Title: Myeloproliferative neoplasm patient symptom burden and quality of life: evidence of significant impairment compared to controls

Short title: Myeloproliferative neoplasm patient symptom burden

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Scientific category:

Key point

- Myeloproliferative neoplasm patients have significantly higher symptom burden and lower overall quality of life when compared to that of the general population.

Abstract

Rationale: The myeloproliferative neoplasms (MPNs) including polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (PMF) are rare diseases contributing to significant morbidity. Symptom management is a prime treatment objective but current symptom assessment tools have not been validated compared to the general population.

Objectives: The MPN-Symptom Assessment Form (MPN-SAF), a reliable and validated clinical tool to assess MPN symptom burden, was administered to MPN patients (n=106) and, for the first time, population controls (n=124) as part of a UK pilot case-control study. Mean symptom scores were compared between patients and controls adjusting for potential confounders. Mean patient scores were compared to data collected by the Mayo Clinic, USA on 1,446 international MPN patients to determine patient group representativeness.

Results: MPN patients had significantly higher mean scores than controls for 25 of the 26 symptoms measured ($p<0.05$); fatigue was the most common symptom (92.4% and 78.1%, respectively). Female MPN patients suffered worse symptom burden than male patients ($p<0.001$) and substantially worse burden than female controls ($p<0.001$). Compared to the Mayo cohort of MPN patients, MPN-UK patients reported similar symptom burden but lower satiety ($p=0.046$). Patients with PMF reported the worst symptom burden (88.3%); significantly higher than PV patients ($p<0.001$). Overall quality of life was impaired in 78.4% MPN-UK patients compared with 57.4% controls ($p<0.001$).

Conclusion: MPN patients experience significant morbidity compared to the general population highlighting the need to manage symptoms effectively. The results further validate the use of the MPN-SAF as a discriminatory tool to assess MPN disease burden.

Introduction

The *BCR-ABL* negative classic myeloproliferative neoplasms (MPNs) which include polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (PMF) are rare diseases with an estimated incidence rate of 0.84, 1.03 and 0.47 per 100,000, respectively[1]. These heterogeneous diseases are characterised by an acquired abnormality of haematopoietic stem cells resulting in transformed myeloid progenitor cells which overproduce mature and immature cells within the myeloid lineage. Mutations in Janus Kinase 2 (*JAK2*) and the endoplasmic reticulin chaperone calreticulin (*CALR*) are central to the genetic variability of these diseases which contribute to disease pathogenesis, progression and prognosis[2, 3].

Symptom burden in MPNs is severe and prevalent in almost all MPN patients contributing to significant morbidity[4–8]. The MPN-symptom assessment form (MPN-SAF) is a clinically validated assessment tool which measures 26 symptoms related to MPNs and an overall assessment of quality of life (QoL)[5]. A survey of MPN patients (n=1,179 who are part of the comparison cohort included in this report), using the MPN-SAF, identified an array of symptoms including fatigue, pruritus and night sweats in 81%, 53% and 50% of patients, respectively[4]. Comparison of symptom burden across countries has been conducted with overall quality of life, itching and bone pain most severe in patients from Italy compared to those from USA or Sweden[5]. USA patients reported worse fatigue[5]. Utilising the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 the MPN-SAF showed high correlation for similar symptoms. For PV and ET patients the EORTC QLQ-C30 results resembled those of age and gender matched controls while PMF patients displayed worse quality of life[5]. Symptom burden, assessed using the MPN-SAF, has not yet been assessed in those without MPNs. Many current pharmacological treatments for MPN symptoms have side-effects. Understanding the symptom burden of MPN patients in comparison to the general population may improve clinical management and is of utmost importance.

The aim of this study was to determine, for the first time, if the MPN-SAF was able to discriminate between symptom burden experienced by MPN patients and that reported in the general population. It also aimed to compare symptom burden and overall quality of life reported by MPN patients in the UK to those reported internationally.

Methods

MOSAICC pilot case-control study

The pilot MOSAICC (Myeloproliferative Neoplasms: An In-depth Case-Control) study aimed to identify appropriate methodological approaches to roll-out a UK-wide case-control study of MPNs. MPN-UK patients were recruited from two sites: Belfast City Hospital, Belfast, Northern Ireland and University Hospital Southampton NHS Foundation Trust, Southampton, England. Eligible patients were classified according to the WHO diagnostic criterion[9] and identified by their lead consultant (MFMcM and ASD). A study information pack was provided which contained a consent form, study information booklet and the MPN-SAF. Patients were asked to recruit non-blood relative or friend controls to the study by providing them with information flyers. Age (5-year age band) and gender frequency-matched General Practice controls were recruited by sending a study information pack with self-complete MPN-SAF to all controls. The completed MPN-SAFs were returned in pre-paid envelopes. Ethical approval was obtained from the Office for Research Ethics Committee, Northern Ireland (OREC-NI). MPN-UK patients were receiving standard treatment regimens.

Mayo Clinic

Detailed information on a subset of the patients presented in this paper are described in detail elsewhere[5, 10]. Briefly, 1,446 MPN-patients were prospectively recruited to participate in an

assessment of symptom burden at the time of an office visit. Patients were accrued in academic, private, and government-funded medical facilities from approximately November 2009 to January 2011. The patient survey included questions on demographic and disease-related variables including symptom burden assessment via the MPN-SAF. This study included participants from Argentina, France, Germany, Italy, the Netherlands, United Kingdom, United States [including Puerto Rico], Spain, Sweden, and Uruguay and was administered in seven languages. Once collected by our team of international collaborators, data was de-identified and transferred to Mayo Clinic for compilation and analysis.

