The burden and determinants of fatigue in incident and prevalent systemic sclerosis

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ABSTRACT

Objective. *To investigate the burden and clinical associations of fatigue in systemic sclerosis (SSc) as measured by FACIT-Fatigue scores.*

Methods. *Australian Scleroderma Cohort Study participants with ≥1 FACIT-Fatigue score were included. Participants were divided into those with incident SSc (≤5 years SSc duration at recruitment and FACIT-Fatigue score recorded within 5 years of disease onset) or prevalent SSc (first FACIT-Fatigue score recorded >5 years after SSc onset). Generalised estimating equations were used to model change in FACIT-Fatigue scores over time, expressed as an increasing (improving) or decreasing (worsening) score.*

Results. *Of 859 participants, 215 had incident SSc and 644 prevalent SSc. First-recorded FACIT-Fatigue scores were similar in those with incident (37 units, IQR 25-45.5) and prevalent SSc (36 units, IQR 23-44; p=0.17), as were lowest-ever recorded FACIT-Fatigue scores (incident 23 units; prevalent 22 units, p=0.75).*

In incident SSc, higher skin scores (regression coefficient (RC) -1.5 units, 95%CI -2.3 to -0.8), PAH (RC -8.2, 95%CI -16.5 to 0.1) and reduced left ventricular function (RC -10.6, 95%CI -18.3 to -2.8) were associated with more severe fatigue. In prevalent SSc, higher skin scores (RC -0.6, 95%CI -1.3 to 0), gastrointestinal symptoms (RC -6.6, 95%CI -9.0 to -4.2), hypoalbuminaemia (RC -2.8, 95%CI -5.0 to -0.7), BMI<18.5kg/m^2 (RC -6.3, 95%CI -10.3 to -2.2), raised CRP (RC -3.1, 95%CI -4.7 to -1.5), and anaemia (RC -1.7, 95%CI -3.5 to 0.1) were associated with more severe fatigue.

Conclusions. *The burden of fatigue is substantial in both incident and prevalent SSc. Cardiopulmonary and gastrointestinal involvement are associated with worse fatigue.*

Introduction

Up to two-thirds of people living with autoimmune disease report profound or debilitating fatigue (1, 2). Possible contributors include active inflammation and pro-inflammatory cytokines, neurological involvement, metabolic changes, nutritional deficiencies, sleep disturbance, medications, stress, and poor mental health (2). Fatigue is highly prevalent in systemic sclerosis (SSc) and is known to interfere with activities of daily living and reduce quality of life (3, 4). However, the contributors to fatigue in SSc, and in particular how these may differ in incident and prevalent disease, are poorly understood (5). The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue is a 13-item survey which assesses fatigue and its functional impact on a scale of 0-52, with lower scores indicating worse fatigue. While initially designed for use in cancer patients, FACIT-Fatigue has been increasingly applied in rheumatic disease including SSc (5). Accordingly, we sought to quantify the burden and clinical associations of fatigue as measured by the FACIT-Fatigue scale, comparing incident and prevalent SSc cohorts.

Methods

Australian Scleroderma Cohort Study (ASCS) participants meeting ACR/EULAR criteria (6) for SSc with a definable SSc subclass [diffuse (dcSSc) or limited (lcSSc)] (7) were included. FACIT-Fatigue scores were recorded annually from 2016 onwards; accordingly, only participants seen from 2016 onwards were included. All participants had to have recorded ≥1 FACIT-Fatigue score for inclusion. Disease onset was defined as the date of onset of first non-Raynaud SSc manifestation. Participants were divided into those with incident SSc (ASCS recruitment and ≥1 FACIT-Fatigue score within 5 years of SSc onset), or prevalent disease (ASCS recruitment or first FACIT-Fatigue score >5 years from SSc onset). The ASCS has been approved by the Human Research Ethics Committee at St Vincent's Hospital Melbourne (HREC-A020/07) and with all participants providing written informed consent.

Patient-reported outcome measures (PROMs) of health-related quality of life (HRQoL) were recorded at each visit, including the FACIT-Fatigue and 36-item Short Form Survey (SF-36). Disease features were considered pre-

Table I. Characteristics of study population.

