Symptoms in the general Norwegian population - prevalence and associated factors

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Abstract

Background

Patients' own perceptions and evaluations of symptoms, functioning and other health-related factors, i.e. Patient Reported Outcomes (PROs), are important elements for providing good patient care. Symptoms are subjective and best elicited by the patient orally or by using PRO measures (PROMs). Reference values on frequently used PROMs facilitate the interpretation of PROMs scores both in clinics and research settings, by comparing patient data with relevant samples from the general population.

Objectives

Study objectives were to (1) present reference values for the M.D. Anderson Symptom inventory (MDASI) (2) examine the occurrence and intensity of symptoms assessed by the MDASI in a general Norwegian population sample, and (3) examine factors associated with higher symptom burden defined as the sum score of all symptoms, and factors associated with symptoms' interference on functions

Methods

In 2015, MDASI was sent by mail to a representative sample of the general Norwegian population (N = 6165). Medical comorbidities were assessed by the Self-Administered Comorbidity Questionnaire. Depression was self-reported on the Patient Health Questionnaire 9 (PHQ-9). Linear multivariable regression analysis was used to examine for factors associated with MDASI sum score and factors associated with symptoms’ interference on functions.

Results

The response rate was 36%. More females (54%) than males (46%) responded. Mean
age was 55 years (SD 14). The most frequent symptoms were fatigue (59.7%), drowsiness (56.2%) and pain (56.1%). Fatigue, pain and disturbed sleep had the highest mean scores. The presence of one or more comorbidities, increasing PHQ-9 score and lower level of education were associated with higher MDASI sum score (p<0.001). The MDASI sum score and the PHQ-9 score were positively associated with all interference items (p<0.001) except for walking (p=0.22).

Conclusion

This study provides the first Norwegian reference values for the MDASI. The presence of one or more comorbidities, higher level of depressive symptoms and lower level of education were significantly associated with higher MDASI sum score. These covariates must be controlled for when using the reference values.

Introduction

Patient Reported Outcomes (PROs) are patients’ own perceptions and evaluations of symptoms, functioning and other health-related factors, and are important elements for providing good patient care [1]. A symptom is defined as any subjective evidence of a disease, health condition, or treatment-related effect that can be noticed and known only by the patient [1]. In contrast, a “sign” is any objective evidence of disease that can be identified by health care personnel by observations, examinations, biomarkers, imaging etc. or may be noticed and reported by the patient [1]. Symptoms may indicate the presence of a disease or a disorder but may also reflect normal variations in physical or psychological states as commonly experienced by most individuals. Symptoms are common in the general population [2–5]. A large Danish nationwide cohort study with 49 706 respondents representative of the general population demonstrated that symptoms were
common; about 9 out of 10 respondents reported at least one symptom within the preceding four weeks [2]. Other population studies have reported that 75% and 90% had experienced at least one symptom in the previous two weeks and 30 days respectively [3, 5]. Some symptoms have low positive predictive value for disease while others are stronger predictors [6]. As this may vary for different symptoms across diseased populations, reference values from the general population will provide important information about the symptoms` predictive values for disease. The prevalence of symptoms in the general population is found to be associated with factors such as chronic conditions, age, employment status, living situation and psychiatric disorders [3, 7]. The number of symptoms is also documented to have a linear relationship with functional status [4].

Patient-Reported Outcome Measures (PROMs) denote any standardized measure of a PRO, i.e. a questionnaire, of a patient´s health and quality of life (QoL) [8]. These questionnaires are intended for self-completion by patients, in the form of the traditional paper forms or more recently in electronic formats (e-PROMs) for use on different platforms, e.g. cell phones, computers, tablets etc. [9]. PROMs provide information that comes directly from the patient [8]. In clinical care, PROMs can be used alongside laboratory tests and imaging, if properly assessed and followed. Regular and systematic use of PROMs may improve communication between patients and health care providers [10] and be used to monitor treatment response and detect unrecognized problems or problems not reported spontaneously by the patient [11]. Beyond their clinical utility, PROMs are increasingly being used as outcomes in epidemiologic, health economic and clinical research [12]. PROMS are also central components of patient-centered care [13, 14]. Recent studies suggested that active use of PROMs during treatment for advanced cancer may even
prolong survival [15-17].

Clinicians or researchers often request reference data to facilitate the interpretation of patient data or study results [18]. Reference values for PROMs facilitate the interpretation of PROMs scores both in clinics and research settings, by comparing patient data with relevant samples from the general population. Reference values may also be used to evaluate the relative symptom burden of a disease [19]. Hence, a number of datasets with population-based reference data have been published and are frequently being used, e.g. the Patient-Reported Outcomes Measurement Information System [19], European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire C30 [20] and the Functional Assessment of Cancer Therapy-General [21]. Reference values make comparisons between samples possible, but this requires adjusting for known variables that affect the outcomes, e.g. age, sex, residence, education, comorbidities and other sociodemographic variables [20, 22]. The relevance of valid reference data is illustrated in follow-up studies among cancer survivors, which may go beyond 20 years post-treatment. During such a long period, common age-related health problems and life events may influence which symptoms the cancer survivors experience and how they perceive their QoL and level of functioning. By comparing with data from the general population one can ascertain if cancer survivors are at excess risk for specific symptoms and health problems compared to individuals with similar age, sex and other background variables.

The M.D. Anderson Symptom Inventory (MDASI) is a brief, reliable and valid tool for self-report of symptoms commonly experienced by patients with cancer and also assesses their impact on daily functioning [23]. The MDASI is frequently used in clinical cancer care [24, 25]. However, all MDASI symptoms are prevalent in the
general population. Reference values for the MDASI from the general population therefore allow for interpretation of scores from patient samples and for comparison across studies and between relevant populations samples. Up until now, there are no reference values for the MDASI from the Norwegian population, nor have we found this from other countries.

