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Pain and fatigue in adults with Loeys–Dietz syndrome and vascular Ehlers–Danlos syndrome, a questionnaire-based study

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Abstract

The purpose was to study self-reported chronic pain and fatigue symptoms among adults with molecularly verified Loeys–Dietz and vascular Ehlers–Danlos syndrome using a cross-sectional questionnaire design. Seventy adults were invited through a National Resource Centre for Rare Disorders. A study specific questionnaire including Brief Pain Inventory, Standardized Nordic Questionnaire, Fatigue Severity Scale, Hospital Anxiety & Depression Scale, questions on physical activity, and disease burden was used. Fifty-two persons participated, $n = 34$ with Loeys–Dietz and $n = 18$ with vascular Ehlers–Danlos syndrome, aged 18–68 years, 58% women. Chronic pain (79%) and fatigue (58%) symptoms were common. Half developed pain during childhood/adolescence. Sleep problems and high multi-organ burden were significantly associated with *chronic pain* ($p = 0.004$, $p = 0.014$) and *high fatigue* ($p < 0.001$, $p < 0.001$). *Chronic pain* was associated with higher scores of *fatigue* ($p = 0.002$). Higher scores of *fatigue* were associated with lower level of physical activity ($p = 0.014$), higher cardiovascular burden ($p = 0.025$), and higher symptoms of anxiety ($p = 0.001$). In this study, symptoms of chronic pain, fatigue, sleep problems, and disease burden seemed to mutually reinforce each other. Initiatives should consider interventions aimed at postponing the onset and reducing symptoms of pain, fatigue, and sleep problems and thus reduce the total disease burden at an early stage in patients with these complex conditions.

KEYWORDS
adults, chronic pain, fatigue, Loeys–Dietz syndrome, sleep problems, vascular Ehlers–Danlos syndrome

1 | INTRODUCTION

Loeys–Dietz syndrome (LDS) and vascular Ehlers–Danlos syndrome (vEDS) are potentially life-threatening diseases within the umbrella term of rare hereditary thoracic aortic diseases (HTAD). The most serious medical complications are vascular events. LDS hallmarks are early and aggressive aneurysms and dissections of the aorta and/or other large arteries (Velchev et al., 2021). vEDS hallmarks include arterial, intestinal, and/or uterine fragility with risk of rupture of the internal organs in addition to risk of aneurysm and dissection of middle-sized arteries (Byers et al., 2017). Other organs affected may include the musculoskeletal system, craniofacial structures, ocular system, and cutaneous features (Meester et al., 2017). LDS is caused by a mutation of genes encoding for transforming growth factor-beta signaling

pathways *TGFBR1*, *TGFBR2*, *SMAD3*, and *TGFB2* (Velchev et al., 2021). vEDS results from pathogenic variants in *COL3A1*, encoding type III collagen that is the major expressed collagen in blood vessels and hollow organs (Byers et al., 2017). Both diagnoses are suspected on the basis of family history, or a clinical history of arterial rupture, dissection or aneurysm, rupture of the large intestine, or pregnancy complications at young ages (Meester et al., 2017). Since there is clinical overlap between HTADs, the diagnoses should be confirmed by identification of pathogenic gene variants to allow for appropriate surveillance, treatment and family studies (Meester et al., 2017).

Typically, most individuals with LDS or vEDS live with family members with the same HTAD condition, and many have experienced close relatives die at an early age (Johansen et al., 2020a). Persons with HTADs are recommended for regular cardiovascular monitoring, including control of blood pressure with medications, and scheduling of prophylactic surgery (Byers et al., 2017; Milewicz & Regalado, 2017; Velchev et al., 2021). In connection with the diagnostic process, they receive information on lifestyle changes, including physical activity (PA) restrictions (Cheng & Owens, 2016; Thijssen et al., 2019; Johansen et al., 2020b) and sometimes job restrictions to avoid unhealthy stress or heavy physical work (Johansen et al., 2020b).

