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# 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

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**Objective:** The Department of Hematology, Zealand University Hospital, Denmark, and the National Institute of Public Health, University of Southern Denmark, created the first nationwide, population-based, and the most comprehensive cross-sectional health-related quality of life (HRQoL) survey of patients with myeloproliferative neoplasms (MPNs). In Denmark, all MPN patients are treated in public hospitals and treatments received are free of charge for these patients. Therefore, MPN patients receive the best available treatment to the extent of its suitability for them and if they wish to receive the treatment. The aims of this article are to describe the survey design and the characteristics of respondents and nonrespondents.

**Material and methods:** Individuals with MPN diagnoses registered in the Danish National Patient Register (NPR) were invited to participate. The registers of the Danish Civil Registration System and Statistics Denmark provided information regarding demographics. The survey contained 120 questions: validated patient-reported outcome (PRO) questionnaires and additional questions addressing lifestyle.

**Results:** A total of 4,704 individuals were registered with MPN diagnoses in the NPR of whom 4,236 were eligible for participation and 2,613 (62%) responded. Overall, the respondents covered the broad spectrum of MPN patients, but patients 70–79 years old, living with someone, of a Danish/Western ethnicity, and with a higher level of education exhibited the highest response rate.

**Conclusion:** A nationwide, population-based, and comprehensive HRQoL survey of MPN patients in Denmark was undertaken (MPNhealthSurvey). We believe that the respondents broadly represent the MPN population in Denmark. However, the differences between respondents and nonrespondents have to be taken into consideration when examining PROs from the respondents. The results of the investigation of the respondents' HRQoL in this survey will follow in future articles.

**Keywords:** survey design, cross-sectional survey, nationwide survey, patient-reported outcomes, health-related quality of life, myeloproliferative neoplasms

## Introduction

The chronic myeloproliferative neoplasms (MPNs) encompass two disease groups: 1) chronic myeloid leukemia (CML) with the Philadelphia chromosome and 2) the main diseases essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF) without the Philadelphia chromosome.<sup>1</sup> The diseases are caused by acquired damage to hematopoietic stem cells.<sup>1</sup> The nature of MPNs is a chronic disease course, but mean lifespan is decreased, which is most pronounced in MF patients.<sup>2,3</sup> Philadelphia-negative MPNs may change from an early cancer stage (ET and PV) to an advanced cancer stage (MF) with intervening transitional stages.<sup>4,5</sup> CML may turn into blast crisis.<sup>6</sup> Philadelphia-negative MPNs may also turn into blast crisis/acute myeloid leukemia (AML).<sup>1</sup> For MPN patients who develop blast crisis/AML, the mean survival is only a few months.<sup>7,8</sup> Previously, the management of these diseases aimed to relieve symptoms and to reduce the risk of thrombotic complications.<sup>8</sup> Allogeneic stem cell transplantation is potentially curative, but unfortunately this treatment possibility only exists for a minority of patients.<sup>8,9</sup> However, due to increased knowledge of specific genetic defects and molecular properties, a new targeted medical treatment era has evolved. Because of targeted treatment, overall survival of CML patients is prolonged significantly and, hopefully, the lifespan approaches that of the general population.<sup>10,11</sup> Targeted treatment for ET, PV, and MF patients is expected to prolong overall survival.<sup>12–16</sup>

Previous studies have investigated health-related quality of life (HRQoL) in MPN patients.<sup>17–41</sup> The presentation of symptoms depends on the MPN subtype, and the symptom profiles vary greatly from asymptomatic to burdensome.<sup>17–41</sup> Given the knowledge of burdensome symptom profiles and impaired HRQoL in many MPN patients, a comprehensive patient-reported outcome (PRO) survey of a large, representative MPN population is warranted. A more extensive understanding of the patients' health conditions and the influences on quality of life is likely to improve both medical treatments and thus prevent disease progression and worsening of symptoms, rehabilitation, and care. Given that CML patients have an overall longer lifespan that possibly approaches the lifespan of the general population in the new targeted treatment era,<sup>3</sup> it is relevant to investigate whether the HRQoL of these patients correspondingly approach those of the general population.