On this background, study objectives were to (1) present reference values for the M.D. Anderson Symptom inventory (MDASI) (2) examine the occurrence and intensity of symptoms assessed by the MDASI in a general Norwegian population sample, and (3) examine factors associated with higher symptom burden defined as the sum score of all symptoms, and factors associated with symptoms` interference on functions

**Methods**

**Data collection**

In the spring 2015, 6165 subjects, aged 18–80 years, and representative of the general Norwegian population with respect to age, gender and place of residence, were randomly drawn by Bring Dialog [26]. They received a mailed questionnaire packet on paper containing the Short-Form Health Survey (SF-36), version 1 [27, 28], the M.D. Anderson Symptom Inventory (MDASI) [23], the Fatigue Questionnaire (FQ) [29] and the Patient Health Questionnaire-9 (PHQ-9) [30, 31]. The questionnaire packet also included questions covering 13 comorbidities [32] and 14 questions related to sociodemographics, physical activity, general health and contact with health care providers. Background variables (see below), comorbidities, the MDASI and the PHQ-9 were used in this study.
Results

The overall response rate was 36%. Of the 2130 returned questionnaires, 23 were blank, 21 had no data on sex, and 65 had responded to less than half of the individual MDASI symptoms. All these respondents were omitted, giving a sample of 2021. Missing values of the MDASI ranged from 0.1% (n = 3, numbness) to 1.4% (n = 28, fatigue).

More females (54%) than males (46%) responded. As shown in a previous publication from the same material [28], the response rate for both men and women was 5% in the youngest age group (≤ 29 years) which was significantly lower compared to the other groups (p < 0.001). Mean age of the study sample was 55 years (SD 14) (Table 1). Forty-six percent of the respondents had university college or university education.

| Variables                          | Population (N = 2021) | Mean MDASI sum score (SD)* |
|-----------------------------------|-----------------------|---------------------------|
| Age                               | 55 (14)               | 18.78 (20.24)             |
| Min.-Max.                         | 18–79                 |                           |
| Age groups, N (%)                 |                       |                           |
| ≤29 years                         | 101 (5.0)             | 18.76 (20.65)             |
| 30–39 years                       | 197 (9.7)             | 15.76 (18.89)             |
| 40–49 years                       | 390 (19.3)            | 14.68 (18.15)             |
| 50–59 years                       | 467 (23.1)            | 15.46 (17.88)             |
| 60–69 years                       | 499 (24.7)            | 15.13 (18.63)             |
| ≥70 years                         | 367 (18.2)            | 15.84 (17.91)             |
| Gender, N (%)                     |                       |                           |
| Women                             | 1101 (54)             | 16.71 (18.83)             |
| Men                               | 920 (46)              | 14.03 (17.65)             |
| Education, N (%), Missing 10 (0.5)|                       |                           |
| Second level, first stage         | 344 (17.1)            | 18.63 (20.55)             |
| Second level, second stage        | 751 (37.3)            | 16.98 (19.57)             |
| Third level (university college or university) | 916 (45.5) | 12.98 (15.95) |
*Min-max 0-130

Table 2 shows the frequency of comorbidities. Forty-two percent reported no comorbidities, 45% reported one or two while 13% reported three comorbidities or more. The most frequent were hypertension, arthrosis and depression. Arthrosis and depression were more common in women (23.6% and 15.3% vs. 12.5% and 9.3%),
while there was no difference regarding hypertension between men and women. Depression was more common among women in the youngest age group (23.1%) compared to women ≥ 70 years (15.3%).

| Comorbidity                  | All N (%) | Women N (%) | Men N (%) |
|------------------------------|-----------|-------------|-----------|
| Heart disease                | 135 (6.7) | 34 (3.1)    | 101 (11.0) |
| Hypertension                 | 482 (23.8)| 262 (23.8)  | 220 (23.9) |
| Chronic lung disease         | 205 (10.1)| 116 (10.5)  | 89 (9.7)   |
| Diabetes                     | 113 (5.6) | 44 (4.0)    | 69 (7.5)   |
| Kidney disease               | 40 (2.0)  | 17 (1.5)    | 23 (2.5)   |
| Liver disease                | 23 (1.1)  | 9 (0.8)     | 14 (1.5)   |
| Stomach/Bowel disease        | 123 (6.1) | 62 (5.6)    | 61 (6.6)   |
| Rheumatic disease            | 145 (7.2) | 100 (9.1)   | 45 (4.9)   |
| Arthrosis                    | 375 (18.6)| 260 (23.6)  | 115 (12.5) |
| Epilepsy                     | 22 (1.1)  | 16 (1.5)    | 6 (0.7)    |
| Stroke                       | 60 (3.0)  | 27 (2.5)    | 33 (3.6)   |
| Depression                   | 259 (12.8)| 169 (15.3)  | 90 (9.8)   |
| Other psychiatric conditions | 155 (7.7) | 99 (9.0)    | 56 (6.1)   |

*The Self-Administered Comorbidity Questionnaire [32]*

The most frequent symptoms (cut off ≥ 1) were fatigue (59.7%), drowsiness (56.2%) and pain (56.1%). When using a cut off ≥ 3, the prevalence was 34.8% for fatigue, 34.2% for pain and 26.7% for drowsiness. The mean scores for the 13 symptoms by age and gender are presented in Table 3. Fatigue, pain and disturbed sleep had the highest mean scores overall (Fig. 1). Fatigue had the highest mean score; 2.39 in women and 1.90 in men. The mean scores for fatigue were highest in the youngest age group (< 30 years), with higher score for women (3.45) than in men (2.36).

Overall, the mean scores for pain were 2.24 in women and 1.94 in men, and the mean scores for disturbed sleep were 1.93 in women and 1.42 in men.

| Symptom                  | 18–29 years | 30–39 years | 40–49 years | 50–59 years | 60–69 years | 70–80 years | Total |
|--------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------|
| Pain                     | 1.69 (n=64–65) | 1.69 (n=115–116) | 1.69 (n=222–227) | 1.69 (n=251–257) | 2.39 (n=207–210) | 2.53 (n=242–248) | 2.21 (n=174–179) | 2.10 (n=1084–1101) | 2.24 (n=914–920) |
Univariable regression analysis showed a significant positive association between
the presence of one or more comorbidities (p < 0.001) and between PHQ- score and
MDASI sum score (p < 0.001). Level of education was also associated with MDASI
sum score (p < 0.001), while no association was found with age (p = 0.5). Further, because of the low response rate in youngest age group separate analyses were done without this age group yielding similar results.