MPN-SAF

The MPN-SAF is an adaptation of the Myelofibrosis-SAF which includes symptoms common to PV and ET patients based on an internet survey. The MPN-SAF has questions regarding: fatigue (current, usual, worst in last 24 hours), measured on a scale from 0 (absent) to 10 (worst-imaginable), and how fatigue affects general activity, mood, walking ability, normal work, relations with other people and enjoyment of life, measured on a scale of 0 (Does not interfere) to 10 (Completely interferes). In addition questions on early satiety (filling up quickly when you eat), abdominal pain, abdominal discomfort, inactivity, problems with headaches, concentration, dizziness/vertigo/light headedness, numbness/tingling, difficulty sleeping, depression or sad mood, problems with sexual desire or function, cough, night sweats, pruritis (itching), bone pain (diffuse not joint pain or arthritis), fever (>37.8^{oC}), unintentional weight lost in last 6 months were measured on a scale from 0 (absent) to 10 (worst-imaginable). Finally participants were asked to rate their overall quality of life on a scale from 0 (As good as it can be) to 10 (As bad as it can be).

Statistical Analysis

Symptom prevalence was calculated for all variables by dividing the number of patients reporting a score above 1 by all respondents. Mean scores were calculated for each symptom variable and

standard deviations calculated. Regression analyses were conducted initially comparing symptom scores in MPN-UK patients and controls to determine, for the first time, the extent of MPN symptoms compared to the general population. MPN-UK cases were then compared to MPN-Mayo patients, adjusting for age (continuous) and gender, to evaluate the representativeness of the MOSAICC study MPN patients.

Symptom and overall quality of life scores were categorised into three groups [0 (baseline), 1-5 and 6-10] and logistic regression analyses utilised to compare symptom burden in MPN-UK patients and controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were adjusted for age, gender, education status, presence of a chronic medical condition (heart disease, asthma, diabetes, hypertension, psoriasis, hyper/hypothyroidism, rheumatoid arthritis or other self-reported chronic condition), smoking (pack years), alcohol consumption (units) and body mass index (current weight/height^2). Trend analysis compared MPN-UK patients and controls with regards to each unit increase in the symptom score.

Mean symptom scores were calculated for MOSAICC PV, ET and PMF patients respectively and for male and female MPN patients and controls. Symptom scores were compared between male and female MPN patients, male and female controls, male MPN patients and male controls and female MPN patients and female controls. For all statistical tests a $p<0.05$ was considered statistically significant. Statistical analysis was conducted using STATA 12.0 (Stata-Corp, College Station, TX).

Results

Two hundred and thirty surveys were completed by MOSAICC study participants (106 MPN-UK patients, 124 controls) and 1,446 surveys completed by MPN-Mayo patients after excluding those

without age or gender information available (n=24). Overall, more female MPN-UK patients, UK controls and MPN-Mayo patients (60.4%, 62.1% and 54.7%, respectively) than males completed the survey. MPN-UK patients, UK controls and MPN-Mayo patients were of a similar mean age (62.2. 60.8 and 63.2 years, respectively).

MPN-UK patients were more likely than controls to report a higher score for all symptoms, with the exception of fever, when analyses were adjusted for age and gender, Table 1. Conversely, both patient groups reported similar symptom scores for most variables, Figure 1, with patients from the Mayo Clinic study more likely to report early satiety when adjusted for age and gender than MPN-UK patients (p=0.046) , Table 1.

When comparing symptom burden in MPN-UK patients and controls MPN-UK patients were more likely than controls to experience worse fatigue, fatigue affecting general activity, mood, walking ability and normal work, enjoyment of life, abdominal pain and discomfort, inactivity, headaches, lack of concentration, dizziness, numbness, difficulty sleeping, depression, sexual problems, cough, night sweats, pruritus, bone pain, fever, weight loss and overall quality of life, Figure 2/Table 2. All symptoms showed an increasing trend per unit increase in score with the exception of relations with other people, Table 2.

Of the MPN subtypes PV patients were more likely to report difficulty with lack of concentration, sleeping, depression, sexual problems, pruritus and lower overall quality of life than ET and PMF patients but differences did not reach statistical significance (data not shown), Figure 1. ET patients had the highest burden for mood, relations with other people, headaches and bone pain. PMF patients displayed the highest burden for fatigue, fatigue affecting general activity, walking, normal work and enjoyment of life, satiety, abdominal discomfort, inactivity, dizziness, numbness, cough, night sweats, fever and weight loss, Figure 1. The mean symptom score for cough was significantly

higher in PMF patients than PV (p=0.039) or ET (p=0.024) patients. Symptom scores for fever were also higher in PMF than PV patients (p=0.050).

Within the pilot MOSAICC study female MPN patients displayed the worst symptom burden for all variables with the exception of sexual problems which were more common in male MPN patients, Figure 2. Female MPN patients were significantly more likely than male MPN patients to report higher mean scores for fatigue, mood, early satiety, headaches, lack of concentration, dizziness, difficulty sleeping, depression and night sweats, Table 3. Female MPN patients were significantly more likely than female controls to report higher symptom burden for all variables except fever and for overall quality of life. Quality of life in male MPN patients did not differ to that of male controls and there were fewer significant differences compared with females. Male and female controls did not report different symptom scores for any of the variables or overall quality of life, Table 3.

Discussion

The MPN-SAF is a clinically validated tool for assessing symptom burden in patients with MPNs. For the first time we report the extent of symptoms in MPN patients compared to the general population demonstrating the significant burden experienced by MPN patients, particularly females. All symptoms assessed were more common in MPN patients than controls, with the expectation of 'relations with other people', after adjusting for potential confounders. Female MPN patients also reported a poorer quality of life. Furthermore, symptom burden appeared worst in patients with PMF. The MOSAICC study MPN-UK patients reported similar symptom spectrums to those previously published by the Mayo Clinic, supporting the use of the MPN-SAF as a valid and reliable tool for symptom assessment in other populations[5].