In Denmark, all MPN patients are treated in public hospitals. The diagnoses of all patients are obtained in the hospital, and diagnosis codes are recorded in the National Patient Register (NPR).<sup>42,43</sup> As the treatment is free of charge

for MPN patients, majority of these patients receive the best available treatment. The best available treatment may not be suitable for a minority of MPN patients and there may be some MPN patients who do not wish to receive the best available treatment. We decided to undertake the first nationwide, population-based, and the most comprehensive HRQoL survey of MPN patients, who receive the best available treatment to the extent of its suitability for the patients and if they wish to receive the treatment. The PROs will be adjusted for potential confounding variables based on information from national registers.<sup>42–45</sup>

## Objective

The purpose of this article is to present the survey design and the results of an examination of whether the respondents are representative of the entire MPN population in Denmark prior to analyzing PROs from the respondents. The results of the PRO examination will follow in future articles. Furthermore, this article with description of the survey design and characteristics of the respondents and nonrespondents to the survey will serve as a reference for future research articles because the MPN population and the PROs from the MPNhealthSurvey will serve as mainstays for future research.

## Material and methods

### Participants

The inclusion criteria were the following: 1) An MPN diagnosis of ET, PV, MF, unclassified MPN, or CML according to international diagnostic criteria<sup>9,11</sup> registered in the NPR<sup>43</sup> between 1977 (the year of creation) and March 31, 2013. The diagnosis codes in the NPR are based on the International Classification of Diseases (ICD). ICD-8 was used from 1977 to 1993, and ICD-10 was used from 1994 to 2013 (Table 1). Some ICD-10 MPN diagnosis codes changed between 1994 and 2013. A patient's MPN diagnosis may change due to disease progression,<sup>4,5</sup> and a change in diagnosis is reported to the NPR. Therefore, if more than one diagnosis of MPN was registered for a patient, the last registered diagnosis was used. Denmark has a Cancer Register. All patients with diagnoses of cancer must be registered in the NPR, and all of these registrations are automatically passed on to the Cancer Register. We decided to use the NPR to identify the MPN patients for this survey. 2) The MPN diagnosis had to have been registered at least once at a department of hematology or at a department of internal medicine that treats or previously treated MPN patients in Denmark. Today, MPN patients are almost exclusively treated in departments of hematology. 3) The patient had to be 16 years or older on September 4, 2013. 4) The patient had to be alive on September 4, 2013.

**Table 1** The survey population was formed from the following diagnoses

ICD-8 codes	Diagnoses
208.99	Polycythemia vera
287.29	Essential thrombocythemia
209	Myelofibrosis
205.19	Chronic myeloid leukemia
ICD-10 codes	Diagnoses
D45	Polycythemia vera
D47.3	Essential thrombocythemia
D75.2	Essential thrombocythemia
D47.4	Osteomyelofibrosis
C94.4	Osteomyelofibrosis acuta
C94.5	Osteomyelofibrosis acuta
C92.1	Chronic myeloid leukemia
D47.1	Chronic myeloproliferative disease

**Abbreviation:** ICD, international classification of diseases.

## Data collection

The names and personal identification numbers of all individuals in Denmark with MPN diagnoses were extracted from the NPR on September 4, 2013. All postal addresses were obtained from the Civil Registration System (CRS).<sup>42,44,45</sup> The patients who were alive, fulfilled all of the inclusion criteria, and who were not protected from inquiries during scientific surveys received a postal letter that was mailed on September 11, 2013. The mailing contained an introduction letter, a survey booklet, a prepaid stamped envelope, and a unique username for online login. The letter invited the patients to participate in the survey, described the survey's purpose and content, and emphasized that participation was voluntary. A mixed-mode approach was used to collect the data. The respondents either could complete the enclosed survey booklet and return it in the enclosed envelope or answer the questions online. A reminder was sent to everyone who had not responded on October 25, 2013. The survey ended on December 31, 2013. The patients were not offered compensation for participation.