Multivariable linear regressions (Table 4) showed positive significant associations between the MDASI sum score and depression on the PHQ (p < 0.001) and the presence of one or more comorbidities (p < 0.001). Participants with the highest education level had significantly lower MDASI sum score than respondents with education in levels one (p = 0.006) and two (p = 0.003). Females had significantly higher MDASI sum score than males in univariable analyses (p = 0.001), but not in the multivariable regression model. The overall model fit was $R^2 = 0.45$.

| Table 4 |
|-----------------|-----------------|-----------------|---------------|
| Multiple linear regression on the MDASI sum score with age, sex, education, comorbidity and depression as explanatory variables (N = 2021) |
| MDASI sum score* | Adjusted $R^2 = 0.45$ |
| Age groups | B | 95% CI | p |
| 18–29 years | 0.397 | -2.761, 3.555 | 0.446 |
| 30–39 years | -0.449 | -2.985, 2.087 | 0.805 |
| 40–49 years | -1.214 | -3.318, 0.890 | 0.258 |
| 50–59 years | 0.735 | -1.244, 2.715 | 0.466 |
| 60–69 years | 0.292 | -1.583, 2.167 | 0.760 |
| 70–80 years (ref) | - | - | 0.109 |
| Sex | - | - | 0.109 |
| Women | 0.99 | -0.222, 2.202 | 0.109 |
| Men (ref) | - | - | - |
| Education | - | - | 0.002 |
| Second level, first stage | 2.591 | 0.759, 4.423 | 0.006 |
| Second level, second stage | 2.029 | 0.695, 3.363 | 0.003 |
| Third level (ref) | - | - | - |
| Comorbidities | - | - | 0.000 |
| 0 (ref) | - | - | 0.000 |
| 1–2 | 3.452 | 2.116, 4.789 | 0.000 |
| ≥ 3 | 10.693 | 8.627, 12.760 | 0.000 |
| Depression | PHQ score | 4.685 | 4.412, 4.958 | 0.000 |

*Demographic and disease-related variables that were significantly correlated with MDASI sum score in the univariable analyses were entered as covariates

Each interference item was used as the dependent variable in separate multivariable linear regression analyses (Table 5), with age, sex, education,
comorbidity, PHQ score and MDASI sum score as independent variables.

Comorbidities, PHQ score and MDASI sum score were significantly associated with both general activity and work as the dependent variables ($p \leq 0.001$). Increased number of comorbidities and higher MDASI sum score were significantly associated with higher score on the interference item walking ($p < 0.001$). Further, the multivariable regression analyses showed that PHQ score and MDASI sum score were significantly associated ($p < 0.001$) with mood, relations and enjoyment of life as dependent variables.

Table 5
Multiple linear regression with the six interference items as the outcomes for all respondents included ($N = 2021$) *

|          | General activity | Mood | Working | Relations | Walking | Enjoyment of life |
|----------|------------------|------|---------|-----------|---------|-------------------|
|          | Adjusted R$^2$ = 0.460 | Adjusted R$^2$ = 0.584 | Adjusted R$^2$ = 0.516 | Adjusted R$^2$ = 0.543 | Adjusted R$^2$ = 0.291 | Adjusted R$^2$ = 0.589 |
| B        | 95% CI | B | 95% CI | B | 95% CI | B | 95% CI | B | 95% CI | B | 95% CI |
| Age groups |       |       |       |       |       |       |       |       |       |       |       |
| 18-29 years | 0.10   | -0.3 | 0.53  | 0.65 | 0.66 | 0.32  | 0.85  | 0.00 | 0.04 | 0.00  | 0.01  | -0.17  |
| 30-39 years | 0.18   | 0.17 | 0.53  | 0.31 | 0.58 | 0.32  | 0.85  | 0.00 | 0.00 | 0.00  | 0.00  | 0.00  |
| 40-49 years | 0.38   | 0.08 | 0.67  | 0.01 | 0.54 | 0.32  | 0.76  | 0.00 | 0.00 | 0.00  | 0.00  | 0.00  |
| 50-59 years | 0.23   | -0.0 | 0.50  | 0.09 | 0.13 | 0.00  | 0.34  | 0.21 | 0.07 | 0.07  | 0.00  | 0.00  |
| 60-69 years | -0.0  | 0.09 | 0.48  | 0.09 | 0.07 | 0.00  | 0.27  | 0.21 | 0.07 | 0.00  | 0.00  | 0.00  |
| 70-80 years (ref) |       |      |       |       |       |       |       |       |       |       |       |
| Sex       |       |       |       |       |       |       |       |       |       |       |       |
| Women     | 0.08  | -0.0 | 0.33  | 0.02 | -0.1 | 0.75  | 0.22  | 0.06 | 0.02 | -0.1  | 0.77  | -0.1  |
|          | 0.25  | 0.15 | 0.01  | 0.39 | 0.23 | 0.16  | 0.03  | 0.23 | 0.06 | 0.23  | 0.07  | 0.12  |

*
| Education | Men (ref) | 3 | - | - | - | - | - | - |
|-----------|----------|---|---|---|---|---|---|---|
| 1st stage  | 0.14     | 0.11 0.40 2 | 0.26 7 | 0.11 0.1 0.36 7 | 0.38 | 0.36 0.10 0.00 7 | 0.08 | 0.1 0.1 0.29 0.44 6 |
| 2nd stage  | 0.02     | 0.1 0.21 2 | 0.78 9 | 0.10 0.0 0.28 | 0.31 0.05 0.1 0.4 0.23 0.61 | 0.1 0.4 0.02 0.07 7 |
| 3rd stage  | 0.0       | - | - | - | - | - | - | - |
| Comorbidities | ≥ 3 (ref) | 0 | - | - | - | - | - | - |
| 0          | -0.6 72 0 0 | -0.9 0.7 0.3 0 | -0.0 0 7 | -0.3 0.16 0.53 0 | -0.4 0.7 0.1 7 | -0.2 0.02 0.26 0 | 0.02 0.50 0.03 | -0.8 -0.1 0.1 1 | -1.1 0.0 0 1 | -0.4 0.1 0.07 0.16 0 |
| 1-2        | -0.3 84 0 | -0.6 0.6 0.1 0 | 0.00 7 | 0.0 0 | -0.3 0.2 0.96 2 | -0.3 0.6 0 0.05 0 | 0.02 0.34 0 | 0.12 0.56 0 | 0.00 0.00 0.00 0 | -0.4 0.1 0.04 0.10 7 |
| ≥ 3 (ref)  | -        | - | - | - | - | - | - | - |
| Depression | 0.17 7 0.04 | 0.12 0 | 0.00 0 | 0.34 0.30 0 | 0.00 0.26 0 | 0.21 0.31 0 | 0.00 0.36 0 | 0.32 0.40 0 | 0.00 0 | 0.22 0.47 0.43 0.51 0 |
| PHQ score  | 0.07 8 0.08 | 0.06 0 | 0.00 0 | 0.06 0.06 0 | 0.00 0.08 0 | 0.07 0.08 0 | 0.00 0.06 0 | 0.05 0.06 0 | 0.00 0 | 0.05 0.05 0.06 0.00 0 |
| Symptom burden | MDA SI sum | 0.07 5 | 0.06 0 | 0.00 0 | 0.06 0.06 0 | 0.00 0.08 0 | 0.07 0.08 0 | 0.00 0.06 0 | 0.05 0.06 0 | 0.00 0 | 0.05 0.05 0.06 0.00 0 |

