Self-reported physical activity and fatigue and its associations to anxiety and depression in adult patients with idiopathic inflammatory myopathies: a MIHRA psychological impact and MIHRA exercise and rehabilitation scientific working groups collaboration

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Abstract

Objective

To evaluate self-reported physical activity (PA) levels as well as the relationship between PA, anxiety, depression, quality of life, pain, fatigue, disease activity, and organ damage in patients with idiopathic inflammatory myopathies (IIM).

Methods

All adult patients registered at the rheumatology clinic at Karolinska University Hospital in Stockholm, Sweden (2019-2022) were eligible to participate. Questionnaires measuring anxiety, depression (HADS), and PA (IPAQ) were provided during yearly check-up or by mail, due to reduced in-person visits amid the Covid-19 pandemic. Additional data was obtained from the Swedish Rheumatology Quality Registry.

Results

Of 488 invited patients, 336 agreed to participate, and 246 completed the questionnaires. Median (range) age was 64 (20-88) years, median disease duration five (0.3-61) years and two-thirds were women. Notably, 82% reported moderate/high level of PA. Probable anxiety and depression were experienced by 25% and 14%, respectively. The findings indicated a potential protective effect of PA against depression (OR 0.23, CI 0.06-0.95). Conversely, patients who were physically inactive had poorer mental health, reduced muscle function, increased organ damage, and fatigue. Fatigue demonstrated a progressive link to heightened risks of anxiety (2%, 2-4%) or depression (3%, 1-6%).

Conclusion

Most patients with IIM reported being physically active. The study highlights the potential influence of PA on mental health and its role in mitigating risks associated with depression and fatigue among IIM-patients. It also underscores the importance of patient-reported outcomes, and their role in understanding and improving healthcare interventions. Further research is needed to uncover causes and confirm these associations.

Key words

anxiety, depression, fatigue, idiopathic inflammatory myopathies, myositis, physical activity, self-reported

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Introduction

Idiopathic inflammatory myopathies (IIM), or myositis, is a group of rare and heterogeneous autoimmune diseases with muscle weakness as a hallmark symptom. IIMs are classified as polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM), juvenile dermatomyositis (JDM) and now with advancements in antibody discovery and more granular attention to phenotypes, includes antisynthetase syndrome (ASyS), and immune-mediated necrotising myopathy (IMNM) (1). IIMs are systemic disorders involving inflammation of several organ systems, *e.g.* skeletal muscles, lungs, the heart, skin, the gastrointestinal tract, and joints. Patients are usually treated with high dose oral glucocorticoids in combination with other immunosuppressive agents. IBM differs from the other IIMs by developing slowly progressive muscle weakness and muscle atrophy. IBM is refractory to current medical treatment while exercise may be a potentially influential therapy halting the decline, and in some cases, improve muscle function (1).

Although non-IBM IIMs are responsive to medical treatment, reduced muscle endurance, and to some extent reduced muscle strength, can occur at both early and later stages of the disease. Aerobic capacity in these populations may be reduced by approximately 25% compared to healthy controls (2, 3), with even lower aerobic capacity in patients with ASyS than DM (4). Impaired physical function is a likely causation of low physical activity levels in IIMs, thus measuring physical function and physical activity levels may be the ground for pivotal intervention in IIMs (5, 6). Based on accelerometer data, patients across IIMs seem to engage in approximately 187 minutes daily of any physical activity (7) with 37-69% being sedentary during waking hours (8). Self-reported physical activity levels to our knowledge have not been studied in patients with IIM. Current knowledge suggests that exercise is safe, regardless of the time from diagnosis and subtype of IIM. Further, exercise is associated with improved aerobic capacity, muscle function, aerobic muscle metabolism and health-related quality of life (HRQoL), as well as reduced inflammation (9). Of additional importance, review of available evidence supports that physical exercise exerts a favourable impact on pain perception and the subjective experience of fatigue in patients with IIM (10). General populations and disease populations such as inflammatory arthritis, chronic pain, and stress-related disorders, mirror these results of physical exercise and physical activity alleviating the burden of chronic pain, fatigue, mental performance, anxiety, and depression (11-14). While large cohorts have demonstrated physical activity to be preventive of depression, sedentary behaviour is associated with anxiety (15, 16).

Pain and fatigue are two significant and early symptoms in IIM that require evaluation according to both patients and healthcare professionals (17). As assessed by the Short Form-36 (SF-36), people with IIM experience significantly more pain than population-based reference values and comparable pain to patients with other inflammatory rheumatic diseases (18). People with IIM continuously report worse HRQoL, in both physical and mental domains, compared to the general population (19-23). Patients with IIM have lower HRQoL compared to other chronic diseases (*e.g.* rheumatic- and cardiac disease, depression, and diabetes) in relation to energy, social isolation, and physical disability (6, 24). Anxiety and depression are common in other rheumatic diseases, such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) (25). Anxiety and depression are not well studied in IIM. However, a small study found that 44% of DM patients experienced anxiety and/or depression to a level requiring treatment, a third of which went untreated (26), indicating a probable real-world prevalence of undetected and untreated anxiety and depression among patients with IIM.