The comparison of MPN-UK and MPN-Mayo patients identified 'early satiety' as the only significantly different symptom with MPN-UK patients less likely to report experiencing early satiety. Early satiety is more common in patients with splenomegaly[11], which can be present at MPN diagnosis particularly in patients with PMF. A higher proportion of PMF patients were included in the Mayo Clinic survey (20.4%) compared to the pilot MOSAICC study (13.2%) which may explain the observed difference. Additionally, effective MPN treatment, particularly with the newly licensed JAK2 inhibitor Ruxolitinib[12], can reduce splenomegaly (present in 10/106 MOSAICC patients), and associated early satiety[13] and usage may differ between countries. However, given that all other symptoms were similar between MPN-UK and MPN-Mayo patients differences in diet, cultural norms, and portion sizes could contribute.

MPN patients have been shown to have levels of fatigue far in excess of that of published norms[4] but to date no other studies have compared the broad spectrum of MPN symptoms, evaluated by the MPN-SAF, with rates in the general population. Fatigue was the most commonly reported symptom among MPN-UK patients consistent with other reports in the literature[4, 5, 10, 11, 14, 15]. Fatigue is a common symptom reported in clinical practice with 58% of patients in primary care reporting chronic fatigue[16]. Evaluation of fatigue is difficult due to differing levels of patient perception and tolerance. Fatigue correlates with a number of disease measures including time since diagnosis, treatment, disease status, complications, comorbidities and lifestyle factors such as smoking[4]. Male fatigue levels were lower than that of females in both MPN patients and controls. However, male MPN-UK patients and male controls reported similar levels of fatigue when adjusted for potential confounders while MPN-UK women reported significantly more fatigue that female controls. Further evaluation of these gender differences, particularly in relation to treatment, is warranted. In a previous study male patients scored higher than females for experiencing sexual problems and weight loss[15]. While sexual problems appeared more common in male than female MPN patients in the MOSAICC study no significant association was observed. This could be due to the limited sample size included in the pilot study and will be further explored in the planned

UK-wide study. However, sexual problems and weight loss were significantly more common in male MPN-UK patients than controls.

The extent of symptom burden is an important consideration in the management of MPN patients. Clinical response to treatment as set forth by the European Leukemia Net and the International Working Group recommends consideration of symptoms when determining complete and partial treatment response or clinical improvement[17]. In their designation, a symptom response is represented as greater than 50% reduction in the MPN-SAF total symptom score. Average five-year relative survival for PV and ET patients within Europe is 84.8% and 89.9% respectively[18]. Swedish data shows that 32% of PV and 44% of ET patients survive for more than 20 years post diagnosis compared to only 6% of PMF patients[19]. With the emergence of new therapies including *JAK2* inhibitors[20], current trials are not only assessing improvements in the clinical aspects of MPNs but on alleviating the symptoms experienced by MPN patients. The COMFORT-I trial, which is assessing the effects of the *JAK2* inhibitor Ruxolitinib versus placebo and COMFORT-II evaluating Ruxolitinib versus best available treatment in PMF patients, have shown marked improvement in overall quality of life with improvements in pruritus, night sweats, abdominal discomfort, and bone pain[21, 22]. However, the symptoms remain higher than those reported by controls within this study demonstrating the need for more effective treatments. Additionally, Ruxolitinib, has a number of common side-effects which limit their use. Ruxolitinib is now licensed by the Federal Drug Administration in the USA for Hydroxyurea refractory or intolerant PV. Investigation of alternative strategies to alleviate symptoms including fatigue, such as physical activity programmes, should be evaluated.

The strengths of this study include the inclusion of a population control group reporting symptoms using the validated MPN-SAF questionnaire. This has enabled us to investigate for the first time the diverse range of symptoms covered by the MPN-SAF in a non-diseased group. However, this was a

pilot investigation and as such the sample size is limited. Expanding the study to a larger number of patients and controls will provide a more robust assessment of the discriminatory ability of the questionnaire. Ability to adjust for potential confounding variables such as co-morbidities, smoking and alcohol consumption have enabled a more accurate comparison of MPN symptom burden with that of controls. Similarities in all symptoms between MPN-UK and MPN-Mayo groups, with the exception of early satiety, demonstrate the usefulness of this questionnaire in symptom evaluation. The study does recognise the potential limitation of self-reporting bias which may differ between patients and controls. While the study was only administered on one occasion elements of the MPN-SAF (including fatigue, early satiety, abdominal pain, abdominal discomfort, inactivity, headache, concentration, dizziness, numbness, difficulty sleeping, depression, sexual problems, night sweats, pruritus, and bone pain) have been shown to have good correlation on repeat measurement[5]. MPN patients included in the pilot MOSAICC study were incident and prevalent cases (mean duration since diagnosis was 5 years) and evaluation of symptom burden by time since diagnosis in comparison to the normative population is warranted.

In conclusion, this study, for the first time compares symptom burden in MPN patients with that of controls and acknowledges the manifestation of symptoms and burden in MPN patients and its effect on overall quality of life. Furthermore, this study supports the need for quality of life assessment in clinical practice and clinical trial settings to manage and reduce disease burden and improve overall patient quality of life. Fatigue is the most prevalent symptom experience, particularly in females, and is an important factor for development of future treatment strategies.

Author Contributions.

LAA is the chief investigator of the MOSAICC study. GJT and LAA undertook the statistical analysis and drafted the article. MFMcM, ASD and FDeV contributed to the design of the MOSAICC study and are PIs for it .. RM, RS and AD developed the MPN-SAF and provided data

for Mayo clinic cases. MC led the methodological component of the MOSAICC study. All authors contributed to the interpretation of the results and writing of the paper. All the authors approved the final version of this article.

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Conflict of Interest.

The authors report no potential conflicts of interest.

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Table 1: Percentage of controls and cases reporting symptoms on the MPN-SAF and symptom mean scores.