Discussion

This study provides the first Norwegian reference values for the MDASI based on data from 2021 men and women aged 18-80 years collected in 2015. The most frequent symptoms overall were fatigue, drowsiness and pain. Fatigue, pain and disturbed sleep had the highest mean scores. The mean scores for fatigue were
highest in the youngest age group (18–29 years). The presence of one or more comorbidities, increasing levels of depressive symptoms and lower level of education were significantly associated with a higher MDASI sum score. Comorbidity showed the strongest association; having three or more comorbidities increased the MDASI sum score with 10 points in average. Sex was not significantly associated with MDASI sum score when education, depression and comorbidities were controlled for in the regression model.

The Health Study of Nord-Trøndelag County (HUNT 3) found that the prevalence of chronic pain was 36% among women and 25% among men, and that the prevalence increased with age [39]. A random sample of participants were followed with annual measures over 4 years [40]. Here, pain intensity ranging from no pain to very mild, mild, moderate, severe and very severe pain was included to identify clinically important pain. A cut-off between mild and moderate pain may identify individuals with complex pain [41]. In our study, a cut off ≥ 1 was chosen to identify the presence of a symptom. By increasing the cut off to ≥ 3, the prevalence was about 34% for pain, which corresponds to the finding in the HUNT 3 study. Previous studies have shown that women generally report a higher number of symptoms than men [3, 5, 42, 43]. A Norwegian population study [43] also found that women reported a higher number of symptoms than men, although the association between somatic symptoms and anxiety and depression was equally strong in men and women indicating that the difference in prevalence of these conditions between the sexes could not explain the difference in the reported number of somatic symptoms. Elnegaard et.al. [2] found no sex differences for almost 2/3 of the reported symptoms leading to contact with a general practitioner in their population study. In our study, more females (15%) than males (9%)
reported depression on the PHQ-9. This might explain why sex was not associated with symptom sum score when controlling for depression.

Across the lifespan, depression is almost twice as common in women as in men. The prevalence of major depressive episode worldwide is approximately 5% [44]. However, major depressive disorder is different from feelings of sadness which also may lead to increased symptom score. The PHQ-9 is a tool that can be used to identify and assess depression, but it is important to also assess contextual factors like alternative psychiatric diagnoses, a medical illness, or the side-effects of medication [45]. We used the PHQ-9 as a measure of depressive symptoms, and not as a measure of depressive disorder. Symptom criteria for depression overlap symptoms of cancer and other comorbidities, e.g. fatigue, poor appetite and sleep problems [46]. In patients with increased symptom burden, exclusion of somatic symptom criteria in the PHQ-9 may reduce the likelihood of being false positive categorized as depressed [38]. In this study, the four somatic depression symptoms in the PHQ-9 were excluded to avoid overlap with the MDASI. We found a significant association between higher levels of depressive symptoms and higher MDASI sum score.

Comorbidities were significantly associated with an increased MDASI sum score in our study. A cross-sectional study from the USA [47] found that symptom scores on all domains were significantly worse in people with multiple sclerosis than in the general population, also after adjusting for age and sex. Similarly, a study found that patients with systemic lupus erythematosus (SLE) had symptom scores that indicated poorer average health status in SLE patients compared with the general population [48]. A survey among patients with type 2 diabetes in primary care found that the study population reported more problems with physical functioning and
pain compared to the general population [49]. This illustrates the importance of reference values when comparing differences in daily function for populations with a specific disease and the general population. It is important to adjust for comorbidities when comparing different populations in terms of level of symptom scores. This also applies to other variables that significantly affect the symptom level, like depression and education. The independent variables included in the multiple regression model explained 45% of the variance in MDASI sum score. By controlling for relevant associated factors, potential bias is likely to be reduced.

Comorbidity, depression and MDASI sum score were significantly associated with the interference items general activity and work. Depression and MDASI sum score were negatively associated with enjoyment, mood and relations to other people. Bruusgaard et.al. [4] found a strong linear association between the number of self-reported symptoms and decreased functional status in the Norwegian Ullensaker population study. Anxiety and depression were symptoms that had substantially higher explanatory power on functional status than other symptoms [4]. This in agreement with the findings in our study, with depressive symptoms being associated with all interference items but walking. These findings indicate that interference is influenced by other variables than just symptoms. This does not only apply to the emotional domains like enjoyment and mood, but also to the more functional ones like work and general activity.

Limitations

The randomly drawn sample was assumed to be representative of the general Norwegian population with respect to age, sex, and place of living. However, only 36% of the sample responded to the survey. Compared to collection of Norwegian reference values for the SF-36 in 1996 and 2002 this response rate was low [28].
The decline in response rates from 67% in 1996 to 36% in 2015 is in line with other postal surveys [3, 22, 50, 51]. Another Norwegian study found that health-related quality of life was relatively stable in two cross-sectional studies over an eight year period despite the response rate being 68% in the first study and 35% in the second [52]. Surveys are used to describe large populations, and high response rates are valued to reduce the risk of bias. However, nonresponse bias is only indirectly related to nonresponse rates and there is little empirical support for the notion that low response rates are more prone to nonresponse bias than samples with higher response rates [53]. The fact that response rates in sample surveys in general have declined over the past decades is challenging for population studies [53]. Innovation in epidemiologic studies should involve development of recruitment techniques that optimize participation [54]. A large Danish population study from 2015 [2] used web-based questionnaires and had a response rate of 52%. In our study, the paper-based questionnaire was not available in an electronic version.