There is a paucity of knowledge on levels of physical activity, anxiety, and depression among patients with IIM, as well as their association to other patient-reported outcomes, inflammatory markers, and physicians' assessment of

disease. To the best of our understanding, there are no previous studies investigating self-reported physical activity, anxiety, and depression or their association to pain, fatigue, quality of life, organ damage and measures of disease activity in a larger group of patients with IIM.

The aim of this study was to evaluate self-reported levels of physical activity as well as the relationship between physical activity, anxiety, depression, quality of life, pain, fatigue, disease activity, and organ damage in adult patients with IIM.

Fig. 1. Flowchart of invitation and recruitment.

Patients and methods

This study accesses prospective data collection from the Swedish Rheumatology Quality Registry (SRQ) and supplements two additional cross-sectional questionnaires over the period of 2019 through 2022. The study was initially approved by the Regional Ethics Board (2016-2444/31), and supplementary permits by the Swedish Ethical Review Authority (2021-04313).

All adult patients with IIM registered at the rheumatology clinic at Karolinska University Hospital in Stockholm, Sweden were matched with the SRQ to confirm diagnosis, and subsequently invited to complete two supplemental surveys, the Hospital Anxiety and Depression Scale (HADS) (27) and the International Physical Activities Questionnaire-Short Form (IPAQ) (28). SRQ is a prospective national database that captures granular and broad information on diagnosis, biomarkers, functional testing, imaging, physical function, physical activity, HRQoL, symptoms, and treatment. SRQ uses validated outcome measures such as 36-Item Short Form Health Survey (SF-36) (29), the Health Assessment Questionnaire (HAQ) (30), Manual Muscle Test 8 muscle groups (MMT-8) (31), the Myositis Disease Activity Assessment tool (MDAAT) including the 6-item core set of disease activity measures (32). A specific module of the SRQ is purposefully built to prospectively collect myositis-specific data. The SRQ may list more than one diagnosis per case, for example PM and IMNM, or DM and ASyS, therefore, to limit the number of diagnosis categories, a single diagnosis was assigned. PM, DM, or IBM were always used if the patient had an additional IIM-related diagnosis. IMNM and ASyS were employed for patients lacking a diagnosis of PM, DM, or IBM. Patients with MCTD or overlap myositis were categorised as "overlap". Diagnostic verification was confirmed using patient records, and those with unclear diagnoses were excluded.

Procedures

Patients were invited to complete the two questionnaires additional to the SRQ database, the HADS and IPAQ, either a) during a clinic visit which could be completed during visit or at home or b) due to the Covid-19 pandemic questionnaires were sent by mail along with study information and were returned with signed informed consent if the patient chose to participate. To reduce missing data, patients completing HADS and IPAQ by post were requested to register their yearly SRQ questionnaires online, as they do yearly with clinical visits.

The HADS is a widely validated screening instrument, however, not intended to be a diagnostic tool (27). It measures the likelihood for anxiety or depression by two separate sub-scales, and a score of eight or higher per sub-scale indicates anxiety or depression. The IPAQ is a widely validated inventory that queries a person's physical activity during the past week, including the number of days and duration of moderate or vigorous activity, walking, and sitting (28). The total physical activity is calculated by energy expenditure using metabolic equivalent of task (MET). Time spent on various activities are approximated through MET-minutes. The total score is then categorised into low (IPAQ-1), moderate (IPAQ-2), or high (IPAQ-3) level of physical activity. To be classified as moderate or high, specific criteria must be met, such as engaging in at least three days/week of vigorous activity for a certain duration or combining activities to reach 600 MET-minutes for IPAQ-2 or 3000 MET-minutes for IPAQ-3.

The myositis module of the SRQ carries several instruments: the MDAAT which is a core-set measure validated for adult IIM that includes both a patient and physician global of disease activity on a 0-100mm Visual Analog Scale (VAS), MMT-8, HAQ, muscle enzymes (33), and extra muscular assessments of lungs, heart, gastrointestinal, skin, skeletal, and constitutional manifestations (32). The Myositis Damage Index (MDI) (34) measures global damage compositing scores from each organ system by symptoms and signs that have been present for at least six months. The module further includes patient-reported pain and fatigue using VAS, the SF-36 and the Functional Index 2 (FI-2), a dynamic test of muscle endurance and impairment, which is validated for IIMs but not included in previously mentioned core set measures (35).

The data collection started in February 2019 and ended in October 2022, it was thus conducted before, during and after the Covid-19 pandemic. The date of April 1st, 2020 was used as the start of the pandemic, the day that national restrictions were put in place in Sweden. The end of the pandemic was set

to March 29th, 2022, as it was the day Covid-19 was no longer regarded as a disease posing a danger to the public and society. Vaccines were made available in Sweden from December 27th, 2020 (33).

Data analysis

The IPAQ-2 and IPAQ-3 groups were clustered for statistical analysis as both groups achieved recommended levels of physical activity. Participants were also categorised as having probable anxiety or depression by their HADS score.

To analyse group differences based on HADS-score and IPAQ-level, non-parametric statistics were used as the data was not normally distributed. To explore the association between HADS-score and potential explanatory variables, demographic and clinical covariates were analysed with chi-square or Mann-Whitney U-test (when appropriate), and those statistically significant ($p<0.05$) were included in logistic regression analysis to measure the level of association. Certain variables were excluded from the regression model to avoid overfitting, such as SF36-MH and PtGA. Further, common confounders such as age, sex, disease duration, and type of diagnosis were included in the logistic regression analysis. Significant variables from the univariate regression analyses were then included in a multivariate regression analysis.