	MOSAICC Controls (n=124)		**MOSAICC MPN-UK patients (n=106)**		**MOSAICC MPN-UK patients vs Controls *p-value****	**MPN-Mayo patients (n=1,446)**		**MPN-UK vs MPN-Mayo Patients* *p-value***
Variable/Score	**Symptom Prevalence (%)**	**Mean Score (SD)**	**Symptom Prevalence (%)**	**Mean Score (SD)**		**Symptom Prevalence (%)**	**Mean score (SD)**	
Fatigue Now	65.1	2.25 (2.32)	83.6	3.72 (2.74)	**<0.001**	85.3	3.54 (2.55)	0.574
Fatigue Usual 24 Hours	74.0	2.36 (2.12)	90.3	3.89 (2.62)	**<0.001**	88.1	3.67 (2.49)	0.454
Fatigue Worst 24 Hours	78.1	3.40 (2.81)	92.4	4.79 (3.02)	**<0.001**	89.8	4.43 (2.81)	0.264
General Activity	54.1	1.55 (2.07)	72.1	3.29 (2.89)	**<0.001**	77.9	3.22 (2.67)	0.903
Mood	58.9	1.76 (2.21)	72.1	2.74 (2.71)	**<0.001**	75.7	2.93 (2.65)	0.477
Walking ability	44.4	1.18 (2.02)	64.1	2.87 (2.89)	**<0.001**	71.2	2.96 (2.93)	0.599
Normal Work	54.8	1.56 (2.08)	75.0	3.28 (2.87)	**<0.001**	77.6	3.26 (2.84)	0.959
Relations	52.4	1.33 (1.88)	54.8	1.88 (2.31)	**<0.001**	66.1	2.33 (2.55)	0.085

Enjoyment	54.9	1.32 (1.89)	70.2	2.77 (2.66)	**<0.001**	69.2	2.69 (2.79)	0.813
Early satiety	39.2	1.12 (1.82)	55.7	2.00 (2.50)	**0.004**	64.7	2.53 (2.76)	**0.046**
Abdominal Pain	20.4	0.51 (1.38)	43.8	1.37 (2.10)	**0.001**	46.5	1.49 (2.26)	0.570
Abdominal Discomfort	28.5	0.72 (1.52)	54.6	1.90 (2.41)	**<0.001**	53.4	1.84 (2.44)	0.861
Inactivity	29.5	0.92 (1.91)	65.7	2.38 (2.55)	**<0.001**	62.2	2.38 (2.69)	0.900
Headaches	24.6	0.66 (1.57)	47.6	1.81 (2.72)	**<0.001**	53.3	1.76 (2.42)	0.856
Concentration	31.4	0.98 (1.99)	63.8	2.45 (2.80)	**<0.001**	64.2	2.54 (2.78)	0.742
Dizziness	27.7	0.84 (1.71)	63.2	2.25 (2.48)	**<0.001**	57.0	2.02 (2.55)	0.429
Numbness	23.6	0.78 (1.81)	58.5	2.15 (2.59)	**<0.001**	63.3	2.48 (2.77)	0.208
Difficulty Sleeping	62.6	2.13 (2.42)	67.0	3.19 (3.16)	**0.005**	68.1	3.02 (3.06)	0.731
Depression	39.9	1.02 (1.78)	65.1	2.28 (2.46)	**<0.001**	62.4	2.38 (2.71)	0.696
Sexual Problems	27.8	1.02 (2.14)	56.9	2.96 (3.38)	**0.001**	61.3	3.16 (3.50)	0.632
Cough	23.5	0.75 (1.65)	51.9	1.79 (2.41)	**<0.001**	45.9	1.51 (2.29)	0.262
Night Sweats	30.1	0.96 (1.90)	55.7	2.52 (3.05)	**<0.001**	53.9	2.17 (2.84)	0.224
Pruritus	21.3	0.70 (1.74)	54.3	2.55 (3.21)	**<0.001**	53.3	2.18 (2.92)	0.230

Bone Pain	19.7	0.67 (1.85)	50.0	1.91 (2.67)	**<0.001**	49.3	1.96 (2.75)	0.693
Fever	4.9	0.08 (0.40)	16.0	0.39 (1.32)	0.056	18.0	0.37 (1.14)	0.857
Weight Loss	6.5	0.24 (1.17)	23.6	0.98 (2.23)	**0.006**	30.7	1.08 (2.26)	0.638
Overall Quality of life	57.4	1.47 (1.92)	74.6	2.55 (2.36)	**<0.001**	78.7	2.87 (2.74)	0.176

Symptom prevalence = percentage of participants scoring 1 or higher for each symptom.

* Regression analysis adjusted for age and gender.