Variable	Whole cohort (n=859)	Incident SSc (n=215, 25.0%)[1]	Prevalent SSc (n=644, 75.0%)[2]	*p*-value
Age at SSc onset (years)	47.2 (35.6-55.6)	55.4 (22.7-64.5)	44.2 (34.1-54.1)	<0.01
Female sex	735 (85.6%)	167 (77.7%)	568 (88.2%)	<0.01
Caucasian	731 (89.0%)	169 (83.7%)	562 (90.8%)	0.01
Diffuse SSc	209 (24.3%)	69 (32.1%)	140 (21.7%)	<0.01
SSc duration at first FACIT-Fatigue score (years)	11.1 (5.0-19.6)	2.4 (1.3-3.5)	14.4 (9.5-22.6)	<0.01
First-recorded FACIT-Fatigue Score	36 (23.8-44)	37 (25-45.5)	36 (23-44)	0.17
Lowest (worst) recorded FACIT-Fatigue score	22.8 (11-35)	23 (10-36)	22 (12-35)	0.75
ANA Centromere	380 (45.1%)	67 (32.5%)	313 (49.2%)	<0.01
Scl70	138 (16.5%)	43 (21.0%)	95 (15.1%)	0.05
RNA Polymerase-3	109 (14.8%)	32 (17.5%)	77 (13.9%)	0.23
PAH*	65 (7.6%)	10 (4.7%)	55 (8.5%)	0.06
ILD*[3]	276 (32.1%)	69 (32.1%)	207 (32.1%)	0.99
Limited ILD*[4]	174 (67.6%)	47 (77.1%)	128 (64.7%)	0.07
Extensive ILD*[4]	84 (32.4%)	14 (23.0%)	70 (35.4%)	
FVC (%, baseline[5])	96 (83-107)	94 (82-105)	96 (84-108)	0.24
DLCO (%, baseline[5])	71 (58-84)	76 (62-91)	69 (57-81)	<0.01
LVEF<50%*	55 (6.5%)	12 (5.7%)	43 (6.8%)	0.60
Digital ulcers*	508 (59.1%)	103 (47.9%)	405 (62.9%)	<0.01
Raynaud's phenomenon*	856 (99.7%)	213 (99.1%)	643 (99.8%)	0.10
SSc renal crisis*	28 (3.3%)	9 (4.2%)	19 (3.0%)	0.38
BMI<18.5kg/m^2*	84 (9.9%)	21 (10.1%)	63 (9.9%)	0.91
Gastrointestinal symptoms*[6]	828 (96.5%)	197 (91.6%)	631 (98.1%)	<0.01
Multimorbidity[7]	228 (26.5%)	42 (19.5%)	186 (28.9%)	<0.01
Anaemia (Hb<120g/L)*	379 (44.5%)	71 (33.5%)	308 (48.2%)	<0.01
Hypoalbuminaemia (Albumin<35g/L)*	296 (34.8%)	69 (32.6%)	227 (35.6%)	0.42
SF-36 MCS (baseline[5])	47.6 (37.3-55.3)	45.9 (38.4-54.5)	47.9 (37.1-55.5)	0.41
SF-36 PCS (baseline[5])	40.5 (30.4-50.7)	39.7 (31.3-51.0)	40.6 (30.2-50.5)	0.39
Prednisolone*	399 (46.5%)	84 (39.1%)	315 (48.9%)	0.01
Non-corticosteroid immunosuppression*[8]	474 (55.2%)	132 (61.4%)	342 (53.1%)	0.03

ANA: antinuclear antibody; ILD: interstitial lung disease; LVEF: left ventricular ejection fraction; MSS: Medsger Severity Score; PAH: pulmonary arterial hypertension; SSc: systemic sclerosis.
*Denotes ever from SSc onset. [1]Incident SSc defined as ≤5 years from SSc onset to recruitment with a FACIT-Fatigue score recorded within 5 years of recruitment. [2]Prevalent SSc defined as >5 years from SSc onset to recruitment, or those with no FACIT-Fatigue score recorded within 5 years' of SSc onset. [3]ILD defined as radiographic disease on chest high-resolution computed tomography. [4]ILD severity was defined by the extent of radiological involvement and percent-predicted forced vital capacity (FVC) (limited: <20% HRCT involvement or 20-30% with FVC≥70%, or extensive: >30% HRCT involvement or 20-30% with FVC<70%). [5]Baseline values recorded within first 5 study visits. [6]Gastrointestinal symptoms defined as reflux, dysphagia, vomiting, constipation, diarrhoea, bloating or faecal incontinence at each study visit. [7]Multimorbidity defined as Charlson Comorbidity Index Scores ≥4. [8]Non-corticosteroid immunosuppression defined as use of any non-corticosteroid immunosuppressive agent from recruitment, including conventional synthetic or biologic disease-modifying antirheumatic drugs or IVIG.

sent if ever reported from SSc diagnosis. Disease features, comorbidities and medication use were recorded at each study visit from patient-reported history and medical record review. Multimorbidity was calculated using Charlson Comorbidity Index Scores (Supplementary Appendix 1).

