.44)
Score 0–60.00	25.07 (14.42–46.34)
Role functioning (EORTC QLQ-C30)	
Score 100	Reference
Score 83.34–99.99	3.57 (1.88–6.73)
Score 66.68–83.33	6.56 (3.96–11.19)
Score 0–66.67	20.10 (12.73–33.17)
Emotional functioning (EORTC QLQ-C30)	
Score 100	Reference
Score 83.34–99.99	2.55 (1.05–6.79)
Score 66.68–83.33	10.71 (5.11–26.18)
Score 0–66.67	74.49 (36.96–177.92)
Cognitive functioning (EORTC QLQ-C30)	
Score 100	Reference
Score 83.34–99.99	2.04 (1.13–3.83)
Score 66.68–83.33	7.95 (4.60–14.43)
Score 0–66.67	34.19 (20.66–60.11)
Social functioning (EORTC QLQ-C30)	
Score 100	Reference
Score 66.68–99.99	6.44 (4.23–10.05)
Score 0–66.67	28.08 (18.50–43.81)
Global health/quality of life (EORTC QLQ-C30)	
Score 83.33–100	Reference
Score 66.67–83.32	14.18 (5.49–48.28)
Score 50.00–66.66	50.09 (20.58–165.43)
Score 0–49.99	131.92 (54.67–433.74)

Notes: Symptom burden, sexual problems, fatigue, functioning, and global health/quality of life scores presented as quartiles; social functioning score divided into three levels, because half the population had a score >100. *Adjusted for age, sex, and comorbidity.

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; MPN, myeloproliferative neoplasm; MPN-SAF: Myeloproliferative Neoplasm Symptom Assessment Form; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; OR, odds ratio.

MPNhealthSurvey,[12] and the prevalence of depression was found to be 13%, fairly similar to the MPNhealthSurvey. In the international survey by Scherber et al, the prevalence of depression was as high as 23% in MPN patients.[6] The preva-

lence of anxiety and depression in the MPNhealthSurvey was found to be quite similar to those found in a meta-analytically pooled prevalence of 18% for anxiety and 12% for depression found in long-term cancer survivors.[30] The prevalence of depression in the MPNhealthSurvey was also roughly equal with that found in a meta-analysis of cancer patients from hematological and oncological settings,[31] with 16% prevalence for depression, but only 10% for anxiety. Among these previous studies, that by McFarland et al[12] and certain studies presented in the meta-analysis by Mitchell et al[30,31] used the HADS, like the MPNhealthSurvey, whereas in the study by Scherber et al[6] and several of the studies in the meta-analysis, other tools were used to estimate the prevalence of anxiety and depression. These different approaches to measuring anxiety and depression make comparing results among these studies difficult. Furthermore, because MPN patients are chronic cancer patients, their disease trajectory differs from that of cancer patients with a fulminant trajectory, cancer patients who can potentially be cured, and long-term survivors. It is nevertheless interesting to compare anxiety and depression among MPN participants in the MPNhealthSurvey with patients included in the meta-analyses, particularly in terms of how burdened MPN participants were from anxiety and depression compared to cancer patients with other disease trajectories. Among respondents to the MPNhealthSurvey, prevalence of anxiety, in particular, but also that of depression, was closer to prevalence rates found in long-term cancer survivors than those found in patients with a hematological or oncological disease currently in a hospital setting. Potentially, this is because the uncertainty involved with the risk of disease relapse among long-term cancer survivors and the risk of disease progression in MPN patients, as well as the burden of sequelae in long-term cancer survivors and the burden of symptoms in MPN patients, are comparable in terms of mental strain. In a large Swedish study of the general population of 6,659 individuals by Djukanovic et al, prevalence of anxiety was 11%, whereas that of depression was 10%.[32] The mean age of the general population in the Swedish study was higher than was that of the population in the MPNhealthSurvey (71.2 vs 68.9 years), and the youngest participant in the Swedish study was 65 years, whereas in the MPNhealthSurvey some participants were in their 20s. In the MPNhealthSurvey, higher age was associated with lower odds of anxiety and depression. A comparison of the prevalence of psychological distress in the general population in the Swedish study and the population in the MPNhealthSurvey suggests that notably more MPN patients suffer from anxiety compared to the general population, whereas slightly more individuals in the general population suffer from depression compared to MPN patients. However, the difference in mean age and age span in the populations might mean that the actual difference in psychological distress is somewhat different than what we find by comparing the prevalence of psychological distress in these two populations.

In the studies by McFarland et al[12] and Scherber et al,[6] MPN subtype was not associated significantly with anxiety or depression. The findings of the MPNhealthSurvey support these findings. Similarly, Scherber et al found younger age, higher fatigue and total symptom burden, and reduced QoL were associated with depression,[6] which is supported by the results of this study.