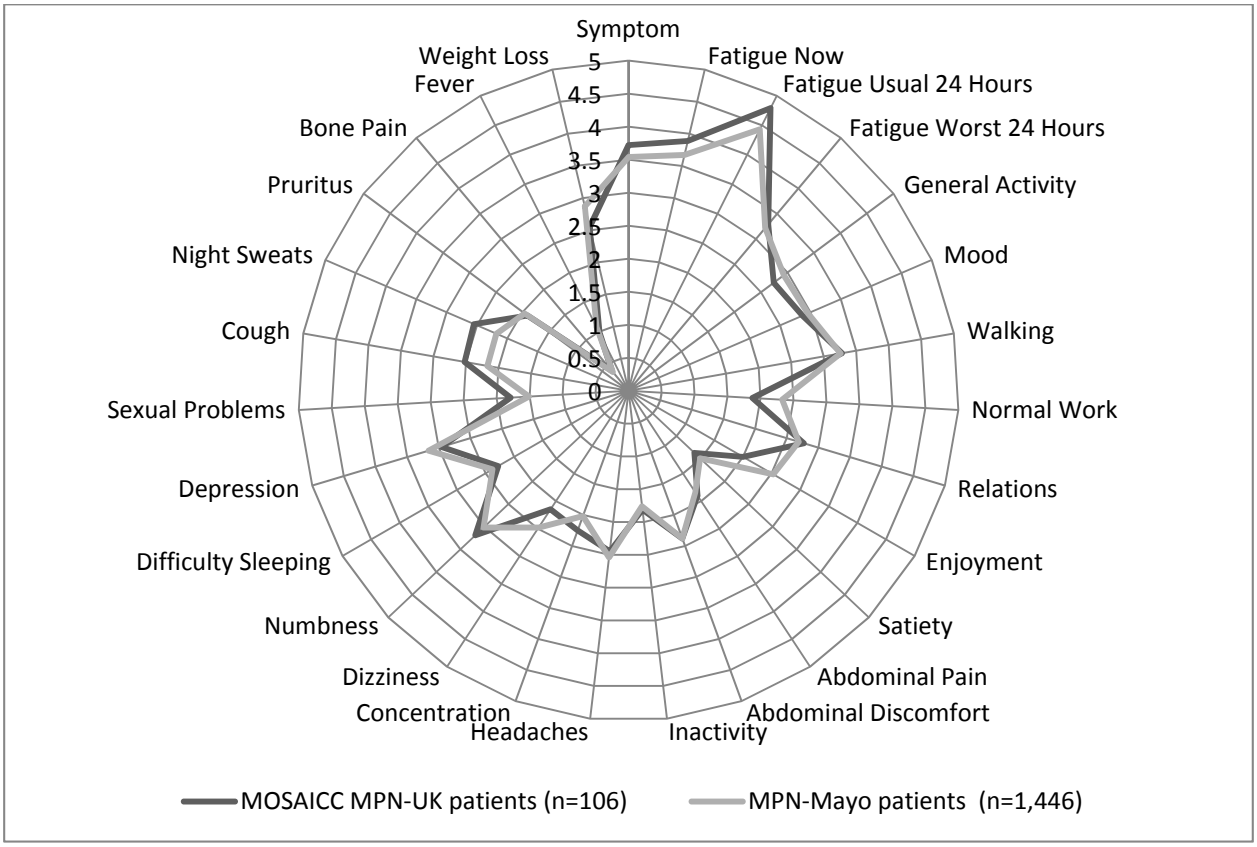

Figure 1: Comparison of MPN-UK and MPN-Mayo patient reported symptom scores.

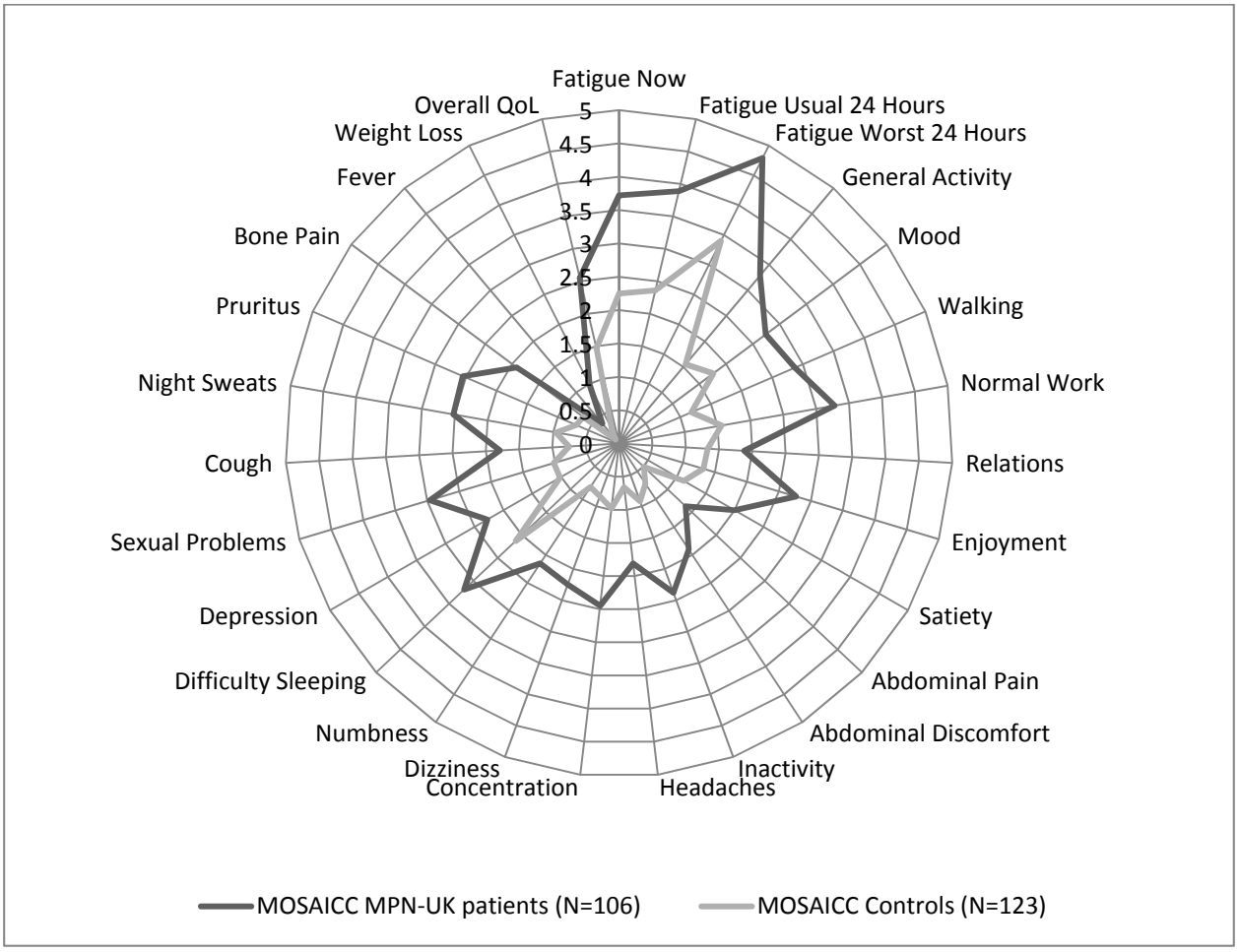

Figure 2: Comparison of MOSAICC MPN-UK patient and control reported symptom scores.