Chronic pain is a complex phenomenon covering both physiological and psychosocial aspects (Chapman & Gavrin, 1999). It is commonly described as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage, lasting more than 12 weeks" (Chapman & Gavrin, 1999). Chronic pain is the main cause of long-term sick-leave and disability in Norway (Rustøen et al., 2004) and Europe (Breivik et al., 2006). In the Norwegian general population (NGP), chronic pain is often found to be widespread, generalized and associated with female gender, high age, low educational level, psychological distress, chronic illness, and low PA (Breivik et al., 2006; Landmark et al., 2013; Rustøen et al., 2004). Studies of patient groups or the general population emphasize that chronic pain tends to create a cluster of problems such as chronic fatigue, sleep problems, withdrawal from activity, reduced sexual activity, compromised immune function, and mood disorders (Chapman et al., 2008).

Fatigue is often defined as an "overwhelming sense of tiredness, lack of energy and feeling of mental or physical exhaustion, or both" (Dittner et al., 2004). Fatigue is also prevalent in the NGP (Lerdal et al., 2005), and a common symptom in various chronic diseases (Dittner et al., 2004). Fatigue has been found to be a major determinant of disability, which significantly influences quality of life and impairs people's work ability (Bathen et al., 2014; Lerdal et al., 2005).

We have found sparse knowledge on chronic musculoskeletal pain and fatigue in persons with LDS and vEDS. However, from our clinical experience and descriptions of the diagnoses, we know these patients have high disease burden, including pain and fatigue symptoms (Byers et al., 2017; Johansen et al., 2020b; Meester et al., 2017). On the other hand, in Marfan syndrome (MFS), the most well-known HTAD condition, more studies have explored the prevalence of chronic pain and fatigue (Bathen et al., 2014; Velvin et al., 2016). These studies have indicated that chronic pain and fatigue symptoms are common in these patients, and limit their daily lives and reduce quality of life (QOL) (Velvin et al., 2015). Nevertheless, there is an agreement that more research on chronic pain and fatigue within the HTADs is necessary (Velvin et al., 2016).

In two previous articles on health burden perspectives (Johansen et al., 2020a) and physical activity (Johansen et al., 2020b) among adults with LDS and vEDS, we showed that the participants reported high prevalence of pain and fatigue symptoms. With data collected from the same study group, the aim of this article was to present a more detailed description of self-reported chronic pain (intensity, locations, and perceived impact on certain activities of daily life) and fatigue symptoms. Another aim was to explore the associations between chronic pain and fatigue scores with demographic and clinical factors in this study group of adults with LDS and vEDS.

2 | MATERIALS AND METHODS

2.1 | Participants and recruitment

This cross-sectional postal questionnaire survey was part of a larger study on physical function and psychosocial aspects in adults with HTADs (Johansen et al., 2020a; Johansen et al., 2020b; Johansen et al., 2021; Velvin et al., 2019).

In January 2018, all patients ($n = 70$), aged 18 years and older, with molecularly verified LDS or vEDS (evaluated by a clinical geneticist and with confirmed pathogenic or likely pathogenic variant in *TGBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, or *COL3A1*), registered at the TRS National Resource Centre for Rare Disorders (2020) in Norway were invitd to participate in the study Eligible individuals received a letter with study information, a consent form to be signed, the questionnaire and a prepaid return-addressed envelope. The non-responders received a written reminder three weeks later.

2.2 | Questionnaire

A study-specific questionnaire for self-report was developed in cooperation with representatives from the Norwegian Marfan and Loeys-Dietz Association and the Norwegian Ehlers-Danlos Association. Variables included were:

2.2.1 | Demographic factors

Gender, age, place of residence, family member(s) with LDS or vEDS (yes/no), educational level (≤13 years *or* > 13 years), current work participation, and/or degree of disability pension (yes/no) questions from "Labor force Survey" in Norway (Køber & Bø, 2018).