According to Statistics Norway, 18% of the population was 67 years or above, while 27% of the responders were in the same age group [28]. About 21% of the population in this study was between 18 and 29 years, while only 5% of this age group participated in the survey. The high mean symptom scores for the youngest age group may not be representative for the general population in the same age, due to the very low response rate in this age group. For the older population, the opposite pattern was observed. The relatively high symptom scores in the youngest age group compared to the older age groups may indicate an unhealthy bias in the youngest age group and a healthy bias among the older age groups. Taken together, these factors suggest that the reference values might be biased due to selection among the youngest participants. Regrettably, our data did not permit
further analyses to illuminate this.

Conclusion

This study provides the first Norwegian reference values for the MDASI. The presence of one or more comorbidities, increased levels of depressive symptoms and lower level of education were significantly associated with higher MDASI sum score. These covariates must be controlled for when using the reference values.

declarations

Ethics approval and consent to participate

The study was performed according to the rules of the Helsinki declaration. All respondents received written information about the study. Return of the questionnaires was taken to indicate written, informed consent. The Regional Committee for Medical and Health Research Ethics (REC) South East Norway approved the survey (2014/1172).

Consent for publication

Not applicable

Availability of data and materials

The dataset used and analysed during the current study is available from the corresponding author on reasonable request.

Competing interests

HK, KSG, ØS, CEK and MJH have no declared conflicts of interests. Eir Solutions AS was established in 2015 with SK, JHL, and NTNU Technology Transfer AS as shareholders. No income, dividend, or financial benefits are related to the work presented here nor in relation to Eir in any way.
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Authors contributions
Conzeptualization: JHL, MJH. Methodology: MJH, KSG, JHL. Formal analysis: HK, ØS. Project administration: MJH, KSG, JHL. Writing original draft: HK. Supervision, writing-review and editing: JHL, KSG, SK, ØS, CEK, MJH. All authors read and approved the final manuscript

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**Figures**

![Figure 1](image-url)  

*Figure 1*  

Distribution of scores 0-10 on pain, fatigue, sleep
Results

The overall response rate was 36%. Of the 2130 returned questionnaires, 23 were blank, 21 had no data on sex, and 65 had responded to less than half of the individual MDASI symptoms. All these respondents were omitted, giving a sample of 2021. Missing values of the MDASI ranged from 0.1% (n = 3, numbness) to 1.4% (n = 28, fatigue).

More females (54%) than males (46%) responded. As shown in a previous publication from the same material [28], the response rate for both men and women was 5% in the youngest age group (≤ 29 years) which was significantly lower compared to the other groups (p < 0.001).

Mean age of the study sample was 55 years (SD 14) (Table 1). Forty-six percent of the respondents had university college or university education.

| Variables                        | Population (N = 2021) | Mean MDASI sum score (SD)* |
|----------------------------------|-----------------------|-----------------------------|
| **Age**                          |                       |                             |
| Mean (± SD)                      | 55 (14)               |                             |
| Min.-Max.                        | 18–79                 |                             |
| **Age groups, N (%)**            |                       |                             |
| ≤29 years                        | 101 (5.0)             | 18.78 (20.24)               |
| 30–39 years                      | 197 (9.7)             | 15.76 (18.89)               |
| 40–49 years                      | 390 (19.3)            | 14.68 (18.15)               |
| 50–59 years                      | 467 (23.1)            | 15.46 (17.88)               |
| 60–69 years                      | 499 (24.7)            | 15.13 (18.63)               |
| ≥70 years                        | 367 (18.2)            | 15.84 (17.91)               |
| **Gender, N (%)**                |                       |                             |
| Women                            | 1101 (54)             | 16.71 (18.83)               |
| Men                              | 920 (46)              | 14.03 (17.65)               |
| **Education, N (%), Missing 10 (0.5)** |       |                             |
| Second level, first stage        | 344 (17.1)            | 18.63 (20.55)               |
| Second level, second stage       | 751 (37.3)            | 16.98 (19.57)               |
| Third level (university college or university) | 916 (45.5) | 12.98 (15.95)               |

*Min-max 0-130

Table 2 shows the frequency of comorbidities. Forty-two percent reported no comorbidities, 45% reported one or two while 13% reported three comorbidities or more. The most frequent were hypertension, arthrosis and depression. Arthrosis and depression were more common in women (23.6% and 15.3% vs. 12.5% and 9.3%), while there was no difference regarding
hypertension between men and women. Depression was more common among women in the youngest age group (23.1%) compared to women ≥ 70 years (15.3%).

Table 2
Comorbidities *, overall and by sex

| Comorbidity                  | All       | Women N (%) | Men N (%) |
|-----------------------------|-----------|-------------|-----------|
| Heart disease               | 135 (6.7) | 34 (3.1)    | 101 (11.0)|
| Hypertension                | 482 (23.8)| 262 (23.8)  | 220 (23.9)|
| Chronic lung disease        | 205 (10.1)| 116 (10.5)  | 89 (9.7)  |
| Diabetes                    | 113 (5.6) | 44 (4.0)    | 69 (7.5)  |
| Kidney disease              | 40 (2.0)  | 17 (1.5)    | 23 (2.5)  |
| Liver disease               | 23 (1.1)  | 9 (0.8)     | 14 (1.5)  |
| Stomach/Bowel disease       | 123 (6.1) | 62 (5.6)    | 61 (6.6)  |
| Rheumatic disease           | 145 (7.2) | 100 (9.1)   | 45 (4.9)  |
| Arthritis                   | 375 (18.6)| 260 (23.6)  | 115 (12.5)|
| Epilepsy                    | 22 (1.1)  | 16 (1.5)    | 6 (0.7)   |
| Stroke                      | 60 (3.0)  | 27 (2.5)    | 33 (3.6)  |
| Depression                  | 259 (12.8)| 169 (15.3)  | 90 (9.8)  |
| Other psychiatric conditions| 155 (7.7) | 99 (9.0)    | 56 (6.1)  |

*The Self-Administered Comorbidity Questionnaire [32]

The most frequent symptoms (cut off ≥ 1) were fatigue (59.7%), drowsiness (56.2%) and pain (56.1%). When using a cut off ≥ 3, the prevalence was 34.8% for fatigue, 34.2% for pain and 26.7% for drowsiness. The mean scores for the 13 symptoms by age and gender are presented in Table 3. Fatigue, pain and disturbed sleep had the highest mean scores overall (Fig. 1).