Results

Out of the 488 invited patients, 336 accepted to participate, with 246 participants completing the questionnaires which comprised the final analysis (Fig. 1). There were fewer clinical visits due to the pandemic and data collection procedures were modified, which led to missing data. The median disease duration was five years, median age 64 years and two-thirds were women, with age and sex distribution being like nationwide IIM-population in Sweden (36) (Table I).

Most of the participants (82%) reported to be physically active on a moderate or high level (IPAQ-2 & 3) and therefore reaching or surpassing recommended levels of physical activity (Table II). Regarding HADS-A and HADS-D, 25% and 14% of the participants scored ≥8, respectively, indicating a strongly positive screening for anxiety and depression. However, there were no differences in number of patients scoring ≥8 between IIM diagnoses (Table III).

Most individuals participated during and after the pandemic (36% and 37% respectively) and 64% participated after vaccines were available. There were no differences in HADS and IPAQ in relation to pre-, during-, or post-pandemic response (data not shown).

Participants who scored <8 on any HADS subscales had significantly better patient global assessment (PtGA),

Table I. Demographics of participants.

	n (%)
Total n of participants	246 (100)
Sex	
Women	154 (63)
Men	92 (37)
Age	
≥64 years (n=128)	128 (52)
<64 years (n=118)	118 (48)
Disease duration, years	5.1 (2.3 – 11.0)
Oral glucocorticoids mg/day (n=200)	0 (0 – 5)
DMARD (n=200)	116 (47)
bDMARD (n=200)	53 (22)
Diagnosis n (%)	
Dermatomyositis	84 (34)
Polymyositis	88 (36)
Inclusion Body Myositis	25 (10)
Immunomediated necrotising myopathy	15 (6)
Antisynthetase syndrome	7 (3)
Juvenile dermatomyositis	6 (2)
Amyopathic dermatomyositis	3 (1)
Other	18 (8)
MDAAT VAS 0–100, n=150	
Constitutional	0 (0 – 0)
Cutaneous	0 (0 – 0)
Skeletal	0 (0 – 0)
Gastrointestinal	0 (0 – 0)
Pulmonary	0 (0 – 0)
Cardiovascular	0 (0 – 0)
Other	0 (0 – 0)
Extra-muscular	0 (0 – 10)
Muscle	0 (0 – 0)
PhyGA, VAS 0–100, n=141	5 (0 – 15)
PtGA VAS 0–100, n=165	21 (4 – 42)
MMT-8 0–80, n=148	80 (75 – 80)
HAQ 0–3.0, n=165	0.38 (0 – 0.75)
CK μcat/L, n=163	1.6 (1.2 – 3.0)
FI-2, 0–100 (n= 115)	50 (25 – 68)
IPAQ	
Level 1 (43)	43 (18)
Level 2+3 (203)	203 (82)
Global Damage (n=206)	
Damage high (≥20/100)	74 (36)
Damage low (<20/100)	132 (64)
Pain VAS 0–100, n=176	13 (2 – 31)
Fatigue VAS 0–100, n= 176	27 (4 – 49)
SF36-MH, n=137	80 (60 – 92)

Values presented in number and percentage or median and interquartile range.
DMARD: disease modifying anti-rheumatic drug; bDMARD: biological disease modifying anti-rheumatic drug; MDAAT: Myositis Disease Activity Assessment Tool; VAS: Visual Analog Scale; IQR: Interquartile Range; PhyGA: Physician Global Assessment; PtGA: Patient Global Assessment; MMT-8: Manual Muscle Test 8 groups; HAQ: Health Assessment Questionnaire; CK: creatin phosphokinase; μcat/L: microkat per litre; FI-2: Functional index-2; IPAQ: International Physical Activities Questionnaire; Level 1: low physical activity; level 2: moderate physical activity; level 3: high physical activity; SF36-MH: 36-Item Short Form Health Survey – Mental Health domain.
Normative values for CK: women >3.5 and men >6.7 μcat/L.

Table II. Group differences based on IPAQ.