Questions concerning PA were derived from the HUNT study (The Nord-Trøndelag Health Study) (HUNT Research Centre, 2019). Questions included PA frequency (never; < once a week; once a week, 2–3 times a week; nearly every day), PA duration of each session (<15 min; 15–29 min; 1/2–1 h; >1 h) and usual PA intensity (light; moderate; high). For each patient, a summary score of PA frequency (coded 1–5), PA duration (coded 1–4), and PA intensity (coded 1–3)

was calculated according to the method by Nilsen et al. (2008). The score summarized each participant's responses to give equal weight to each measure according to the following equation: 1/5 × frequency + 1/4 × duration + 1/3 × intensity. This approach gave a maximum score of 1.0 for each of the three components, and a PA summary score from 0.0 to 3.0. The study group's median score was 2.0, and a score at median or above was classified as high PA level (Johansen et al., 2020b; Nilsen et al., 2008).

2.2.2 | Clinical factors

A history of aneurysm/dissection of the aorta *and/or* of other arteries, undergone acute/prophylactic vascular surgery *and/or* mitral valve surgery, a history of impaired vision and/or hearing, hernia, neck instability, organ rupture, pneumothorax, scoliosis, affected skin-, joint, and asthma/allergy (yes/no). To explore disease burden, two sum-scores were calculated on the basis of the number of the above-mentioned self-reported health problems: *Cardiovascular burden* (0–7) and *Multi-organ symptom burden* (0–11) (Johansen et al., 2020a). For clinical interpretation, levels of cardiovascular and multi organ symptom burden were classified as high if equal to or above the study group's median scores, i.e. ≥3.0 or ≥4.5.

Pain was measured using questions from the Brief Pain Inventory (Cleeland & Ryan, 1994) and the Standardized Nordic Questionnaire (Kuorinka et al., 1987; Palmer et al., 1999). These instruments have shown satisfactory psychometric properties (Cleeland & Ryan, 1994; Kuorinka et al., 1987; Palmer et al., 1999) are validated for the NGP (Rustøen et al., 2004; Svebak et al., 2006) and other patient groups (von Korff et al., 2000) but not for HTADs. The following variables were used: (1) A history of *chronic musculoskeletal pain*, lasting for more than three months past year (yes/no); (2) Self-reported *pain intensity* (*PI*) during activity/ at rest the last seven days, assessed with an 11-point Numeric Pain Rating Scale (NPRS) with 0 = "no pain" and 10 = "pain as bad as it can be." A pain score of 1–3 indicates "mild pain," a score of 4–6 indicates "moderate pain," and a score of 7–10 indicates "severe pain" (Breivik et al., 2008). (3) Pain drawings: The participants were asked to mark their pain experience during the past two weeks on silhouettes of the human body (front and back). The locations of marked areas were scored using a modified procedure of the Brief Pain Inventory (Cleeland & Ryan, 1994): Each drawing was divided into 14 areas using a template (head, jaw, neck, shoulder, elbow, wrist/hand, upper back, lower back, front chest, abdomen/bowel, lower abdomen, hip, knees, ankles/feet) (yes/no). Summing up the number of marked areas, we made a *number of pain locations* (NPL) score. The NPS was then categorized into three groups: "Few pain locations" (0–3), "moderate pain locations" (4–6), and "many pain locations" (7–14) (Rustøen et al., 2004). (4) Debut of present pain: "In childhood" (0–12 years), "during adolescence" (13–18 years), "in adulthood" (≥ 19 years). (5) Pain impact on participation (yes/no) in: "housekeeping," "working," "leisure activities." (6) What reduces and what increases pain; (possibility to tick off several predefined answer options) reduces pain: PA, medication (pain killers), rest, heat, cold, other; increases pain: PA, stress, inactivity, static work, cold, and others.