## Questionnaires and additional questions

The survey booklet/website had 120 questions. The following six validated questionnaires were used in the survey: 1) Short Form 36 Health Survey (SF-36) version 2.0,<sup>46</sup> 2) Brief Fatigue Inventory (BFI),<sup>47</sup> 3) Multidimensional Fatigue Inventory 20 (MFI-20),<sup>48</sup> 4) Hospital Anxiety and Depression Scale (HADS),<sup>49</sup> 5) European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) version 3.0,<sup>50</sup> and 6) Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF).<sup>18</sup> For all questionnaires, the required permissions for use in

the MPNhealthSurvey were obtained. The questionnaires were available in Danish and validated, with exception of the MPN-SAF questionnaire. The MPN-SAF questionnaire was available in English and validated. This questionnaire was translated into Danish according to guidelines arranged by the research group prior to this survey.<sup>51</sup>

SF-36 is a generic questionnaire that investigates physical and mental health in addition to physical, mental, and social functioning.<sup>46</sup> The questionnaire has 36 items that can be combined into eight scales and two summary measures: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health, a physical component summary measure, and a mental component summary measure. Role-physical measures limitations due to physical health and role-emotional measures limitations due to emotional health, including limitations in daily work or other daily activities and limitations in pursuing hobbies or other leisure activities. The physical component summary measure and the mental component summary measure are derived and scored using a component analysis and takes into account all of the physical or mental components in the questionnaire. The scores and summary measures range from 0 to 100. Higher scores or summary measures indicate the more favorable conditions.

BFI and MFI-20 are symptom-specific fatigue questionnaires.<sup>47,48</sup> BFI has nine items that cover the severity of fatigue and the impact on daily functioning. A score for each item can range from 0 to 10. Higher scores indicate more fatigue. A global fatigue score is found by averaging the scores of all items in the questionnaire. MFI-20 has 20 items and the following five scales: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. A score can range from 4 to 20. Higher scores indicate more fatigue.

HADS is a symptom-specific questionnaire that investigates anxiety and depression.<sup>49</sup> HADS has 14 items and two scales: anxiety and depression. A score can range from 0 to 21. A score <8 is assessed as no anxiety/depression, a score of 8–10 is assessed as mild anxiety/depression, a score of 11–14 is assessed as moderate anxiety/depression, and a score of 15–21 is assessed as severe anxiety/depression.

EORTC QLQ C-30 is a cancer disease-specific questionnaire that investigates HRQoL.<sup>50</sup> The questionnaire has 30 items that can be combined into five functional scales, three symptom scales, six single items, and global health status/QoL. The functional scales cover physical, role, emotional, social, and cognitive functioning. The symptom scales cover fatigue, pain, and nausea/vomiting. The single items assess dyspnea, insomnia, appetite loss, constipation, diarrhea, and

financial difficulties. The scores can range from 0 to 100. Higher scores on functional scales represent a great/healthy level of functioning. Higher scores on symptom scales represent high level of symptomatology. A high score on the global health/QoL represents a high HRQoL. Danish population-based reference data for EORTC QLQ C-30 will be used in future investigation of potential differences in HRQoL between the MPN subgroups and the general population.<sup>52</sup>

The MPN-SAF is a disease-specific questionnaire that specifically investigates the symptoms and QoL in MPN patients.<sup>18</sup> MPN-SAF is co-administered with BFI. MPN-SAF co-administered with BFI includes a total of 26 symptom items and one QoL item. The items are measured on 0–10 rating scale. High numbers indicate higher level of symptomatology or QoL impairment. The MPN-SAF Total Symptom Score (MPN-SAF TSS), which is an abbreviated symptom score developed from MPN-SAF and BFI, was also used in the survey.<sup>19</sup> MPN-SAF TSS has 10 items, and the score ranges from 0 to 100.

A total of 25 items in the questionnaire booklet/on the website covered lifestyle, including physical activity, smoking, and alcohol consumption, in addition to height, weight, social life, regularity in the intake of medication prescribed by a doctor, and if someone helped the respondent to complete the questionnaire booklet or to answer the questions on the website. Furthermore, the respondents were able to write in free text.