	IPAQ 1 n=43 (17.5 %)	IPAQ 2 + 3 n=203 (82.5 %)	*p*-value
Sex			
Women n=154	25 (58)	129 (63)	0.6
Men n=92	18 (42)	74 (37)	
Age			
≥64 years (n=128)	30 (70)	98 (48)	**0.016**
<64 years (n=118)	13 (30)	105 (52)	
Disease duration, years	6.8 (3.1 – 15.1)	4.9 (2.3 – 10.7)	0.12
Dermatomyositis, n=73/246	11 (25)	62 (30)	0.6
IBM, n=20/246	6 (14)	14 (7)	0.12
MDAAT VAS 0–100, n=150			
Constitutional	0 (0 – 0)	0 (0 – 6)	0.14
Cutaneous	0 (0 – 0)	0 (0 – 0)	0.73
Skeletal	0 (0 – 0)	0 (0 – 0)	1
Gastrointestinal	0 (0 – 0)	0 (0 – 0)	0.79
Pulmonary	0 (0 – 0)	0 (0 – 0)	0.73
Cardiovascular	0 (0 – 0)	0 (0 – 0)	0.14
Other	0 (0 – 0)	0 (0 – 0)	NA
Extra-muscular	0 (0 – 5)	0 (0 – 12)	0.19
Muscle	0 (0 – 0)	0 (0 – 0)	0.81
PhyGA, VAS 0–100, n=141	10 (0 – 20)	4.5 (0 – 15)	0.09
PtGA VAS 0–100, n=165	36 (3 – 48)	18 (4 – 38)	0.13
MMT-8 0–80, n=148	76 (68 – 80)	80 (77.5 – 80)	**0.004**
HAQ 0–3.0, n=165	0.69 (0.38 – 1.78)	0.25 (0.0 – 0.63)	**0.001**
CK mcat/L, n=163	1.35 (0.8 – 3.5)	1.6 (1.2 – 3.0)	0.2
FI-2, 0–100 (n= 115)	8.3 (0 – 57)	50 (28 – 69)	**0.018**
HADS Anxiety ≥8	17 (39)	45 (22)	**0.028**
HADS Depression ≥8	14 (33)	20 (10)	**0.0002**
Global Damage (n=206)			
Damage high (≥20/100), n=74	18 (54)	56 (32)	**0.02**
Damage low (<20/100), n=132	15 (46)	117 (68)	
Pain VAS 0–100, n=176	31 (1.5 – 57)	12.5 (2.3 – 27)	0.12
Fatigue VAS 0–100, n= 176	42 (8.3 – 67.3)	23 (3.3 – 47)	0.07
SF36-MH, n=137	60 (53 – 75)	80 (64 – 92)	**0.03**

Values presented in number and percentage or median and interquartile range. IPAQ: International Physical Activities Questionnaire; IPAQ 1: low physical activity; IPAQ 2: moderate physical activity; IPAQ 3: high physical activity; IBM: inclusion body myositis; MDAAT: Myositis Disease Activity Assessment Tool; NA: not available, all values are zero in both groups; PhyGA: Physician Global Assessment; VAS: Visual Analogue Scale; PtGA: Patient Global Assessment; MMT-8: Manual Muscle Test 8 groups; HAQ: Health Assessment Questionnaire; CK: creatin phosphokinase; µcat/L: microkat per litre; FI-2: Functional index-2; HADS: Hospital Anxiety and Depression Score; SF36-MH: 36-Item Short Form Health Survey – Mental Health domain.
Normative values for CK: women >3.5 & men > 6.7µcat/L.

muscle strength (MMT-8) and physical function (HAQ), were more physically active (IPAQ 2-3), had lower pain and fatigue and had better score on SF36-MH. Further, those who scored <8 on HADS-D had lower organ damage (Table III). Participants reporting low levels of physical activity (IPAQ-1) had lower muscle strength (MMT-8) and muscle endurance (FI-2), worse physical function (HAQ), higher scores on HADS (both subscales), higher organ damage and worse scores on SF36-MH. There was no difference in disease activity between patients with lower or higher physical activity level (Table II). More than half of the participants did not use oral glucocorticoids, 47% were treated with disease modifying anti-rheumatic drugs (DMARD) and 22% with biological DMARD (bDMARD). Six participants were treated with two bDMARDs. There were no significant differences in physical activity, anxiety or depression depending on medical treatment (Fig. 2 and 3).

Although several parameters were significant predictors of anxiety or depression in the univariate regression analysis, only two parameters remained significant in the multivariate regression model: fatigue VAS, and self-reported level of physical activity (IPAQ). Fatigue significantly predicted a positive screening for anxiety and for every millimetre increase in fatigue, the risk of scoring ≥8 on HADS-anxiety increased by 2% (2-4%) (Table IV). Similarly, fatigue was significantly associated with a strongly positive screening for depression and for every millimetre increase in fatigue, the risk of scoring ≥8 on HADS-depression increased with 3 % (1-6%). The variables significant in the univariate model but not the multivariate might be of clinical value: being a woman, pain, physical inactivity, poor HAQ, and organ damage were all associated with increased risk of anxiety or depression.

Regarding the extent of physical activity, engagement in a moderate or high level of physical activity (IPAQ-2 and IPAQ-3) exhibited a statistically significant association with a 77% risk reduction (odds ratio, OR, equal to 0.23, with a 95% confidence interval, CI, ranging from 0.06 to 0.95) in achieving a score of 8 or higher on the HADS-depression scale, as outlined in Table IV.

Discussion

The level of physical activity as well as the association between level of physical activity and probable anxiety and/or depression in patients with IIM was investigated in this study. In addition, the association of patient and physician reported outcomes and other key measures were compared with level of physical activity, anxiety and/or depression. Most of the participants were physically active according to, or exceeding the recommendations of the World Health Organisation (37). Moderate or high level of physical activity was associated with a 77 % reduced risk of depression. Further, fatigue was associated with a progressively increased risk of anxiety or depression. No previous study has investigated possible factors related to anxiety or depression in patients with IIM or using level of physical activity as the common denominator in such a large population in IIM. However, there is substantial evidence supporting the link between physical activity and anxiety, depression, and fatigue, as well as supporting physical activity as treatment and prevention for depression in other populations (37).