The strengths and limitations of the MPNhealthSurvey have been outlined in detail in a previously published article on its survey design and the characteristics of respondents and nonrespondents.[16] They are summarized in the following. There were major strengths regarding selection bias in our survey. First, MPN patients invited to participate in this survey had equal access to treatment for their hematological disease, because all Danish MPN patients attend public hospitals offering cost-free treatment of MPN financed by taxes. In contrast, however, costs related to medical treatment of psychological distress are partly paid by patients, possibly with attendant inequalities. Second, the survey was nationwide and population-based. The unique NPR and CPR register in Denmark made this survey design possible. Third, patients could participate in the survey by returning a questionnaire booklet with a prepaid return envelope or completing the survey online. These elements of the survey design might have reduced selection bias notably and ensured a large population for investigation. Another strength of this survey is that it used the validated HADS questionnaire, which measures anxiety and depression, and involved a comprehensive investigation of the associated factors of anxiety and depression using questionnaires and additional questions covering lifestyle, as well as comorbidity information from the NPR. To our knowledge, no previous survey has reported a similar design or a similar large number of participants. Finally, another strength was that we considered MPN-U patients in the investigation of anxiety and depression, which has not previously been done.

There are limitations of this survey. First, we assume that some misclassified diagnoses are registered in the NPR. This would have an impact on the number of participants in each MPN subgroup by subclassification and on participants' comorbidities. Second, the survey was cross-sectional. A prospective survey of psychological distress in Philadelphia-

negative MPN patients might have provided more reliable estimations of the prevalence of anxiety and depression and explanations for some of the associations, eg, whether fatigue causes psychological distress or vice versa and whether limited physical activity causes psychological distress or vice versa. Third, anxiety and depression were assessed using a self-report questionnaire, rather than by a diagnostic interview, which is the gold standard for assessment of psychological distress.[33] The HADS has been shown to have assessment capability inferior to a diagnostic interview. Furthermore, patients with symptoms might be overrepresented among respondents compared to patients with no symptoms, because the former might be more interested in research related to their condition. On the other hand, the 120 questions within the survey might have been overwhelming for some patients, such as those with psychological distress and high symptom burden, and the elderly, which might explain some nonresponses. In addition, sexual problems were assessed using one single item from the MPN-SAF questionnaire, and translation of the MPN-SAF into Danish was performed according to international recommendations; however, no validation of the questionnaire translated into Danish was performed. Finally, we did not adjust for living arrangements in our analysis of the factors associated with psychological distress, and this variable might have influenced the results. We had information on marital status from the CPR register, but since relatively many couples in Denmark are cohabitant without being married, we found adjustment for marital status insufficient in these analyses.

The reason patients diagnosed with MPN between March 31, 2013 and September 4, 2013 were not included in this survey was that we could not ethically justify contacting these newly diagnosed patients by postal mail regarding a survey of this type. Likewise, we could not ethically justify sending more than one reminder to these cancer patients.

Nevertheless, the findings do allow us to make some suggestions for clinical practice and research. First, we suggest that outpatient hematological clinics be alert to anxiety and depression among MPN patients. We believe there may be unmet needs in the detection of and treatment and support in handling anxiety and depression in a considerable number of MPN patients.[34] Regular assessment of potential psychological distress via diagnostic interview would be optimal. However, this might not be possible, due to the limited psychologist resources in hematological outpatient clinics. As such, an alternative would be regular screening for anxiety and depression, eg, using the HADS to help identify signs of anxiety and depression early in the psychological distress trajectory. Second, we suggest that medical staff pay attention not only to signs of anxiety and depression but also their related factors to better detect and help vulnerable patients. An unhealthy lifestyle, reduced functioning, and a high symptom burden were all associated with psychological distress. Therefore, lifestyle interventions, rehabilitation, and symptom reduction might be essential for the prevention and at least as a part of treatment of anxiety and depression in MPN patients. Future research could fruitfully explore the utility of such interventions.

Author contributions

ADZ, NB, HCH, KJ, EMF, and CLA conceptualized and designed the survey. NB organized the survey, in collaboration with AIC and ADZ. NB, NR, and ADZ performed the analysis of the results related to HADS presented in this article. MB evaluated MPN and comorbidity diagnoses in the NPR for inclusion in CCI calculation. EMF carried out the statistical analyses. NB drafted the manuscript. All authors contributed toward data analysis, drafting and critically revising the manuscript, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Campbell PJ, Green AR. The myeloproliferative disorders. *N Engl J Med*. 2006;355(23):2452–2466.
2. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391–2405.
3. Geyer HL, Mesa RA. Therapy for myeloproliferative neoplasms: when, which agent, and how? *Blood*. 2014;124(24):3529–3537.
4. Mesa R, Miller CB, Thyne M, et al. Myeloproliferative neoplasms (MPNs) have a significant impact on patients' overall health and productivity: the MPN Landmark survey. *BMC Cancer*. 2016;16:167.
5. Geyer HL, Andreasson B, Kosiorek HE, et al. The role of sexuality symptoms in myeloproliferative neoplasm symptom burden and quality of life: An analysis by the MPN QOL International Study Group. *Cancer*. 2016;122(12):1888–1896.
6. Scherber RM, Kosiorek HE, Senyak Z, et al. Comprehensively understanding fatigue in patients with myeloproliferative neoplasms. *Cancer*. 2016;122(3):477–485.
7. Anderson LA, James G, Duncombe AS, et al. Myeloproliferative neoplasm patient symptom burden and quality of life: evidence of significant impairment compared to controls. *Am J Hematol*. 2015; 90(10):864–870.