Table 2: Comparison of symptom burden between MOSAICC MPN-UK patients and controls adjusted for potential confounding variables.

Variable (Score)	**MPN-UK Patients (n)**	**Controls (n)**	**AOR* (95% CI)**
Fatigue Now			
No fatigue (0)	17	43	1.00
Some fatigue (1-5)	59	65	**2.31 (1.12-4.77)**
Worst imaginable (6-10)	28	15	**5.42 (2.12-13.87)**
p for trend			**<0.001**
Fatigue Usual 24 Hours			
No fatigue (0)	10	32	1.00
Some fatigue (1-5)	64	75	**3.84 (1.53-9.67)**
Worst imaginable (6-10)	29	16	**7.29 (2.45-21.67)**
p for trend			**<0.001**
Fatigue Worst 24 Hours			
No fatigue (0)	8	27	1.00
Some fatigue (1-5)	48	61	**4.04 (1.48-11.03)**
Worst imaginable (6-10)	48	35	**6.36 (2.26-18.01)**
p for trend			**0.001**
General Activity			
Does not interfere (0)	29	57	1.00
Somewhat interferes (1-5)	52	59	1.85 (0.97-3.51)
Completely interferes (6-10)	23	8	**5.17 (1.82-14.68)**
p for trend			**<0.001**
Mood			
Does not interfere (0)	29	51	1.00
Somewhat interferes (1-5)	53	62	1.63 (0.86-3.10)

Completely interferes (6-10)	22	11	**3.89 (1.47-10.27)**
p for trend			**0.007**
Walking ability			
Does not interfere (0)	37	69	1.00
Somewhat interferes (1-5)	42	47	1.78 (0.95-3.38)
Completely interferes (6-10)	24	8	**4.54 (1.70-12.11)**
p for trend			**<0.001**
Normal Work			
Does not interfere (0)	26	56	1.00
Somewhat interferes (1-5)	50	62	1.71 (0.88-3.33)
Completely interferes (6-10)	28	6	**8.97 (2.95-27.23)**
p for trend			**<0.001**
Relations			
Does not interfere (0)	47	59	1.00
Somewhat interferes (1-5)	45	60	1.01 (0.56-1.83)
Completely interferes (6-10)	12	5	2.23 (0.64-7.78)
p for trend			0.125
Enjoyment			
Does not interfere (0)	31	56	1.00
Somewhat interferes (1-5)	59	61	1.82 (0.97-3.41)
Completely interferes (6-10)	14	7	**3.38 (1.06-10.80)**
p for trend			**<0.001**
Early satiety			
Absent (0)	47	73	1.00
Moderate (1-5)	45	39	1.52 (0.81-2.86)
Worst imaginable (6-10)	14	8	2.32 (0.81-6.63)
p for trend			**0.023**

Abdominal Pain			
Absent (0)	59	98	1.00
Moderate (1-5)	40	21	**2.98 (1.49-5.97)**
Worst imaginable (6-10)	6	4	2.44 (0.59-10.10)
p for trend			**0.004**
Abdominal Discomfort			
Absent (0)	48	88	1.00
Moderate (1-5)	48	31	**3.00 (1.56-5.77)**
Worst imaginable (6-10)	10	4	**4.56 (1.22-17.02)**
p for trend			**<0.001**
Inactivity			
Absent (0)	36	86	1.00
Moderate (1-5)	56	29	**4.98 (2.57-9.65)**
Worst imaginable (6-10)	13	7	**3.63 (1.16-11.36)**
p for trend			**<0.001**
Headaches			
Absent (0)	55	92	1.00
Moderate (1-5)	34	27	**2.45 (1.22-4.92)**
Worst imaginable (6-10)	16	3	**10.04 (2.52-39.96)**
p for trend			**0.001**
Concentration			
Absent (0)	38	83	1.00
Moderate (1-5)	50	31	**3.60 (1.88-6.89)**
Worst imaginable (6-10)	17	7	**4.87 (1.64-14.48)**
p for trend			**<0.001**
Dizziness			
Absent (0)	39	89	1.00

Moderate (1-5)	54	30	**4.44 (2.28-8.66)**
Worst imaginable (6-10)	13	4	**6.03 (1.71-21.33)**
p for trend			**<0.001**
Numbness			
Absent (0)	44	94	1.00
Moderate (1-5)	47	23	**3.89 (1.99-7.59)**
Worst imaginable (6-10)	15	6	**5.27 (1.70-16.38)**
p for trend			**<0.001**
Difficulty Sleeping			
Absent (0)	35	46	1.00
Moderate (1-5)	43	63	0.91 (0.48-1.75)
Worst imaginable (6-10)	28	14	2.32 (0.99-5.43)
p for trend			**0.015**
Depression			
Absent (0)	37	74	1.00
Moderate (1-5)	54	42	**2.79 (1.48-5.27)**
Worst imaginable (6-10)	15	7	**4.51 (1.46-13.91)**
p for trend			**<0.001**
Sexual Problems			
Absent (0)	44	88	1.00
Moderate (1-5)	33	27	**3.02 (1.47-6.18)**
Worst imaginable (6-10)	25	7	**9.34 (3.34-256.08)**
p for trend			**<0.001**
Cough			
Absent (0)	51	94	1.00
Moderate (1-5)	44	26	**3.07 (1.57-5.99)**
Worst imaginable (6-10)	11	3	**6.08 (1.42-26.08)**