Table III. Group differences based on HADS.

	HADS Anxiety		HADS Depression	
	Yes n=62 (25%)	No N=184 (75%)	Yes n=34 (13%)	No N=212 (87%)
Sex				
Women n=154	46 (59)	108 (74) *	23 (68)	131 (62)
Men n=92	16 (41)	76 (26)	11 (32)	81 (38)
Age				
≥64 years (n=128)	30 (52)	98 (47)	18 (47)	110 (48)
<64 years (n=118)	32 (48)	86 (53)	16 (53)	102 (52)
Disease duration, years	4.1 (1.9 – 11.4)	5.7 (2.4 – 11.0)	4.05 (1.4 – 14.3)	5.3 (2.4 – 11)
MDAAT VAS 0–100, n=150				
Constitutional	0 (0 – 3.5)	0 (0 – 0)	0 (0 – 9)	0 (0 – 0)
Cutaneous	0 (0 – 10)	0 (0 – 0)	0 (0 – 11)	0 (0 – 0)
Skeletal	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)
Gastrointestinal	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)
Pulmonary	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)
Cardiovascular	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)
Other	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)	0 (0 – 0)
Extra-muscular	5 (0 – 15)	0 (0 – 10)	5 (0 – 15)	0 (0 – 10)
Muscle	0 (0 – 0)	0 (0 – 1.5)	0 (0 – 5)	0 (0 – 0)
Oral glucocorticoids mg/day (n=200)	1.88 (0 – 5)	0 (0 – 5)	1.25 (0 – 5)	0 (0 – 5)
DMARD (n=200)				
Two	3 (5)	3 (2)	0 (0)	6 (3)
One	25 (40)	85 (46)	14 (41)	96 (45)
None	16 (26)	68 (37)	14 (41)	70 (33)
bDMARD (n=200)				
Yes	17 (27)	36 (20)	10 (3)	43 (20)
No	27 (44)	120 (65)	18 (53)	129 (61)
Diagnosis (n=246)				
Dermatomyositis	22 (35)	62 (34)	10 (29)	74 (35)
Polymyositis	20 (33)	68 (37)	14 (41)	74 (35)
Inclusion Body Myositis	4 (6)	21 (11)	3 (9)	22 (10)
Immunomediated necrotising myopathy	3 (5)	12 (6,5)	2 (6)	13 (6)
Antisynthetase syndrome	3 (5)	4 (2)	1 (3)	6 (3)
Juvenile dermatomyositis	4 (6)	2 (1)	2 (6)	4 (2)
Amyopathic dermatomyositis	0 (0)	3 (2)	0 (0)	3 (1)
Other	6 (10)	12 (6,5)	2 (6)	16 (8)
Dermatomyositis 84/246	22 (35)	62 (34)	10 (29)	74 (35)
No dermatomyositis, 162/246	40 (65)	122 (66)	24 (71)	138 (65)
PhyGA, VAS 0–100, n=141	12 (0 – 21)	4 (0.0 – 11)	8 (0, 18)	5 (0 – 15)
PtGA VAS 0–100, n=165	41 (26 – 56)	13 (2.8 – 32.8) ***	47 (31 – 60)	14 (3 – 35) ***
MMT-8 0–80, n=148	77.5 (70.3 – 80)	80 (78 – 80) **	76 (71 – 79)	80 (77 – 80) *
HAQ 0–3.0, n=165	0.94 (0.38 – 1.5)	0.25 (0.0 – 0.63) ***	1.0 (0.63 – 1.65)	0.25 (0.0 – 0.63) ***
CK µcat/L, n=163	1.4 (1.1 – 3.6)	1.6 (1.2 – 2.9)	1.4 (1.0 – 4.1)	1.6 (1.2 – 3.0)
FI-2, 0–100 (n= 115)	44.5 (22 – 61.5)	49 (26 – 69)	34 (12 – 51)	49 (27 – 69)
IPAQ				
Level 2+3 (203)	45 (73)	158 (86) *	20 (59)	183 (86) ***
Level 1 (43)	17 (27)	26 (14)	14 (41)	29 (14)
Global Damage (n=206)				
Damage high (≥20/100), n=74	22 (47)	52 (33)	16 (62)	58 (32) **
Damage low (<20/100), n=132	25 (53)	107 (67)	10 (38)	122 (68)
Pain VAS 0–100, n=176	31.5 (15.3 – 60.8)	9 (1.3 – 22.8) ***	22 (8.3 – 50.8)	12 (2 – 28) *
Fatigue VAS 0–100, n= 176	50.5 (36.3 – 66.5)	14 (3.0 – 41.8) ***	51.5 (38.8 – 65.8)	15.5 (3.0 – 42) ***
SF36-MH, n=137	56 42 – 60)	84 (72 – 92) ***	44 (38 – 60)	80 (64 – 92) ***

p-values: *<0.05, **0.01, ***<0.001.
HADS: Hospital Anxiety and Depression Score; PhyGA: Physician Global Assessment; VAS: Visual Analogue Scale; PtGA: Patient Global Assessment; MMT-8: Manual Muscle Test 8 groups; HAQ: Health Assessment Questionnaire; CK: creatin phosphokinase; µcat/L: microkat per litre; FI-2: Functional index-2; IPAQ: International Physical Activities Questionnaire; Level 1: low physical activity; level 2: moderate physical activity; level 3: high physical activity); SF36-MH: 36-Item Short Form Health Survey – Mental Health domain. Normative values for CK: women > 3.5 & men > 6.7 µcat/L.