Statistical analysis

Characteristics of study participants are presented as mean [standard deviation (SD)], median [interquartile range (IQR)], or as number (percentage) as appropriate. Between group comparisons were made using the chi-squared test, two-sample t-test or Wilcoxon rank-sum test as appropriate. Statistical significance was defined as two-tailed *p*-value <0.05. Generalised estimating equations (GEE) using an exchangeable correlation structure were used to model FACIT-Fatigue scores longitudinally. 95% confidence intervals (CI) are presented. Models for determinants of FACIT-Fatigue scores were established in both incident and prevalent SSc cohorts. As the minimum clinically-important change in FACIT-Fatigue scores in SSc is undefined, we analysed FACIT-Fatigue as a continuous variable (range 0-52 units), with higher scores indicating less fatigue, and lower scores indicating more fatigue. Covariates were selected based on clinical significance, and statistical significance in univariable analyses. Variables that introduced significant confounding into the multivariable models were excluded. Analyses were performed using STATA 17.0 (Statacorp, USA).

Results

Of 1233 potentially eligible participants, 859 participants had a definable disease subclass, disease onset date and ≥1 FACIT-Fatigue score available (Suppl. Fig. S1). The most common reason for exclusion was absence of a FACIT-Fatigue score (25.1%). Demographic and disease features of those included and excluded from GEE modelling were similar other than more frequent multimorbidity in included participants (Suppl. Table S1). The study cohort (n=859) had a median age of 47.2 (IQR 35.6-55.6) years and were predominantly Caucasian (89.0%) and female (85.6%), with dcSSc in 24.3% (Table

I). Median SSc duration was 11.1 (IQR 5.0-19.6) years at the time of the first FACIT score, and 215 (25.0%) participants had incident SSc. Those with incident SSc were older at SSc onset and were more likely to be men with dcSSc and Scl70 positivity. Participants with prevalent SSc were more likely to have digital ulcers, lcSSc, ANA centromere positivity and multimorbidity. While there were no differences in frequency of PAH or ILD overall, baseline diffusion capacity for carbon monoxide (DLCO) was lower in the prevalent cohort (p<0.01), with more extensive ILD in this group although not meeting statistical significance (p=0.07). Short Form-36 Survey (SF-36) mental and physical component summary (MCS & PCS) scores were similar between groups at baseline.

FACIT-Fatigue scores in incident and prevalent cohorts

First-recorded FACIT-Fatigue scores were obtained 2.4 (IQR 1.3-3.5) years after SSc onset in those with incident SSc, and 14.4 (IQR 9.5-22.6) years after SSc onset in those with prevalent SSc. In the cohort overall, median first-recorded FACIT-Fatigue score was 36 (IQR 23.8–44) units, while median lowest (worst) recorded score was 22.8 (IQR 11–35) units. Median time from first-recorded to lowest-recorded FACIT-Fatigue scores was 1.3 years (IQR 0–3.3 years) in incident SSc, and 1.0 year (IQR 0–3.5 years) in prevalent SSc. First-recorded FACIT-Fatigue scores were similar between groups (incident 37 units (IQR 25–45.5); prevalent 36 units (IQR 23-44), p=0.17) (Fig. 1). Lowest-recorded FACIT-Fatigue scores were also similar between groups [incident 23 (IQR 10–36) units; prevalent 22 (IQR 12–35) units, p=0.75].