Fatigue symptoms were measured by the Fatigue Severity Scale (FSS) (Krupp et al., 1989), a nine-item questionnaire, rated on a 7-point scale; higher score indicates higher level of fatigue symptoms. Cut-off values for clinically relevant fatigue (high/severe fatigue) = FSS mean score >5, and borderline to non-fatigue = FSS mean score ≤5 (Lerdal et al., 2005). FSS has been found valid and reliable (Krupp et al., 1989; Lerdal et al., 2005).

To study psychological *distress*, the Hospital Anxiety & Depression Scale (HADS) was used (Zigmond & Snaith, 1983). HADS consists of two subscales, HADS-A to capture symptoms of anxiety and HADS-D to capture symptoms of depression, with 7 items each rated on a 4-point scale (0–3). Higher scores indicate more symptoms of anxiety/depression. A HADS-A and/or HADS-D summary score of ≥8 indicates clinically relevant anxiety or depression, respectively (Zigmond & Snaith, 1983). The Norwegian version of HADS is well validated (Mykletun et al., 2001).

Sleep problems were measured with one overall- and five follow-up dichotomous questions (yes/no): Do you have sleep problems, if yes: do you have (a) problems with falling asleep, (b) sleeping coherently, (c) with early wake up, (d) stay awake during the day and (e) sleep medication usage the last 4 weeks.

None of the study instruments are validated for the study population (HTAD), most instruments are validated for NGP (Labour Force Survey, HUNT, Brief Pain Inventory, Standardized Nordic Questionnaire, FSS, HADS), and some questions are study specific and not validated at all (cardiovascular burden, multi-organ symptom burden, what reduces and what increases pain, sleep problems).

To illustrate pain locations in the LDS and vEDS group, we compared with published data from an US MFS population (Nelson et al., 2015 95% with age range 18–70 years, 67% women), and a NGP (Rustøen et al., 2004 age range 18–81 years, 52% women), both studies used pain drawing for measuring pain locations.

To illustrate fatigue severity in the LDS and vEDS group, we compared with published data from a Norwegian MFS population (Bathen et al., 2014 age range 20–71 years, 57% women) and a NGP (Lerdal et al., 2005 age range 18–81 years, 52% women), both studies used FSS to measure symptoms of self-reported fatigue.

2.3 | Data analysis

Descriptive statistics are presented as frequencies, proportions, range, and means (*SD*). We used $\chi 2$ Chi-square tests for categorical- and one-way ANOVA analyses for continuous variables to compare the responders ($n = 52$) with the non-responders ($n = 18$).

To explore differences between the subgroups, LDS and vEDS, Fisher's exact test was used for categorical variables and Independent Samples *t*-test for continuous variables (after checking close to normal distribution with Q–Q plots).

Bivariate logistic regression analyses were used to explore the associations between the dichotomous dependent variable "chronic musculoskeletal pain" (yes/no) and demographic and clinical independent factors: Dichotomous variables (yes/no) included: diagnosis (LDS), gender (women), education level ≥ 13 years, full-time work

participation, overall sleep problems. Continuous variables included: age, PA level, time since confirmed diagnosis (years), mean score cardiovascular burden, mean score multi-organ symptom burden, mean FSS score, and mean HADS-A and mean HADS-D scores. Bivariate linear regression models were used to examine the association between the mean FSS score (dependent variable) and the independent variables (dichotomous and continuous as mentioned above). First, Q–Q plots were used to assess whether the mean FSS score for the analyzed subgroups was close to a normal distribution. Multivariate analyses were considered inappropriate due to the small sample size.

For clinical reasons, we present findings for LDS and vEDS separately. For statistical reasons and because the two diagnostic groups were quite similar we merged the groups in the final analyses. Because there were few missing data, no imputation method was used. The exact number of patients for each of the analyses are given in Tables. The statistical analyses were conducted by using SPSS Statistics for Windows version 25. A statistical significant level was set at $p \leq 0.05$.