p for trend			**0.004**
Night Sweats			
Absent (0)	47	86	1.00
Moderate (1-5)	38	31	**2.88 (1.43-5.79)**
Worst imaginable (6-10)	21	6	**8.20 (2.76-24.41)**
p for trend			**<0.001**
Pruritus			
Absent (0)	48	96	1.00
Moderate (1-5)	38	21	**4.16 (2.06-8.40)**
Worst imaginable (6-10)	19	5	**8.79 (2.81-27.44)**
p for trend			**<0.001**
Bone Pain			
Absent (0)	53	98	1.00
Moderate (1-5)	40	19	**4.63 (2.20-9.75)**
Worst imaginable (6-10)	13	5	**5.07 (1.51-17.05)**
p for trend			**0.001**
Fever			
Absent (0)	89	117	1.00
Moderate (1-5)	14	6	**3.86 (1.27-11.75)**
Worst imaginable (6-10)	3	0	-
p for trend			**0.047**
Weight Loss			
Absent (0)	81	115	1.00
Moderate (1-5)	17	5	**5.84 (1.90-17.96)**
Worst imaginable (6-10)	8	3	2.05 (0.43-9.74)
p for trend			**0.015**
Overall Quality of life			

As good as it can be (0)	27	52	1.00
Moderate (1-5)	68	64	**2.22 (1.15-4.30)**
As bad as it can be (6-10)	11	6	3.04 (0.88-10.46)
p for trend			**0.003**

*AOR (Adjusted Odds Ratio) and 95% CI (Confidence Interval) per point increase in response variable adjusted for age, gender, education status, presence of a chronic medical condition (heart disease, asthma, diabetes, hypertension, psoriasis, hyper/hypothyroidism or rheumatoid arthritis), smoking (pack years), alcohol consumption (units) and body mass index.

p for trend is per unit increase in symptom variable/quality of life score.

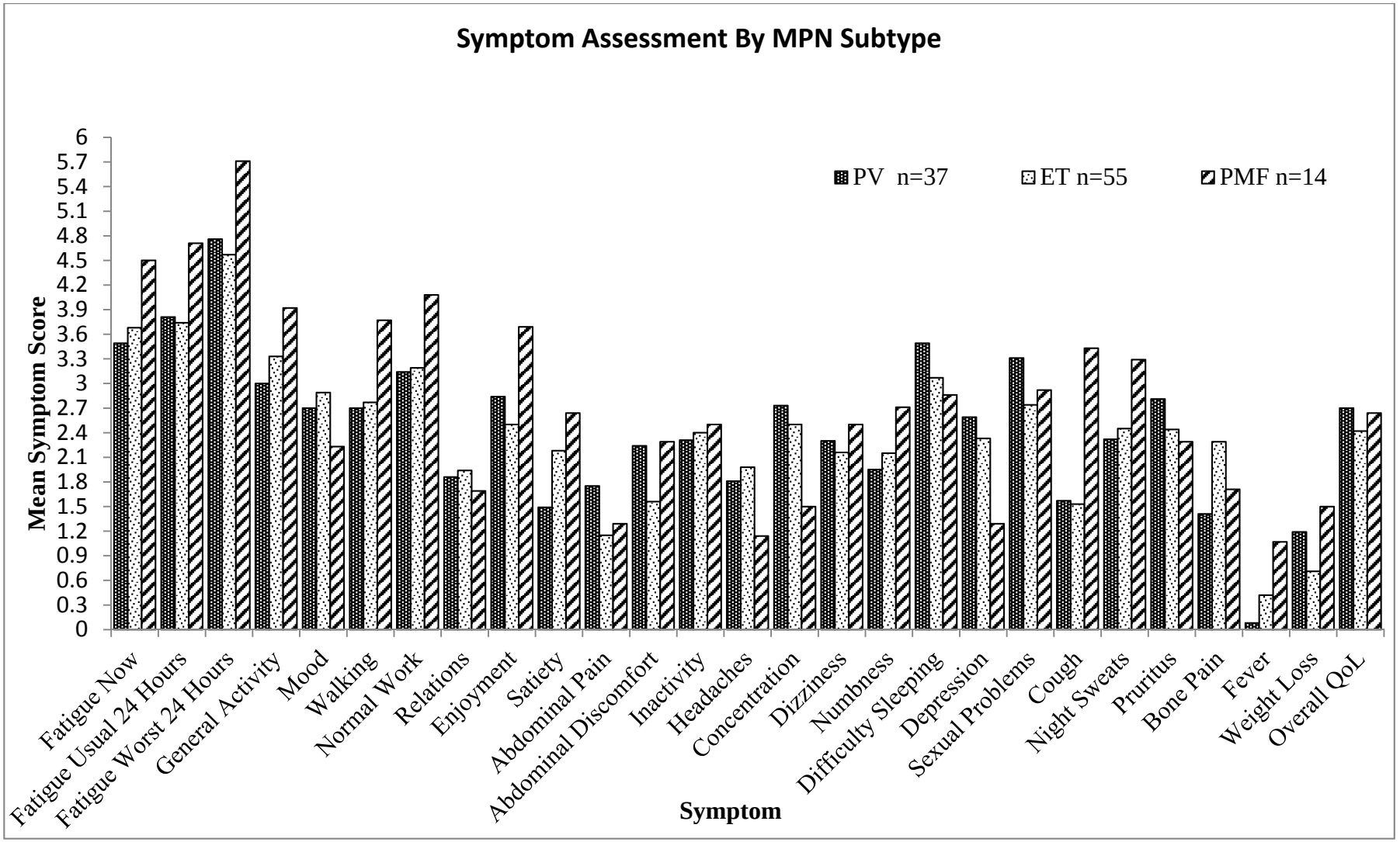

Figure 1: Mean symptom scores in MOSAICC cases by myeloproliferative neoplasm subtype.