Fatigue had the highest mean score; 2.39 in women and 1.90 in men. The mean scores for fatigue were highest in the youngest age group (< 30 years), with higher score for women (3.45) than in men (2.36). Overall, the mean scores for pain were 2.24 in women and 1.94 in men, and the mean scores for disturbed sleep were 1.93 in women and 1.42 in men.

Table 3
Mean MDASI scores (SD)* by sex and age groups, N = 2021

| Symptom | Age groups | Total |
|---------|------------|-------|
|         | 18-29 years| 30-39 years |
|         | W M (n = 64-65 | n = 36) | W M (n = 80-81 | n = 116) | W M (n = 222-227 | n = 227) | W M (n = 251-257 | n = 257) | W M (n = 207-210 | n = 210) | W M (n = 242-248 | n = 248) | W M (n = 182-188 | n = 188) | W M (n = 174-179 | n = 179) | W M (n = 1084-1101 | n = 1101) | W M (n = 914-920 | n = 920) |
| Pain    | 1.69 (2.44 | 1.17 (2.12 | 1.64 (2.35 | 2.22 (2.71 | 1.90 (2.34 | 2.39 (2.65 | 1.97 (2.58 | 2.53 (2.78 | 2.04 (2.24 | 2.15 (2.51 | 2.10 (2.66 | 1.94 (2.46 | 2.34 (2.66 | 1.90 (2.34 | 2.24 (2.66 | 1.94 (2.46 |
| Fatigue | 3.45 (2.86 | 2.36 (2.58 | 2.87 (2.75 | 2.96 (2.32 | 2.53 (2.78 | 1.94 (2.43 | 2.57 (2.67 | 1.87 (2.39 | 2.03 (2.61 | 1.90 (2.31 | 1.78 (2.20 | 1.80 (2.23 | 2.39 (2.66 | 1.90 (2.34 | 2.24 (2.66 | 1.94 (2.46 |
| Nausea  | 1.03 (2.03 | 0.56 (1.59 | 0.74 (1.62 | 0.28 (0.97 | 0.64 (1.70 | 0.22 (0.83 | 0.55 (1.61 | 0.41 (1.51 | 0.40 (1.40 | 0.24 (0.84 | 0.51 (1.37 | 0.40 (1.28 | 0.57 (1.58 | 0.32 (1.16 | 0.57 (1.58 | 0.32 (1.16 |
Univariable regression analysis showed a significant positive association between the presence of one or more comorbidities (p < 0.001) and between PHQ-score and MDASI sum score (p < 0.001). Level of education was also associated with MDASI sum score (p < 0.001), while no association was found with age (p = 0.5). Further, because of the low response rate in youngest age group separate analyses were done without this age group yielding similar results.
Multivariable linear regressions (Table 4) showed positive significant associations between the MDASI sum score and depression on the PHQ (p < 0.001) and the presence of one or more comorbidities (p < 0.001). Participants with the highest education level had significantly lower MDASI sum score than respondents with education in levels one (p = 0.006) and two (p = 0.003). Females had significantly higher MDASI sum score than males in univariable analyses (p = 0.001), but not in the multivariable regression model. The overall model fit was $R^2 = 0.45$.

Table 4

|                      | MDASI sum score* |
|----------------------|------------------|
|                      | Adjusted $R^2 = 0.45$ |
|                      | B                | 95% CI       | p   |
| Age groups           |                  |              |     |
| 18–29 years          | 0.397            | -2.761, 3.555 | 0.805 |
| 30–39 years          | -0.449           | -2.985, 2.087 | 0.728 |
| 40–49 years          | -1.214           | -3.318, 0.890 | 0.258 |
| 50–59 years          | 0.735            | -1.244, 2.715 | 0.466 |
| 60–69 years          | 0.292            | -1.583, 2.167 | 0.760 |
| 70–80 years (ref)    | -                |              |     |
| Sex                  |                  |              |     |
| Women (ref)          | 0.99             | -0.222, 2.202 | 0.109 |
| Men (ref)            | -                |              |     |
| Education            |                  |              |     |
| Second level, first stage | 2.591          | 0.759, 4.423  | 0.006 |
| Second level, second stage | 2.029         | 0.695, 3.363  | 0.003 |
| Third level (ref)    | -                |              |     |
| Comorbidities        |                  |              |     |
| 0 (ref)              | -                |              | 0.000 |
| 1-2                  | 3.452            | 2.116, 4.789  | 0.000 |
| $\geq$ 3             | 10.693           | 8.627, 12.760 | 0.000 |
| Depression           |                  |              |     |
| PHQ score            | 4.685            | 4.412, 4.958  | 0.000 |

*Demographic and disease-related variables that were significantly correlated with MDASI sum score in the univariable analyses were entered as covariates.

Each interference item was used as the dependent variable in separate multivariable linear regression analyses (Table 5), with age, sex, education, comorbidity, PHQ score and MDASI sum score as independent variables. Comorbidities, PHQ score and MDASI sum score were significantly associated with both general activity and work as the dependent variables (p ≤ 0.001). Increased number of comorbidities and higher MDASI sum score were significantly associated with higher score on the interference item walking (p < 0.001). Further, the multivariable regression analyses showed that PHQ score and MDASI sum score were
significantly associated (p < 0.001) with mood, relations and enjoyment of life as dependent variables.