The level of physical activity in our cohort aligns with pre-pandemic IPAQ-scores in healthy population in Sweden (38). In contrast, our cohort reported higher levels of physical activity compared to individuals with rheumatoid arthritis in Sweden where 53–64% reported to reach the same level of physical activity (39). Furthermore, our results are similar to population-based data during the Covid-19 pandemic. Moderate levels were reported by 93% (40)

Table IV. Logistic regression analyses testing predicting factors for anxiety and depression assessed by HADS.

	HADS anxiety				HADS depression			
	Univariate		Multivariate		Univariate		Multivariate	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Woman *vs*. men	**2.02**	1.08 – 3.92	1.98	0.72 – 6.0	1.29	0.61 – 2.88	-	-
≥64 years *vs*. <64 years	0.82	0.46 – 1.46	-	-ì	1.04	0.54 – 2.17	-	-
Disease duration, years	1.00	0.98 – 1.03	-	-	1.0	0.96 – 1.03	-	-
Dermatomyositis *vs*. the other	1.08	0.58 – 1.97	-	-	0.77	0.33 – 1.67	-	-
IBM vs the other	0.53	0.15 – 1.47	-	-	0.67	0.10 – 2.48	-	-
MMT-8 (per unit 0–80)	0.96	0.92 – 1.00	-	-	0.83	0.18 – 2.6	-	-
HAQ (per unit 1–3)	**3.33**	1.93 – 5.96	1.5	0.67 – 3.29	**3.94**	2.16 – 7.63	1.66	0.65 – 4.58
IPAQ level 2+3 *vs*. IPAQ 1	**0.43**	0.21 – 0.88	0.84	0.25 – 3.00	**0.22**	0.1 – 0.5	**0.23**	**0.06 – 0.95**
Damage high *vs*. low	1.81	0.93 – 3.51	**-**	**-**	**3.36**	1.45 – 8.11	2.17	0.62 – 7.91
Pain (per unit VAS)	**1.04**	1.02 – 1.06	1.01	0.99 – 1.04	**1.02**	1.00 – 1.03	0.98	0.95 – 1.00
Fatigue (per unit VAS)	**1.03**	1.02 – 1.04	**1.02**	**1.002 – 1.04**	**1.03**	1.01 – 1.05	**1.03**	**1.01 – 1.06**

HADS: Hospital Anxiety and Depression Scale; IBM: inclusion body myositis; MMT-8: Manual Muscle Test 8 groups; HAQ: Health Assessment Questionnaire; IPAQ: International Physical Activities Questionnaire; VAS: Visual Analogue Scale.

and as the mean physical activity level (41). However, the largest decrease in physical activity was detected in the elderly population. In our cohort individuals older than 64 were less physically active compared to younger individuals. It is likely that the pandemic affected levels of physical activity among elderly in our cohort as well. These two studies were conducted at different time points, one (40) during low number of Covid-19 cases and the other (41) during a rise in cases with more limiting restrictions (42). Notably, the Swedish Public Service and gyms nationwide promoted physical activity through TV, online and outdoor supervised exercise programmes. Myositis patients received additional support from healthcare professionals via telemedicine.

Worse physical function and mental health, higher organ damage, anxiety and depression were more prevalent among physically inactive individuals. This suggests a possible association between physical and mental well-being as well as the clinical value of these variables to identify patients that might need further care from the health professional team. Evaluation of causal associations between physical activity, anxiety, depression, and disease variables was outside the scope of this study but should be prioritised in future studies.

The frequency of anxiety disorder in patients with IIM is similar to the general population in Sweden, pre-pandemic (43). Data during the pandemic report a prevalence of anxiety disorder to 9.5% (44) and 24.2% (45) in Sweden using the General Anxiety Disorder, GAD-7, the difference possibly due to timepoint, recruitment methods and duration of the studies. Our cohort did not differ in response depending on when they participated in relation to the pandemic. The prevalence of depression disorder in our cohort was also similar to the general population, pre-pandemic (43). In comparison to during the pandemic, our cohort had similar or lower prevalence of depression than the population where estimated prevalence was between 15.3% (44) and 30% (45) using the Patient Health Questionnaire, PHQ-9. Here, as well as for anxiety, the difference in methods could explain the variance.

Several variables were significantly better among individuals not suffering from anxiety or depression (PtGA, MMT-8, HAQ, IPAQ, pain, fatigue, SF36-MH) (Table III). This could be explained by less aggressive disease, early diagnosis, and intensive glucocorticoid treatment initially (46). It could also be due to early and individually adapted exercise rehabilitation facilitating a normality in function and counteracting a reduced muscle mass, impaired function, and sustaining strength (47).