Associations of more severe fatigue in incident SSc

Fatigue in incident SSc (n=215) was associated with increasing skin scores (regression coefficient (RC) -1.5 units, 95%CI -2.3 to -0.8, p<0.01) (Fig. 2A; univariable analyses in Supplementary Table S2). Cardiac manifestations including reduced left ventricular (LV) function (RC -10.6, 95%CI -18.3 to -2.8, p<0.01) and PAH (RC -8.2 units, 95%CI -16.5 to 0.1, p=0.05). No significant association was identified between ILD including extensive ILD and fatigue scores. Gastrointestinal symptoms were associated with increasing fatigue although not meeting statistical significance (RC -2.9, 95%CI -6.0 to 0.3, p=0.08). Markers of systemic inflammation such as elevated CRP levels (RC -0.3, 95%CI -3.3 to 2.8, p=0.87), hypoalbuminaemia (RC -2.8, 95%CI -6.9 to 1.3, p=0.18) and anaemia (RC -2.7, 95%CI -6.3 to 0.8, p=0.13) had no significant relationship with fatigue in incident SSc, nor did BMI<18.5kg/m^2 (RC -1.4, 95%CI -7.1 to 4.3, p=0.64). Both poorer mental and physical well-being, as measured by SF-36 mental (MCS) and physical component summary (PCS) scores below the cohort median respectively were associated with increased fatigue burden in univariable analyses (MCS RC -10.1 units, 95%CI -12.3 to -7.7, p<0.01; PCS RC -12.2 units, 95%CI -14.4 to -10.1, p<0.01). However, these variables were excluded from the multivariable models due to confounding.

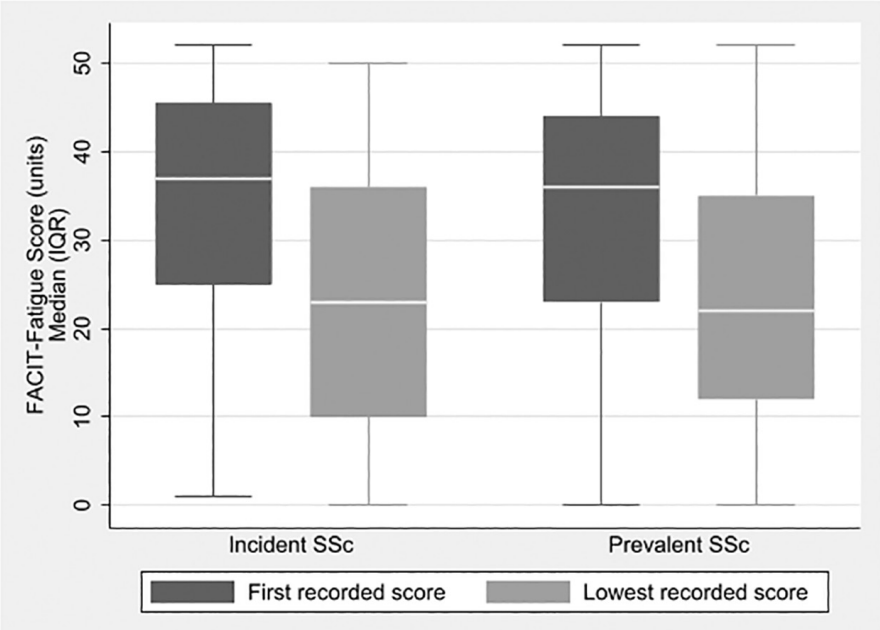

Fig. 1. First and lowest recorded FACIT-Fatigue scores in those with incident and prevalent SSc cohorts.
First-recorded score in incident SSc 37 units, IQR 25-45.5 and prevalent SSc 36 units, IQR 23-44 (p=0.17). Lowest-recorded score in incident SSc 23 units (IQR 10-36) units and prevalent SSc 22 (IQR 12-35) units (p=0.75).
FACIT: Functional Assessment Chronic Illness Therapy; IQR: interquartile range; SSc: systemic sclerosis.

Requirement for prednisolone at each visit (RC -6.0 units, 95%CI -9.3 to -2.7, p<0.01) and non-corticosteroid immunosuppression (RC -5.7 units, 95%CI -8.1 to -3.2, p<0.01) were also associated with worse fatigue, but due to confounding were excluded from the multivariable model.

Associations of more severe fatigue in prevalent SSc

In patients with longstanding disease, gastrointestinal symptoms and signs (RC -6.6 units, 95%CI -9.0 to -4.2, p<0.01), hypoalbuminaemia (RC -2.8 units, 95%CI -5.0 to -0.7, p=0.01) and BMI<18.5kg/m^2 (RC -6.3 units, 95%CI -10.3 to -2.2, p<0.01) were all significantly associated with fatigue (Fig. 2B; univariable analyses in Suppl. Table S2). Increased fatigue was again observed in those participants with increasing skin score (RC -0.6 units, 95%CI -1.3 to 0.0, p=0.05). Raised CRP levels were associated with more severe fatigue (RC -3.1, 95%CI -4.7 to -1.5, p<0.01), as was anaemia (RC -1.7 units, 95%CI -3.5 to 0.1, p=0.06) although not meeting statistical significance. Age, PAH, ILD and reduced