## Comorbidity and lifestyle

Comorbidity and lifestyle will be taken into account in future investigation of HRQoL in the MPN population. We will investigate, if there are differences in comorbidity and lifestyle between ET, PV, and MF participants and differences in lifestyle between the MPN population and the general population. Furthermore, in future research, PROs will be adjusted for comorbidity and lifestyle as confounders.

The Charlson Comorbidity Index (CCI) was used to assess the comorbidity burden. The CCI is a weighted index that consists of disease clusters that include chronic diseases and cancers.<sup>53,54</sup> Information on comorbidities was obtained from the NPR, all diagnosis codes that were recorded between September 4, 2013, and the preceding 5 years were included.<sup>43</sup> MPNs were excluded from the CCI because the CCI will be used to adjust for the comorbidity confounders during the future investigation of the differences between patients with different MPN subtypes in PROs that were related to MPNs. The CCI scores were grouped into three categories: 1) no or low comorbidity (score of 0), 2) moderate comorbidity (score of 1–2), and 3) severe comorbidity (score of 3 or higher).

The participants in the MPNhealthSurvey were asked questions on height, weight, and lifestyle. BMI was divided into four categories: 1) <18.5, 2) 18.5–24.9, 3) 25.0–29.9, and 4)  $\geq 30.0$ . Smoking status was divided into three categories: 1) smoker, 2) ex-smoker, and 3) non-smoker. Alcohol consumption was divided into four categories: 1)  $\leq 7$ , 2) 8–14, 3) 15–21, and 4)  $\geq 22$  units per week. Physical activity in leisure time was divided into four categories: 1) hard training and competitive sports several times per week; 2) training, heavy garden work, or similar  $\geq 4$  hours per week; 3) walking, bicycling, light garden work, or similar  $\geq 4$  hours per week; and 4) reading, watching TV, or other sedentary activities.

Every few years, the National Institute of Public Health conducts a health and morbidity survey of the general population of Denmark. The lifestyle data from the 2013 survey of the general population will serve as reference data in future investigation of potential differences in lifestyle between the MPN subgroups and the general population.<sup>55</sup>

## Characteristics of the respondents and nonrespondents

The CRS provided information regarding the age, sex, and ethnicity (Danish/Western or non-Western).<sup>42,44,45</sup> Statistics Denmark's registers provided information about living arrangement (living alone or living with someone), education (basic school, upper secondary or vocational school, or higher education), and employment (employed or not employed).<sup>56</sup> The distributions of respondents and nonrespondents on MPN subtypes were calculated. The disease duration on September 4, 2013 was established using the registration date for the first MPN diagnosis in the NPR.

## Response rate, effect of the reminder, and response mode

The total response rate was calculated based on the respondents who answered at least some items either initially or after receiving a reminder. The numbers of patients who initially responded and who responded after receiving a reminder were calculated. Both patients who did not respond to the request to participate in the survey and the patients who returned a survey booklet without answering any of the questions were registered as nonrespondents. The reasons for nonresponse were given spontaneously by some of the nonrespondents who either initiated a telephone call or returned the question booklet without any answers but provided a note explaining the reason for the nonresponse. Finally, the distributions of respondents who returned the survey booklet and who answered the questions online were determined.

## Associations between nonresponse and demographic factors

The demographic factors that were considered for potential influence on the nonresponse were age, sex, living arrangement, education, employment, ethnicity, MPN subtype, and duration of disease.

## Statistical analysis

Descriptive statistics were used to present the characteristics of respondents and nonrespondents and the online and paper submitters. Chi square tests were used to test for significant differences in contingency tables for demographic factors, and two sided Student's t-tests were used to test for significant differences in mean age between the groups. Logistic regressions were used to investigate the possible effects of the interactions between age and all other demographic characteristics, between sex and all other demographic characteristics and between MPN subtype and all other demographic characteristics on nonresponse. A significance level of 0.05 was used. SAS version 9.3 was used for all statistical analyses.