Moreover, the SF36-MH and HADS are converging as patients scoring ≥8 on HADS subscales also had worse SF36-MH scores. However, it is not known which of these instruments best reflects mental health in IIM, although SF36 is suggested to be used in studies by International Myositis Assessment & Clinical Studies Group (IMACS). Those who scored ≥8 on HADS had significantly more pain and fatigue, although this difference was not evident based on level of physical activity. This implies that there may be a stronger association between pain and fatigue with anxiety and depression than physical activity. Further, pain has emerged as an early and important patient-reported symptom (17). According to patients, pain does not receive the sufficient attention from health care professionals and is suboptimally treated (48). As PtGA was worse among those with high HADS scores, it could potentially be an important marker to identify those in need of phycological support. These results underscore the importance of patient reported outcome measures (PROMs) in research and clinical settings.

Higher organ damage was more prevalent among depressed individuals. This suggests that aggressive disease, difficult-to-treat disease or low treatment response could be associated with depression. However, there were no significant differences in IPAQ or HADS scores based on medical treatment, or disease activity suggesting few patients were under intensive treatment at participation. Still, the causality needs to be further studied as our study does not reveal treatment- or medical history. Possibly, organ damage could be a clinically crucial factor in identifying those at risk of depression.

Previous research has shown an association of anxiety and depression with

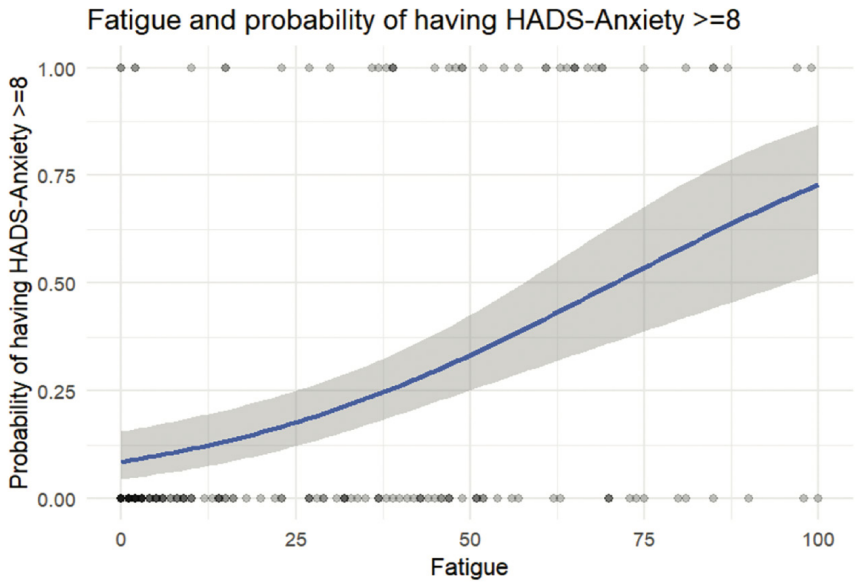

Fig. 2. Fatigue and probability of scoring ≥ 8 on HADS-Anxiety (Hospital Anxiety and Depression Scale).

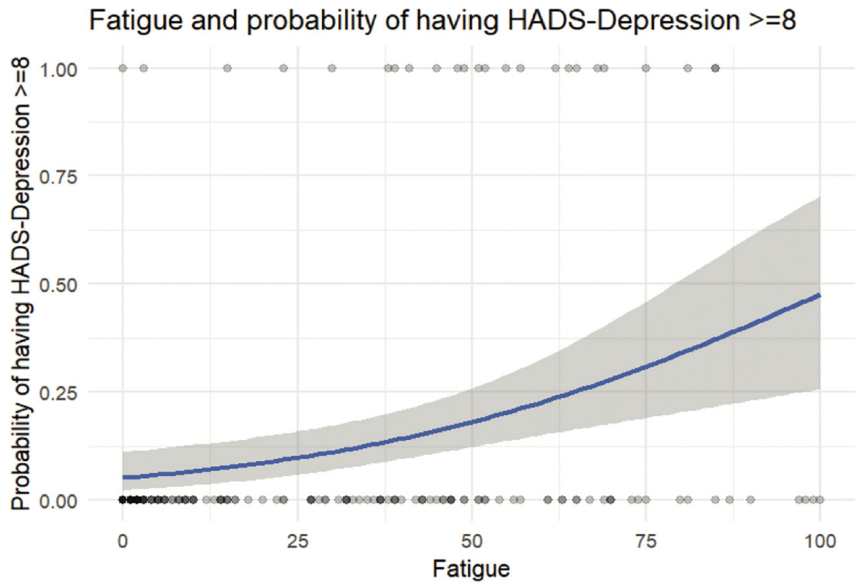

Fig. 3. Fatigue and probability of scoring ≥8 on HADS-Depression (Hospital Anxiety and Depression Scale).

the disease burden of visual cutaneous manifestation, or physical limitations and disruptions of daily life due to cutaneous manifestations (26, 49). Moreover, around 35% of IBM-patients reported anxiety or depression utilising HADS, with depression being associated to a degree of disability (50). However, we did not find any differences in anxiety or depression between IIM diagnoses in our cohort, suggesting anxiety and depression are not limited to cutaneous manifestations or physical limitations in patients with IIM.