Table 5  
Multiple linear regression with the six interference items as the outcomes for all respondents included (N = 2021) *

| General activity | Mood | Working | Relations | Walking | Enjoyment of life |
|------------------|------|---------|-----------|---------|------------------|
| Adjusted R² = 0.460 | Adjusted R² = 0.584 | Adjusted R² = 0.516 | Adjusted R² = 0.543 | Adjusted R² = 0.291 | Adjusted R² = 0.589 |
| B | 95% CI | p | B | 95% CI | p | B | 95% CI | p | B | 95% CI | p | B | 95% CI | p |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age groups** | | | | | | | | | | | | | | |
| 18–29 years | 0.10 | -0.33 | 9 | 0.65 | 0.66 | 0.32 | 0.99 | 0.00 | 0.04 | -0.39 | 0.48 | 0.84 | 0.43 | 0.08 | 0.77 | 0.01 | -0.98 | -0.48 | 0.00 | 0.00 | -0.25 | -0.11 | 0.17 | 0.6 |
| 30–39 years | 0.18 | 0.17 | 3 | 0.58 | 0.32 | 0.85 | 0.00 | 0.27 | -0.08 | 0.62 | 0.12 | 0.35 | 0.08 | 0.63 | 0.01 | 0.77 | -0.77 | -0.42 | 0.00 | 0.00 | -0.10 | -0.39 | 0.47 | 0.3 |
| 40–49 years | 0.38 | 0.08 | 7 | 0.67 | 0.01 | 0.54 | 0.32 | 0.76 | 0.00 | 0.37 | 0.08 | 0.65 | 0.01 | 0.36 | 0.13 | 0.59 | 0.00 | 0.53 | -0.83 | -0.24 | 0.00 | 0.00 | -0.02 | -0.26 | 0.85 | 0.7 |
| 50–59 years | 0.23 | -0.04 | 4 | 0.50 | 0.09 | 0.13 | -0.08 | 0.34 | 0.21 | 0.37 | 0.08 | 0.65 | 0.01 | 0.36 | 0.13 | 0.59 | 0.00 | 0.53 | -0.83 | -0.24 | 0.00 | 0.00 | -0.02 | -0.26 | 0.85 | 0.7 |
| 60–69 years | 0.03 | -0.03 | 6 | 0.48 | 0.09 | 0.07 | -0.30 | 0.27 | 0.27 | 0.04 | -0.22 | 0.29 | 0.77 | 0.14 | -0.07 | 0.35 | 0.18 | -0.14 | -0.41 | 0.12 | 0.28 | 0.06 | -0.16 | 0.27 | 0.6 |
| 70–80 years (ref) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| **Sex** | | | | | | | | | | | | | | | | | | | | | |
| Women | 0.08 | -0.08 | 5 | 0.33 | 0.02 | -0.11 | 0.15 | 0.75 | 0.22 | 0.06 | 0.09 | 0.00 | 0.02 | -0.12 | 0.16 | 0.77 | 0.06 | -0.11 | 0.23 | 0.47 | 0.13 | -0.27 | 0.06 | 0.6 |
| Men (ref) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| **Education** | | | | | | | | | | | | | | | | | | | | | |
| Second level, first stage | 0.14 | -0.11 | 1 | 0.40 | 0.11 | 0.14 | 0.38 | - | 0.38 | 0.36 | 0.07 | 0.10 | 0.61 | 0.00 | 0.08 | 0.13 | 0.29 | 0.44 | 0.44 | 0.06 | 0.6 |
| Second level, second stage | 0.02 | -0.16 | 0 | 0.21 | 0.78 | -0.09 | 0.31 | - | 0.05 | -0.14 | 0.23 | 0.00 | 0.08 | 0.14 | 0.29 | 0.07 | 0.02 | 0.47 | 0.06 | 0.44 | 0.06 | 0.6 |
| Third level (ref) | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Comorbidities | 0 | 1–2 | ≥ 3 (ref) | PHQ score | Symptom burden | MDA SI sum |
|---------------|---|-----|-----------|------------|---------------|------------|
|               | 0.00 | -0.32 | 0.00 | 0.00 | 0.00 | 0.00 |
|               | -0.48 | 0.96 | -0.10 | 0.06 | 0.06 | 0.05 |
|               | -0.77 | -0.32 | -0.10 | 0.00 | 0.08 | 0.05 |
|               | 0.53 | 0.36 | 0.00 | 0.06 | 0.06 | 0.06 |
|               | -0.19 | -0.60 | 0.00 | 0.08 | 0.06 | 0.06 |
|               | 0.00 | 0.02 | 0.00 | 0.00 | 0.00 | 0.00 |
|               | 0.02 | 0.34 | 0.00 | 0.06 | 0.05 | 0.05 |
|               | 0.26 | 0.36 | 0.00 | 0.08 | 0.08 | 0.06 |
|               | 0.00 | 0.34 | 0.00 | 0.05 | 0.05 | 0.05 |
|               | 0.00 | -0.81 | 0.00 | 0.05 | 0.05 | 0.05 |
|               | 0.00 | -0.10 | 0.00 | 0.05 | 0.05 | 0.05 |
|               | 0.00 | 1.00 | 0.00 | 0.00 | 0.00 | 0.00 |

* Demographic and disease-related variables that were significantly correlated with MDASI sum score in the univariable analyses were entered as covariates.

Discussion

This study provides the first Norwegian reference values for the MDASI based on data from 2021 men and women aged 18–80 years collected in 2015. The most frequent symptoms overall were fatigue, drowsiness and pain. Fatigue, pain and disturbed sleep had the highest mean scores. The mean scores for fatigue were highest in the youngest age group (18–29 years). The presence of one or more comorbidities, increasing levels of depressive symptoms and lower level of education were significantly associated with a higher MDASI sum score. Comorbidity showed the strongest association; having three or more comorbidities increased the MDASI sum score with 10 points in average. Sex was not significantly associated with MDASI sum score when education, depression and comorbidities were controlled for in the regression model.

The Health Study of Nord-Trøndelag County (HUNT 3) found that the prevalence of chronic pain was 36% among women and 25% among men, and that the prevalence increased with age [39]. A random sample of participants were followed with annual measures over 4 years [40].
Here, pain intensity ranging from no pain to very mild, mild, moderate, severe and very severe pain was included to identify clinically important pain. A cut-off between mild and moderate pain may identify individuals with complex pain [41]. In our study, a cut off ≥ 1 was chosen to identify the presence of a symptom. By increasing the cut off to ≥ 3, the prevalence was about 34% for pain, which corresponds to the finding in the HUNT 3 study.