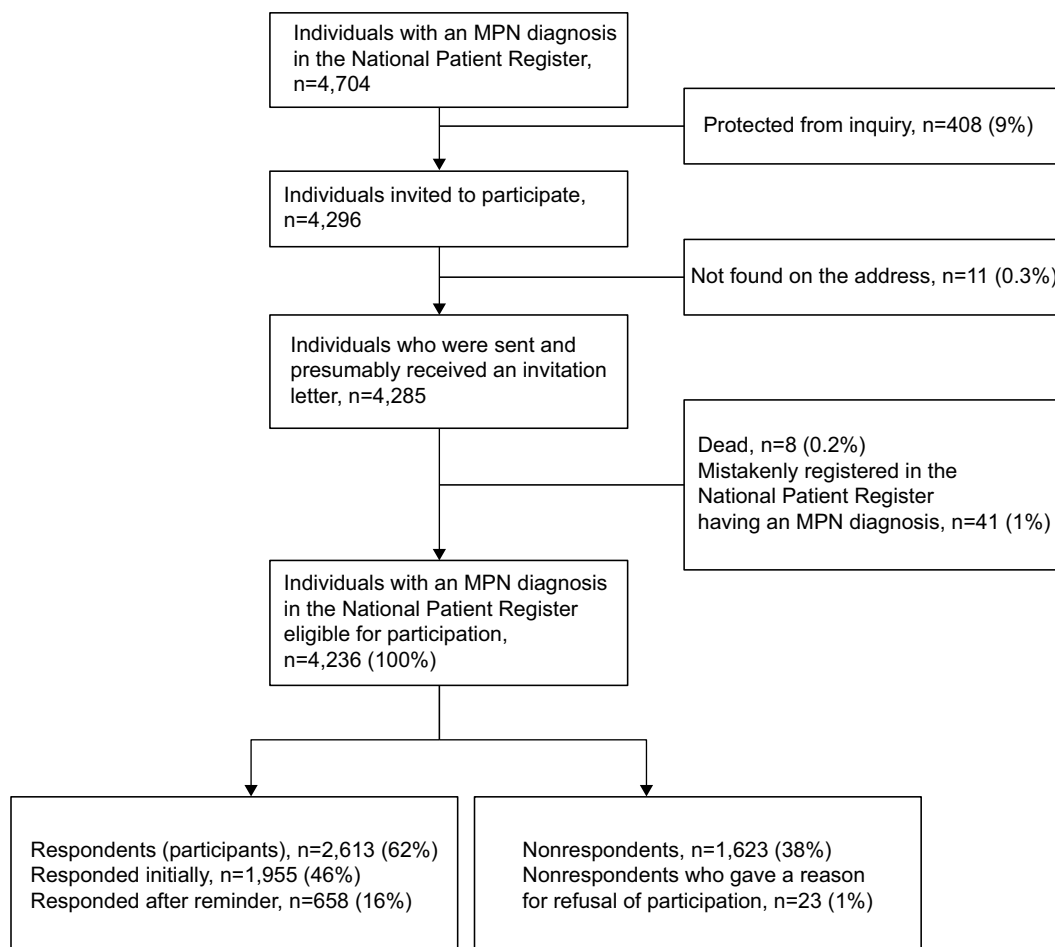
## Ethics

The Danish Data Protection Agency approved the survey (SJ-RO-02). In Denmark, register studies and questionnaire studies are exempted from requirement of approval from the Committee on Health Research Ethics (Committee Act section 14, 2).<sup>57</sup> Future research using the MPN population and the PRO mainstay from the MPN population may require approval from the Committee on Health Research Ethics, which will then be requisitioned.

During the survey, the recipients of the invitation to participate in the survey had the opportunity to contact the research group by phone and by email. Thus, it was possible for them to ask clarifying questions both regarding the invitation to participate in the survey and the survey questions. Completion of survey was deemed to be agreement of consent from the participants.