PV= polycythaemia vera, ET=essential thrombocythaemia, PMF=primary myelofibrosis

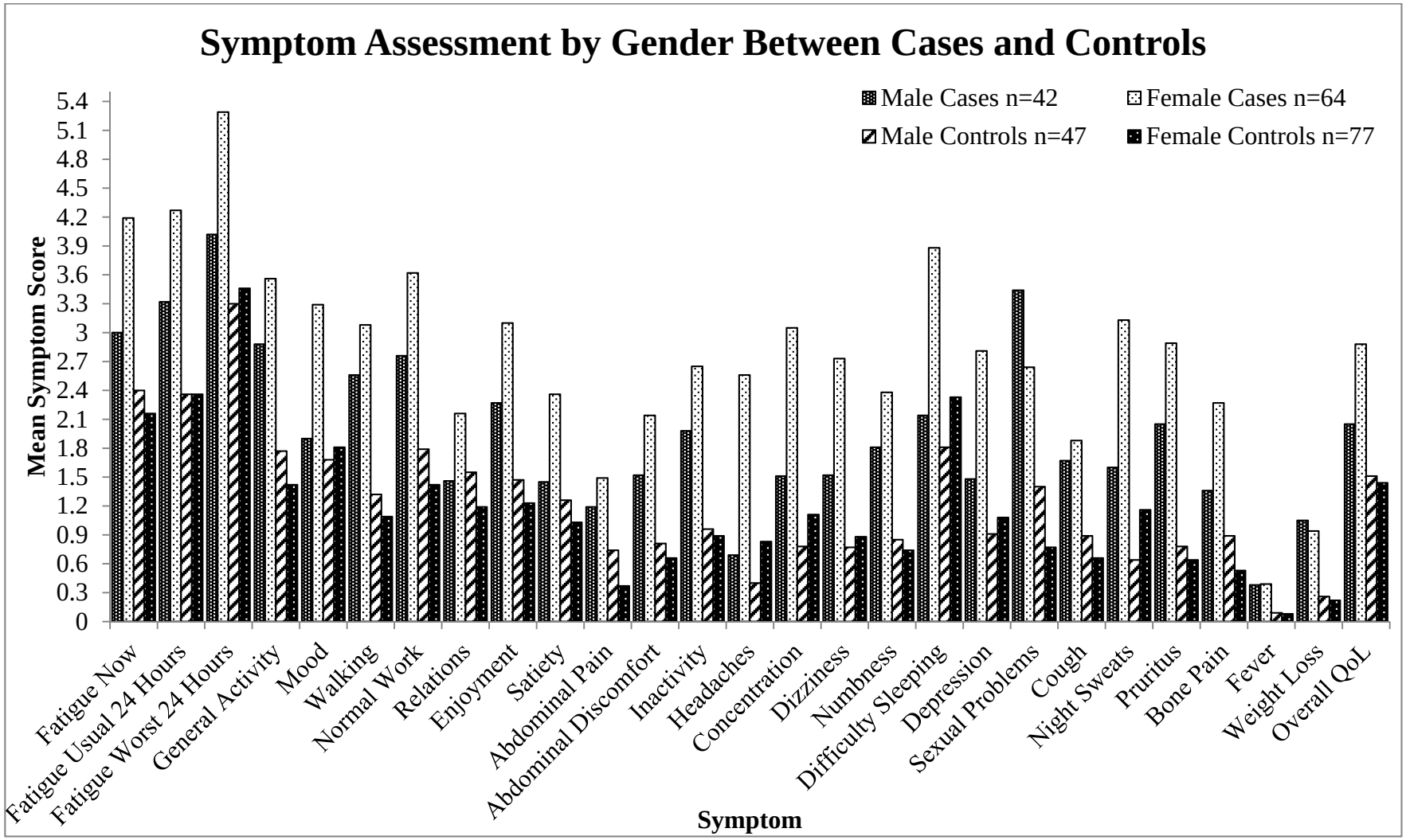

Figure 2: Mean symptom scores in MOSAICC cases and controls by gender.

Table 3: T-tests comparing symptom scores between male and female MOSAICC cases and controls

Variable	**Male vs Female Cases** *p-value*	**Male vs Female Controls** *p-value*	**Male cases vs Male controls** *p-value*	**Female cases vs female controls** *p-value*
Fatigue Now	**0.029**	0.570	0.271	**<0.001**
Fatigue Usual 24 Hours	0.070	0.987	0.068	**<0.001**
Fatigue Worst 24 Hours	**0.037**	0.757	0.261	**<0.001**
General Activity	0.244	0.363	**0.047**	**<0.001**
Mood	**0.010**	0.763	0.647	**<0.001**
Walking	0.375	0.545	**0.026**	**<0.001**
Normal Work	0.135	0.338	0.080	**<0.001**
Relations	0.135	0.305	0.832	**0.009**
Enjoyment	0.122	0.506	0.113	**<0.001**
Early satiety	**0.068**	0.495	0.643	**<0.001**
Abdominal Pain	0.475	0.143	0.261	**<0.001**
Abdominal Discomfort	0.198	0.596	0.093	**<0.001**
Inactivity	0.186	0.857	**0.027**	**<0.001**

Headaches	**<0.001**	0.148	0.320	**<0.001**
Concentration	**0.006**	0.387	0.087	**<0.001**
Dizziness	**0.013**	0.718	0.055	**<0.001**
Numbness	0.274	0.735	**0.026**	**<0.001**
Difficulty Sleeping	**0.005**	0.247	0.523	**0.002**
Depression	**0.006**	0.621	0.169	**<0.001**
Sexual Problems	0.243	0.113	**0.001**	**<0.001**
Cough	0.666	0.444	0.088	**<0.001**
Night Sweats	**0.011**	0.141	**0.040**	**<0.001**
Pruritus	0.190	0.673	**0.019**	**<0.001**
Bone Pain	0.086	0.298	0.330	**<0.001**
Fever	0.971	0.934	0.139	0.057
Weight Loss	0.805	0.885	**0.037**	**0.017**
Overall Quality of life	0.077	0.844	0.223	**<0.001**