8. Abelsson J, Andréasson B, Samuelsson J, et al. Patients with polycythemia vera have worst impairment of quality of life among patients with newly diagnosed myeloproliferative neoplasms. *Leuk Lymphoma*. 2013;54(10):2226–2230.
9. Scherber R, Dueck AC, Johansson P, et al. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF): international prospective validation and reliability trial in 402 patients. *Blood*. 2011;118(2):401–408.
10. Tefferi A, Guglielmelli P, Larson DR, et al. Long-term survival and blast transformation in molecularly annotated essential thrombocythemia, polycythemia vera, and myelofibrosis. *Blood*. 2014;124(16):2507–2513.
11. Hultcrantz M, Kristinsson SY, Andersson TM, et al. Patterns of survival among patients with myeloproliferative neoplasms diagnosed in Sweden from 1973 to 2008: a population-based study. *J Clin Oncol*. 2012;30(24):2995–3001.
12. Mcfarland DC, Polizzi H, Mascarenhas J, Kremyanskaya M, Holland J, Hoffman R. Psychological Symptoms Among Patients With BCR-ABL-Negative Myeloproliferative Neoplasms. *J Natl Compr Canc Netw*. 2016;14(12):1563–1570.
13. Erlangsen A, Fedyszyn I. Danish nationwide registers for public health and health-related research. *Scand J Public Health*. 2015;43(4):333–339.
14. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449–490.
15. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541–549.
16. Brochmann N, Flachs EM, Christensen AI, et al. A nationwide population-based cross-sectional survey of health-related quality of life in patients with myeloproliferative neoplasms in Denmark (MPNhealthSurvey): survey design and characteristics of respondents and nonrespondents. *Clin Epidemiol*. 2017;9:141–150.
17. Christensen AI, Ekholm O, Glümer C, et al. The Danish National Health Survey 2010. Study design and respondent characteristics. *Scand J Public Health*. 2012;40(4):391–397.
18. Matthiessen J, Biltoft-Jensen A, Rasmussen LB, Hels O, Fagt S, Groth MV. Comparison of the Danish Physical Activity Questionnaire with a validated position and motion instrument. *Eur J Epidemiol*. 2008;23(5):311–322.
19. Ekholm O, Strandberg-Larsen K, Christensen K, Grønbaek M. Comparison of assessment methods for self-reported alcohol consumption in health interview surveys. *Eur J Clin Nutr*. 2008;62(2):286–291.
20. Zierau F, Hardt F, Henriksen JH, et al. Validation of a self-administered modified CAGE test (CAGE-C) in a somatic hospital ward: comparison with biochemical markers. *Scand J Clin Lab Invest*. 2005;65(7):615–622.
21. Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–383.
22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361–370.
23. Snaith RP. Zigmond AS. *The Hospital Anxiety and Depression Scale Manual.* London: GL Assessments; 1994.
24. Moorey S, Greer S, Watson M, et al. The factor structure and factor stability of the hospital anxiety and depression scale in patients with cancer. *Br J Psychiatry*. 1991;158:255–259.
25. Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer*. 1999;851(5):1186–1196.
26. Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. *J Clin Oncol*. 2012;30(33):4098–4103.
27. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365–376.
28. Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative (MPN) Symptom Burden Response Thresholds: Assessment Of MPN-SAF TSS Quartiles As Potential Markers Of Symptom Response. *Blood American Society of Hematology Annual Meeting Abstracts*. 2013;122:4067.
29. The National Committee on Health Research Ethics. Guidelines. Available from: www.dnvk.dk/CVK/Home/English.aspx. Accessed January 10, 2018.
30. Mitchell AJ, Ferguson DW, Gill J, Paul J, Symonds P. Depression and anxiety in long-term cancer survivors compared with spouses and healthy controls: a systematic review and meta-analysis. *Lancet Oncol*. 2013;14(8):721–732.
31. Mitchell AJ, Chan M, Bhatti H, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. *Lancet Oncol*. 2011;12(2):160–174.
32. Djukanovic I, Carlsson J, Årestedt K. Is the Hospital Anxiety and Depression Scale (HADS) a valid measure in a general population 65-80 years old? A psychometric evaluation study. *Health Qual Life Outcomes*. 2017;15(1):193.
33. Hartung TJ, Friedrich M, Johansen C, et al. The Hospital Anxiety and Depression Scale (HADS) and the 9-item Patient Health Questionnaire (PHQ-9) as screening instruments for depression in patients with cancer. *Cancer*. 2017;123(21):4236–4243.
34. Mesa RA, Miller CB, Thyne M, et al. Differences in treatment goals and perception of symptom burden between patients with myeloproliferative neoplasms (MPNs) and hematologists/oncologists in the United States: Findings from the MPN Landmark survey. *Cancer*. 2017;123(3):449–458.