## Results Participants

A total of 4,704 individuals registered with MPN diagnoses between 1977 and March 31, 2013, were alive, and fulfilled all of the inclusion criteria (Figure 1). Of these individuals,



**Figure 1** Flowchart of the survey population.

**Abbreviation:** MPN, myeloproliferative neoplasm.

408 were protected from inquiry by scientific surveys. Therefore, 4,296 individuals were invited to participate in the survey. Eleven individuals were not found at the postal addresses registered in the CRS. Thus, presumably 4,285 individuals received an invitation letter. We were informed by relatives that eight individuals had died in the days leading up to receipt of the invitation to participate in the survey. Finally, 41 individuals replied that they did not know about having an MPN diagnosis and that they had never consulted a hematologist or a doctor at a medical department at a hospital for diagnostic investigation. Thus, 4,236 individuals with an MPN diagnosis in the Danish National Patient Register formed the survey population.

## Characteristics of the respondents and nonrespondents

The mean age of the nonrespondents was slightly higher than the mean age of the respondents (respondents: age 67.9 years and nonrespondents: age 69.4 years; Table 2). The response rate was slightly higher for males than females, but the difference was not significant (males: 62% and females: 61%). The highest response rate was that of patients aged 70–79 years (females: 67% and males: 68%). The response rate was remarkably higher among those living with someone compared with those living alone (living with someone: 69% and living alone: 51%). The patients with higher education exhibited a higher response rate than the patients who had attended upper secondary/vocational school or basic school (higher education: 71%, upper secondary/vocational school: 67%, and basic school: 52%). The patients who were Danish or living in Denmark but were born in another Western country exhibited a higher response rate than patients who were living in Denmark but were born in a non-Western country (Danish/Western: 63% and non-Western: 44%). The MF patients exhibited the highest response rate compared to the other MPN subgroups (MF: 69%, ET: 60%, PV: 60%, and CML: 66%). The patients who were diagnosed with MPN <1 year before the survey exhibited a higher response rate than those who were diagnosed with MPN ≥1 year before the survey, but this difference was not significant (<1 year: 67%, 1–4 years: 63%, and ≥5 years: 61%). Furthermore, the CML respondents had a stronger preference for answering the questions online than the other MPN subgroups, but the difference was not significant (CML online: 24%).

## Response rate, effects of the reminder, and response mode

A total of 2,613 (62%) patients responded, including 1,955 (46%) who initially responded and 658 (16%) who responded after receiving a reminder (Figure 1). Of the participants,

2,153 (82%) completed the survey booklet, and 460 (18%) answered the questions online (Table 2).

## Associations between nonresponse and demographic factors

An interaction was found between nonresponse, age, and education ( $p < 0.0001$ ), but this was primarily due to the retired participants for whom the amount of missing information regarding education was significant. There were no other interactions between the nonresponses and the demographic factors.

## Discussion

A nationwide HRQoL survey of MPN patients (MPNhealth-Survey) was undertaken. In total, 2,613 (62%) patients responded. We believe that the respondents overall covered the broad spectrum of MPN patients, but the highest response rate was that of patients 70–79 years old, living with someone, of a Danish/Western ethnicity, and with a higher level of education. The number of MF participants was only 88. The differences in age, sex, living arrangement, ethnicity, and educational level between respondents and nonrespondents in the Danish National Health Survey performed on the general population in 2010 have been examined, and the pattern of differences is the same as in the MPNhealthSurvey.<sup>55</sup>

The MPNhealthSurvey has strengths. This was the first nationwide, population-based HRQoL survey of MPN patients, who receive the best available treatment to the extent of its suitability for the patients and if they wish to receive the treatment.<sup>17–41</sup> The selection bias was minimized because all MPN patients living in Denmark and registered in the NPR were invited to participate. The mixed-mode approach to data collection ensured that access to and ability to navigate the Internet was not a condition of participating. To the best of our knowledge, this MPN population is the largest ever that submitted PROs.<sup>17–41</sup> However, the CML population was larger in, for example, a study by Efficace et al.<sup>32,36</sup> Overall, we believe the respondents are representative of the MPN patients in Denmark. However, the differences in characteristics between the respondents and nonrespondents and the relatively small number of MF participants must be taken into consideration when examining the PROs from the respondents. Furthermore, there may be differences in characteristics between respondents and nonrespondents, which we were not aware of. The HRQoL investigation is comprehensive and has not previously been reported on a MPN population to a similar extent.<sup>17–41</sup> The differences in PROs between the MPN subgroups were adjusted for age, sex, comorbidity, and lifestyle. The adjustment for confounders was appropriate because we wished to examine HRQoL