2.4 | Ethics

The Regional Ethics Committee for Medical and Health Research Ethics in southeastern Norway (No. 2017/745) approved the study. Written informed consent was obtained from all participants. The results are reported in accordance with the STROBE guidelines for observational studies (von Elm et al., 2007).

3 | RESULTS

3.1 | Response rate, demographic-, and clinical characteristics

Fifty-two persons self-completed questionnaires, yielding a 74% response rate. No statistically significant differences between responders and non-responders were detected regarding distribution of gender, age, place of residence (region), or diagnosis.

Table 1 shows the demographic and clinical characteristics for the total study sample, and for LDS and vEDS, separately. Participants with LDS reported statistically significantly higher level of cardiovascular burden versus those with vEDS ($p = 0.004$), while those with vEDS scored higher on HADS-D indicating more symptoms of depression ($p = 0.006$).

3.2 | Pain

Chronic musculoskeletal pain was reported by 85% in the LDS group and 67% in the vEDS group (Table 1). Eleven persons did not report

TABLE 1 Demographic and clinical characteristics in 52 adults with Loeys–Dietz syndrome or vascular Ehlers–Danlos syndrome

	Total study group, $n = 52$	LDS, $n = 34$	vEDS, $n = 18$
Gender, women *n*(%)	30 (58)	19 (56)	11 (61)
Mean age (*SD*)	42.9 (16.2)	43.9 (14.7)	42.1 (18.7)
Living with partner, *n*(%)	28 (54)	20 (59)	8 (44)
Parenthood *n*(%)	27 (52)	21 (62)	6 (33)*
Family member with corresponding diagnose *n*(%)	45 (87)	32 (94)	13 (72)
Time since diagnose, mean year (*SD*)	8.5 (6.9)	8.9 (7.6)	7.7 (5.6)
Formal education >13 years *n*(%)	21 (40)	12 (35)	9 (50)
Full time employed *n*(%)	14 (27)	10 (29)	4 (22)
[a]High level of physical activity (≥2.0), *n*(%)	30 (58)	18 (53)	12 (67)
Chronic musculoskeletal pain, *n*(%)	41 (79)	29 (85)	12 (67)
[b]High cardiovascular burden level (median score ≥3), *n*(%)	31 (60)	25 (74)	6 (33)*
[c]High multi organ burden level (median score ≥4.5) *n*(%)	25 (48)	19 (56)	6 (33)
[d]Indication of moderate/high HADS-A (score ≥8) *n*(%)	49 (94)	33 (97)	16 (88)
[d]Indication of moderate/high HADS-D (score ≥8) *n*(%)	40 (77)	23 (68)	17 (94)*
Sleep problems, *n*(%)	35 (67)	25 (74)	10 (56)
Sleep medication usage the past 4 weeks, *n*(%)	8 (15)	5(15)	3 (17)

Note: Sleep problems: Falling asleep 46%, sleeping coherently 44%, staying awake 37%, early waking up 27%.
Abbreviations: LDS, Loeys–Dietz syndrome, vEDS, vascular Ehlers–Danlos syndrome.
*Statistically significant difference between the study subgroups, $p \leq 0.05$.
[a]Physical activity level including: PA frequency, duration, intensity. Higher scores indicate higher PA level.
[b]Number of cardiovascular burden (0–7): aortic-aneurysm, aorta-dissection, other aneurysm, other dissection, aorta-surgery (acute, prophylactic, or both), mitral valve surgery, use of antihypertensive medication.
[c]Number of multi-organ burden (0–11): impaired vision and/or hearing, neck instability, pneumothorax, hernia, organ rupture, scoliosis, skin problems, joint problems, allergies, and stomach discomfort.
[d]Hospital Anxiety & Depression scale: anxiety (HADS-A) and depression (HADS-D) subscale.