LV function were not associated with fatigue scores in multivariable modelling. As in the incident cohort, both SF-36 MCS and PCS scores below the cohort median (MCS RC -10.1 units, 95%CI -11.3 to -9.0, $p<0.01$; PCS RC -9.5 units, 95%CI -10.7 to -8.4, $p<0.01$) were associated with more severe fatigue in univariable analyses although these variables were excluded from the multivariable models due to significant confounding. In univariable analyses, requirement for prednisolone at each visit was associated with a non-significant worsening in fatigue (RC -1.8 units, 95%CI -3.7 to 0.1, $p=0.07$) whereas non-corticosteroid immunosuppression was not ($p=0.34$).

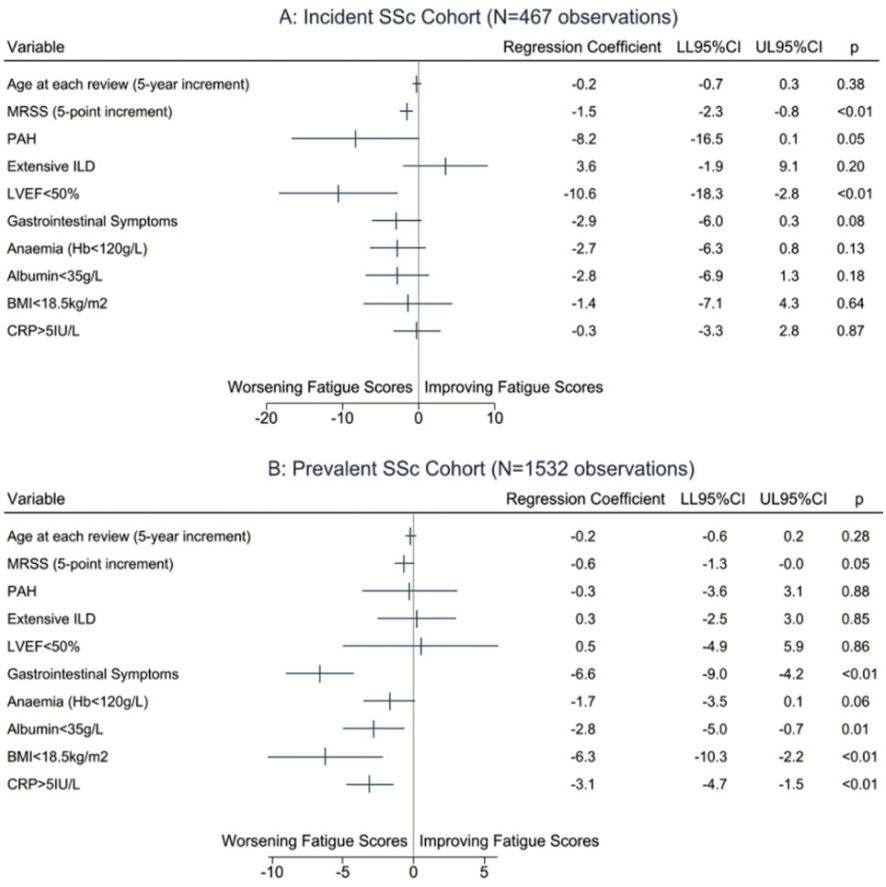

Fig. 2. Multivariable GEE model for the determinants of a change in FACIT-Fatigue Scores.
Extensive ILD defined as >30% involvement on HRCT, or 20-30% HRCT involvement with FVC<70%. Gastrointestinal symptoms defined as reflux, dysphagia, vomiting, constipation, diarrhoea, bloating or faecal incontinence at each study visit.
BMI: body mass index; CRP: C-reactive protein; g/L: grams per litre; ILD: interstitial lung disease; IU/L: international units per litre; kg/m^2: kilograms per meters, squared; LVEF: left ventricular ejection fraction; MRSS: Modified Rodnan Skin Score; n: number; PAH: pulmonary arterial hypertension; SSc: systemic sclerosis.

Discussion

These results highlight the significant burden of fatigue in SSc. American data have demonstrated median FACIT-Fatigue scores of 47 in the general population, 42 in non-anaemic cancer patients and 23 in anaemic cancer patients(8). In comparison, first-recorded FACIT-Fatigue scores were 36–37 in our cohort, with lowest-recorded scores of 22–23. This highlights that the burden of fatigue in SSc is worse than in the general population, including those with active cancer, and at worst is similar to that of anaemic cancer patients (8). Other data also suggest that individuals with SSc experience a similar burden of fatigue to cancer patients (9). Interestingly, we identified similar fatigue scores in both those with incident and prevalent SSc, however there were important differences in clinical associations of fatigue across the SSc disease course. A high burden of fatigue is measurable from SSc onset and persists, rather being limited to incident cohorts with improvement as patients adjust to their illness or the disease becomes less active.