**Table 2** Differences between respondents and nonrespondents and differences between online and paper submitters in demographics, MPN subtype, and duration of disease

Demographic and disease characteristic	Respondents	Nonrespondents	p-Value for difference	Online	Paper	p-Value for difference
<b>Total, n (%)</b>	2613 (62)	1623 (38)		460 (18)	2153 (82)	
<b>Age, mean ± SD, median</b>	67.9±12.9, 69.6	69.4±15.0, 70.9	0.004	60.5±12.1, 62.3	69.5±12.48, 70.9	<0.0001
<b>Sex, n (%)</b>						
Female	1435 (61)	915 (39)	>0.1*	202 (14)	1233 (86)	<0.0001*
Male	1178 (62)	708 (38)		258 (22)	920 (78)	
<b>Female, years, n (%)</b>						
20–29	9 (56)	7 (44)	<0.0001	4 (44)	5 (56)	<0.0001
30–39	29 (54)	25 (46)		8 (28)	21 (72)	
40–49	98 (59)	69 (41)		22 (22)	76 (78)	
50–59	208 (66)	107 (34)		49 (24)	159 (76)	
60–69	375 (67)	181 (33)		76 (20)	299 (80)	
70–79	436 (67)	211 (33)		37 (8)	399 (92)	
80–89	247 (51)	234 (49)		5 (2)	242 (98)	
≥90	33 (29)	81 (71)		1 (3)	32 (97)	
<b>Male, years, n (%)</b>						
20–29	7 (54)	6 (46)	0.003	3 (43)	4 (57)	<0.0001
30–39	29 (57)	22 (43)		13 (45)	16 (55)	
40–49	85 (56)	67 (44)		37 (44)	48 (56)	
50–59	179 (61)	115 (39)		61 (34)	118 (66)	
60–69	331 (64)	185 (36)		87 (26)	244 (74)	
70–79	373 (68)	177 (32)		53 (14)	320 (86)	
80–89	158 (59)	112 (41)		3 (2)	155 (98)	
≥90	16 (40)	24 (60)		1 (6)	15 (94)	
<b>Living arrangement, n (%)</b>						
Living alone	834 (51)	787 (49)	<0.0001**	88 (11)	746 (89)	<0.0001**
Living with someone	1758 (69)	786 (31)		370 (21)	1388 (79)	
Missing, n	21	50		2	19	
<b>Education, n (%)</b>						
Basic school	768 (52)	698 (48)	<0.0001**	64 (8)	704 (92)	<0.0001**
Upper secondary/vocational school	1199 (67)	591 (33)		234 (20)	965 (80)	
Higher education	589 (71)	246 (29)		154 (26)	435 (74)	
Missing, n	57	88		8	49	
<b>Employment, n (%)</b>						
Employed	782 (66)	396 (24)	0.0006**	243 (31)	539 (69)	<0.0001**
Unemployed	62 (56)	49 (44)		20 (32)	42 (68)	
Retired	1768 (60)	1178 (40)		197 (11)	1571 (89)	
Missing, n	1	0		0	1	
<b>Ethnicity, n (%)</b>						
Danish/Western	2481 (63)	1432 (37)	<0.0001**	442 (18)	2039 (82)	0.1**
Non-Western	111 (44)	141 (56)		16 (14)	95 (86)	
Missing, n	21	50		2	19	
<b>MPN subtype, n (%)</b>						
ET	816 (60)	549 (40)	0.02**	164 (20)	751 (80)	>0.1**
PV	915 (60)	606 (40)		143 (16)	673 (74)	
MF	88 (69)	39 (31)		12 (14)	76 (86)	
CML	362 (66)	185 (44)		88 (24)	274 (76)	
MPN unclassified	432 (64)	244 (36)		53 (12)	379 (88)	
<b>Duration of disease, years, n (%)</b>						
<1	176 (67)	86 (33)	0.06**	33 (19)	143 (81)	>0.1**
1–4	909 (63)	544 (37)		172 (19)	737 (81)	
≥5	1528 (61)	993 (39)		255 (17)	1273 (83)	