Previous studies have shown that women generally report a higher number of symptoms than men [3, 5, 42, 43]. A Norwegian population study [43] also found that women reported a higher number of symptoms than men, although the association between somatic symptoms and anxiety and depression was equally strong in men and women indicating that the difference in prevalence of these conditions between the sexes could not explain the difference in the reported number of somatic symptoms. Elnegaard et.al. [2] found no sex differences for almost 2/3 of the reported symptoms leading to contact with a general practitioner in their population study. In our study, more females (15%) than males (9%) reported depression on the PHQ-9. This might explain why sex was not associated with symptom sum score when controlling for depression.

Across the lifespan, depression is almost twice as common in women as in men. The prevalence of major depressive episode worldwide is approximately 5% [44]. However, major depressive disorder is different from feelings of sadness which also may lead to increased symptom score. The PHQ-9 is a tool that can be used to identify and assess depression, but it is important to also assess contextual factors like alternative psychiatric diagnoses, a medical illness, or the side-effects of medication [45]. We used the PHQ-9 as a measure of depressive symptoms, and not as a measure of depressive disorder. Symptom criteria for depression overlap symptoms of cancer and other comorbidities, e.g. fatigue, poor appetite and sleep problems [46]. In patients with increased symptom burden, exclusion of somatic symptom criteria in the PHQ-9 may reduce the likelihood of being false positive categorized as
depressed [38]. In this study, the four somatic depression symptoms in the PHQ-9 were excluded to avoid overlap with the MDASI. We found a significant association between higher levels of depressive symptoms and higher MDASI sum score. Comorbidities were significantly associated with an increased MDASI sum score in our study. A cross-sectional study from the USA [47] found that symptom scores on all domains were significantly worse in people with multiple sclerosis than in the general population, also after adjusting for age and sex. Similarly, a study found that patients with systemic lupus erythematosus (SLE) had symptom scores that indicated poorer average health status in SLE patients compared with the general population [48]. A survey among patients with type 2 diabetes in primary care found that the study population reported more problems with physical functioning and pain compared to the general population [49]. This illustrates the importance of reference values when comparing differences in daily function for populations with a specific disease and the general population. It is important to adjust for comorbidities when comparing different populations in terms of level of symptom scores. This also applies to other variables that significantly affect the symptom level, like depression and education. The independent variables included in the multiple regression model explained 45% of the variance in MDASI sum score. By controlling for relevant associated factors, potential bias is likely to be reduced.

Comorbidity, depression and MDASI sum score were significantly associated with the interference items general activity and work. Depression and MDASI sum score were negatively associated with enjoyment, mood and relations to other people. Bruusgaard et.al. [4] found a strong linear association between the number of self-reported symptoms and decreased functional status in the Norwegian Ullensaker population study. Anxiety and depression were symptoms that had substantially higher explanatory power on functional status than other symptoms [4]. This in in agreement with the findings in our study, with
depressive symptoms being associated with all interference items but walking. These findings indicate that interference is influenced by other variables than just symptoms. This does not only apply to the emotional domains like enjoyment and mood, but also to the more functional ones like work and general activity.

Limitations
The randomly drawn sample was assumed to be representative of the general Norwegian population with respect to age, sex, and place of living. However, only 36% of the sample responded to the survey. Compared to collection of Norwegian reference values for the SF-36 in 1996 and 2002 this response rate was low [28]. The decline in response rates from 67% in 1996 to 36% in 2015 is in line with other postal surveys [3, 22, 50, 51]. Another Norwegian study found that health-related quality of life was relatively stable in two cross-sectional studies over an eight year period despite the response rate being 68% in the first study and 35% in the second [52]. Surveys are used to describe large populations, and high response rates are valued to reduce the risk of bias. However, nonresponse bias is only indirectly related to nonresponse rates and there is little empirical support for the notion that low response rates are more prone to nonresponse bias than samples with higher response rates [53]. The fact that response rates in sample surveys in general have declined over the past decades is challenging for population studies [53]. Innovation in epidemiologic studies should involve development of recruitment techniques that optimize participation [54]. A large Danish population study from 2015 [2] used web-based questionnaires and had a response rate of 52%. In our study, the paper-based questionnaire was not available in an electronic version. According to Statistics Norway, 18% of the population was 67 years or above, while 27% of the responders were in the same age group [28]. About 21% of the population in this study was between 18 and 29 years, while only 5% of this age group participated in the survey. The high mean symptom scores for the youngest age group may not be representative for the general
population in the same age, due to the very low response rate in this age group. For the older population, the opposite pattern was observed. The relatively high symptom scores in the youngest age group compared to the older age groups may indicate an unhealthy bias in the youngest age group and a healthy bias among the older age groups. Taken together, these factors suggest that the reference values might be biased due to selection among the youngest participants. Regrettably, our data did not permit further analyses to illuminate this.

Conclusion

This study provides the first Norwegian reference values for the MDASI. The presence of one or more comorbidities, increased levels of depressive symptoms and lower level of education were significantly associated with higher MDASI sum score. These covariates must be controlled for when using the reference values.

declarations

Ethics approval and consent to participate

The study was performed according to the rules of the Helsinki declaration. All respondents received written information about the study. Return of the questionnaires was taken to indicate written, informed consent. The Regional Committee for Medical and Health Research Ethics (REC) South East Norway approved the survey (2014/1172).

Consent for publication

Not applicable

Availability of data and materials

The dataset used and analysed during the current study is available from the corresponding author on reasonable request.

Competing interests
HK, KSG, ØS, CEK and MJH have no declared conflicts of interests. Eir Solutions AS was established in 2015 with SK, JHL, and NTNU Technology Transfer AS as shareholders. No income, dividend, or financial benefits are related to the work presented here nor in relation to Eir in any way.

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**Authors contributions**

Conzeptualization: JHL, MJH. Methodology: MJH, KSG, JHL. Formal analysis: HK, ØS. Project administration: MJH, KSG, JHL. Writing original draft: HK. Supervision, writing-review and editing: JHL, KSG, SK, ØS, CEK, MJH. All authors read and approved the final manuscript.

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Figures

Figure 1

Distribution of scores 0-10 on pain, fatigue, sleep