These data provide a novel comparison of the determinants of fatigue in both incident and prevalent SSc cohorts. More severe fatigue was associated with cardiopulmonary disease in early disease, while gastrointestinal symptoms had a more prominent impact later in the disease course. These data demonstrate that severe fatigue can be associated with many types of organ involvement. Interestingly, the impact of both PAH and LV systolic dysfunction attenuated over time. We have previously identified that reduced LVEF in our cohort is rare, often occurs at presentation and recovers in around 60% (10); it is thus unsurprising that its impact on fatigue may resolve. Furthermore, the impact of PAH may lessen over time if treatment is initiated to ameliorate symptoms; we had insufficient longitudinal data to explore this. Meanwhile, ILD was associated with worse fatigue in the prevalent cohort only in univariable analyses, with significance attenuated in the multivariable model. This may be because of the small number of observations in the incident cohort which limited the power of our analyses to detect differences in this group, or potentially development or progression of ILD over time. Similarly, low BMI, whilst strongly associated with fatigue in the prevalent cohort, was uncommon in the incident cohort meaning our analyses may have lacked adequate statistical power to detect a potential effect. Gastrointestinal disease tends to accrue over time in SSc (11), so it follows that the impact of gastrointestinal involvement on fatigue was greater over time. Gastrointestinal involvement in SSc may contribute to fatigue in multiple ways: symptoms including reflux, abdominal pain or diarrhoea may interfere with sleep, as well as contribute to malabsorption and micronutrient deficiencies, supporting the identified association between markers of malnutrition and fatigue. This may reflect the impact of malnutrition on

fatigue, or that profound fatigue contributes to reduced oral intake; fatigue has been associated with poor nutrition in elderly persons (12). Predictably, raised inflammatory markers and anaemia were associated with more severe fatigue in the prevalent cohort. Importantly, worse skin thickening, irrespective of disease duration, is associated with severe fatigue.

Further studies are required to determine what interventions are effective in ameliorating fatigue in SSc, particularly those targeted at the SSc manifestations identified as significant in this cohort. Because of the observational nature of our data, it was not possible to accurately assess the impact of treatment on fatigue as our treatment data tend to be confounded by indication. Both current use of prednisolone and other immunosuppression tended to be associated with worse fatigue. Other data suggest that use of thyroxine may improve fatigue in hypothyroid individuals with SSc (13). Current guidelines recommend using a biopsychosocial model to address fatigue, encompassing tailored physical activity and/or psychoeducational interventions, and initiation/change of disease-modifying agents as required (14). Further controlled data would be beneficial to explore the impact of therapies on fatigue in SSc.

This study has limitations. As FACIT-Fatigue scores were only routinely collected in our dataset from 2016 onwards, 54% of the ASCS cohort did not have a FACIT-Fatigue score, predominantly because participants were last seen prior to 2016 (n =288, 25.1%). PROMs are collected annually prior to study visits and thus are more likely to be collected in stable outpatients. Data are not recorded when participants are most severely unwell or hospitalised when fatigue may be at its worst. Also, conceivably as patients become more unwell, they may be less likely to have completed PROMs and therefore the burden of fatigue may be under-reported in our dataset. Furthermore, non-English speaking patients may be less likely to complete PROMs. Our incident cohort was limited by a relatively low number of observations. Annual collection of study data may also miss important change in fatigue that could occur on a more rapid basis. Finally, formal diagnosis of a mood disorder including depression, or treatment, is not collected in the ASCS; nor is ILD pattern on HRCT so these data could not be included.

Conclusions

There is a significant burden of fatigue in SSc, akin to that of patients with active cancer. Fatigue appears to remain problematic throughout the course of SSc, with similar fatigue scores in both incident and prevalent SSc. Higher skin scores, cardiopulmonary disease, poor nutritional status, and gastrointestinal symptoms are significant determinants of fatigue. The role of disease-specific interventions targeting these manifestations should be explored as a strategy to improve fatigue in SSc.

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Competing interests

S. Proudman has received honoraria from Janssen and Boehringer-Ingelheim Pty Ltd.

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