**Notes:** \*Adjusted for age. \*\*Adjusted for age and sex.

**Abbreviations:** CML, chronic myeloid leukemia; ET, essential thrombocythemia; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythemia vera.



related to MPN. The CRS register provided data on age and sex, and the NPR provided data on comorbidity. The registers ensured a high validity in the adjustment for the confounders' age, sex, and comorbidity.

The MPNhealthSurvey has limitations. The NPR is generally considered to be valid, including for hematological malignancies. However, registries are not entirely complete. Because reporting disease diagnoses to the NPR in Denmark is an enforced requirement and is performed systematically, incorrect registrations can only marginally have influenced the results. Individuals who got surprised and frightened when they received an invitation to participate in the survey because they did not know about having an MPN diagnosis registered in the NPR, could contact the research group performing the survey by phone and email. The individuals who turned out not having a connection to a department of hematology or to a department of internal medicine because of MPN, but were registered in the NPR, were recommended to contact their general practitioner to clarify, if the registration in the NPR was a mistake. The large number of questions in the survey may have prevented some patients from participating. The symptomatic patients may have been more motivated to participate than the asymptomatic patients, and the patients with very severe symptom burdens may not have been able to participate, and this may have influenced the PROs. Some MPN patients' disease coping strategy may include not thinking about the potential long-term effects of the disease. These patients may be nonrespondents in this survey. The survey was based on an anonymous self-report and, for example, unhealthy lifestyles may have been underreported. The survey was based on written questions. Therefore, dyslexic patients, patients with visual impairments, and patients who were not familiar with the Danish language may not have been able to participate or may have had difficulties participating. The questionnaire MPN-SAF has been validated in English. The questionnaire was translated into Danish according to guidelines for translation of questionnaires prior to this survey. However, it has not been fully validated in Danish. It would have been appropriate to fully validate the MPN-SAF in Danish by completing cognitive interviews and thus letting MPN patients validate the translation. Cognitive debriefing of MPN-SAF could potentially have led to appropriate linguistic changes in the questionnaire.<sup>51</sup>

The reason for not sending an invitation to participate in the survey to patients diagnosed with MPN within half a year prior to the start of the survey was that we believed that newly diagnosed patients could potentially be in psychological crisis because of the recent diagnosis of incurable cancer.

The MPN patients received a reminder, if they had not responded by October 25, 2013. More reminders could have raised the response rate, but because the target population was patients with chronic cancer, more than one reminder could not be justified.

PROs from the MPN patients who developed AML before this survey was performed, and those who underwent bone marrow transplantation before this survey was performed will be separately analyzed.

## Conclusion

A nationwide HRQoL survey of MPN patients in Denmark termed MPNhealthSurvey was performed. We believe that the respondents broadly represent the MPN population in Denmark. However, the differences between respondents and nonrespondents have to be taken into consideration when examining PROs from the respondents. The participants provided disease-specific and generic PROs for investigation. The MPNhealthSurvey is the first nationwide and population-based survey, has the largest MPN population, and presents the most extensive PRO collection from a MPN population receiving best available treatment to date. The results of the PRO survey will follow in future articles. The PROs and the MPN population will serve as mainstays for future research. Future research will link to the Danish registries to investigate factors, such as 1) the ability to stay employed, 2) the extent of health service utilization, and 3) mortality.

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## Author contributions

ADZ, NB, HCH, KJ, EMF, and CLA conceptualized and designed the survey. NB organized the survey, along with AIC and ADZ. EMF provided the statistical analyses. All authors contributed toward data analyses. NB drafted the manuscript. All authors participated in the revision and final approval of the manuscript. All authors agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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