Our logistic regression model revealed that for each millimetre increase in fatigue, the risk of obtaining a HADS-A or HADS-D score of ≥8 increases by 2–3%. It has, to our knowledge, not previously been studied if there is an association between fatigue and anxiety or depression in patients with IIM. However, fatigue is commonly reported in autoimmune disease and among patients, care givers and health professionals, fatigue is one of the most important aspects of IIM to include in future research (17). The difference in fatigue between the HADS-groups is considerable, and suggests it is an important factor in the clinic, both to aid in the management of fatigue but also to identify those at risk of anxiety or depression disorder. Being physically active was associated with a substantially lower risk of depression. With our approach we cannot conclude if it is physical activity that reduces the risk or if those not suffering from depression are more physically active. However, the role of physical activity as stand-alone or adjuvant treatment in mild to moderate depression is increasingly acknowledged (51). In addition, a recent study described reduced depression after 12 weeks of exercise compared to a non-exercising control group in patients with non-IBM IIM (52). There is a need to study mechanisms, causality, and exercise effects in these aspects in IIM.

Immune mediators often present in IIM are also linked to fatigue (*e.g.* IFNγ, IL-6 and IL-1β), with inflammation being an important contributor of fatigue (53). Although the participants were not recently diagnosed and had low CK-values, sub-clinical levels of inflammatory markers have been shown to affect patient-reported disease activity in IIM (54). Also, due to muscle wasting, CK-levels can be low even during increased disease activity. Moreover, despite observable clinical improvement, cytotoxic tissue-resident memory T-cells may persist within muscular tissue, thereby preserving an active immune response and consequently sustaining fatigue (55). Further investigation into immune infiltrates in longitudinal studies would be helpful to understand disease-related mechanisms in fatigue.

Our study was unable to definitively determine whether factors such as reduced muscle function, poor HAQ and SF36-MH or increased organ damage are driven by disease-related factors, such as aggressive disease and intensive treatment, or if they are influenced more by patient-related factors, such as physical inactivity and lack of exercise. Nevertheless, it is plausible that severe impairments in muscle function, daily functioning, and diminished mental health may restrict physical activity. Consequently, reduced physical activity

may contribute to further limitations in both physical and mental health. While the precise aetiology of anxiety and depression remains elusive based on the present data, a significant statistical association with fatigue was evident. This underscores an intricate interplay between fatigue, anxiety, and depression, highlighting their clinical relevance.

This study exhibits both strengths and limitations. A notable strength is the substantial number of patients, including data that encompasses both patient-reported assessments and objective evaluations from medical professionals. Despite this, certain limitations should be acknowledged. Firstly, the assessment of physical activity relied solely on patient-reported outcome measures, lacking objective confirmation through accelerometers. Patients with RA over-estimated their physical activity in comparison with accelerometer data (56), hence, a parallel objective measure of physical activity would have been preferred. However, we mitigated this limitation by utilising the by IMACS recommended measures for disease activity, organ damage, muscle and physical function, and quality of life in our comprehensive analysis of a substantially sized cohort of IIM patients (57-59). Secondly, we had no information on prevalence or severity of ILD or use of extra oxygen. Comorbidities could only be retrieved from SRQ and was available for only 29 of the participants (including cancer, arthritis, systemic sclerosis, spinal stenosis, sicca, RA and psoriatic arthritis). Thirdly, an important limitation arises from the impact of the Covid-19 pandemic, which resulted in missing registry-based data due to the use of mail-in questionnaires instead of in-person distribution during clinical visits. Unfortunately, we were not able to retrieve data on the number of patients infected by COVID-19 or being hospitalised due to COVID-19 during the study period. However, Sweden had a different approach from many other countries regarding restrictions and most of the society remained open during the pandemic with limitations only in number of people being allowed to gather. Moreover, patients with IIM, even though more likely to experience fatigue, chest pain and breathlessness, did not have more severe infections compared to healthy population and overall beneficial effect from vaccine (60). Further, as this is the first study of its kind, the impact of the pandemic on physical activity and mental health cannot be ascertained, although an overall decrease in physical activity was found in the general population during 2020. Additionally, the study's cross-sectional design restricts the ability to establish causal relationships. Fourthly, it is important to note that while all patients are registered at the Rheumatology clinic at Karolinska University Hospital in Solna, Stockholm, not all exclusively receive treatment at this facility. Some patients were referred for a second opinion or in-ward treatment, subsequently receiving their primary medical care at clinics closer to their residences where they also engaged with the SRQ national database. This dual scenario, while including patients from diverse geographic regions, also introduces the limitation that all patients have, at some point, interacted with the same clinic.

Conclusion

Most of the patients included in our cohort reported to being physically active, on similar levels as the Swedish population. They also reported probable anxiety and depression similar to the general population in Sweden. Physical activity seems to protect from depression, while physical inactivity was associated with poorer mental health, muscle function and more organ damage and fatigue. Fatigue was associated with a progressively increased risk of anxiety or depression. Furthermore, HAQ, SF36-MH, FI-2, VAS pain, VAS fatigue, MDI, and PtGA could be used as indicators of which patients are at risk of anxiety, depression, or physical inactivity, and thus, need more support. These findings highlight the substantial impact of physical activity and fatigue on mental health in this patient population. Encouraging physical activity may serve as a valuable strategy for reducing the risk of anxiety and depression. Nonetheless, further research is warranted to delve into the underlying causal mechanisms and confirm these associations.

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