pain, five with LDS and six with vEDS, mean age (*SD*) 44.9 (19.7), 4 (36%) were women. The mean (*SD*) pain intensity (PI) during activity and at rest and the number of pain locations (NPL) for those reporting pain ($n = 41$), are shown in Table 2. In the total study population, the reported levels of PI during activity or at rest did not differ between genders ($p = 0.452$ and $p = 0.073$), and PI was not significantly associated with age ($p = 0.192$ and $p = 0.360$). The LDS patients reported higher mean PI during activity ($p = 0.006$), but not at rest ($p = 0.122$) compared to the vEDS patients. In the total study population, the reported NPL did not differ between sexes ($p = 0.057$), was not significantly associated with age ($p = 0.721$), and did not differ between persons with LDS versus those with vEDS ($p = 0.912$).

In those reporting chronic musculoskeletal pain ($n = 41$), pain influenced participation in leisure activities ($n = 32$), housekeeping ($n = 31$), and work life ($n = 26$). In seven persons (17%), the pain debuted during childhood, while 16 (39%) developed pain during adolescence, and another 18 (44%) in adulthood.

Pain relief during PA was reported by 49% ($n = 20$) of the responders, 78% ($n = 32$) during rest, and 31% ($n = 13$) both during PA and rest. Some (61%) reported heat, 61% ($n = 25$) pain killers (analgesics), and 10% ($n = 4$) cooling to be pain relieving. While *increased pain* during PA activity was reported by 56% ($n = 23$), 59% ($n = 24$) during inactivity and 24% ($n = 10$) during both PA and inactivity. Some (66%) reported increased pain during stress, 63% ($n = 26$) during static work situations, and 73% ($n = 30$) by cold. In these two questions it was possible to tick off several answer options.

Figure 1 shows the distribution of pain locations in the 41 LDS- and vEDS participants who reported chronic pain compared to a similar distribution of reported pain locations among an US MFS population (Nelson et al., 2015) and a NGP (Rustøen et al., 2004).

TABLE 2 Pain intensity during activity and in rest and number of pain locations among 41 patients with Loeys–Dietz syndrome and vascular Ehlers–Danlos syndrome

	All participants reporting pain, $n = 41$		LDS, $n = 29$		vEDS, $n = 12$	
Pain characteristics	**Activity**	**Rest**	**Activity**	**Rest**	**Activity**	**Rest**
[a]PI (NPRS range: 0–10), mean (*SD*)	4.9 (2.2)	3.3 (2.3)	5.4 (2.3)	3.6(2.4)	3.8(0.4)*	2.7(1.9)
Mild pain (score 1–3) *n*(%)	12 (29)	26 (63)	6 (21)	18 (62)	6 (50)	8 (66)
Moderate pain (score 4–6) *n*(%)	20 (49)	11 (27)	14 (48)	7 (24)	6 (50)	4 (33)
Severe pain (score ≥7) *n*(%)	9 (22)	4 (10)	9 (31)	4 (14)	0	0
[b]NPL (range: 0–14), mean (*SD*)	5.7 (3.3)		5.7 (3.3)		5.8 (3.2)	
Few pain locations (1–3 locations) *n*(%)	13 (33)		10 (35)		3 (25)	
Moderate pain locations (4–6 locations) *n*(%)	12 (30)		8 (28)		4 (33)	
Many pain locations (7–14 locations) *n*(%)	15 (38)		11 (38)		4 (33)	

Abbreviations: LDS, Loeys–Dietz syndrome, vEDS, vascular Ehlers–Danlos syndrome.
*Statistically significant difference $p \leq 0.05$.
[a]PI = Pain intensity, in activity and at rest assessed with the Numeric Pain Rating Scale (NPRS).
[b]NPL (0–14) = Number of pain locations: head, neck, throat, shoulder, upper back, lower back, elbow, wrist/hand, breast, abdomen/bowl, gynecological, hips/thigh, knee/leg, ankles//feet (one vEDS participant was missing).

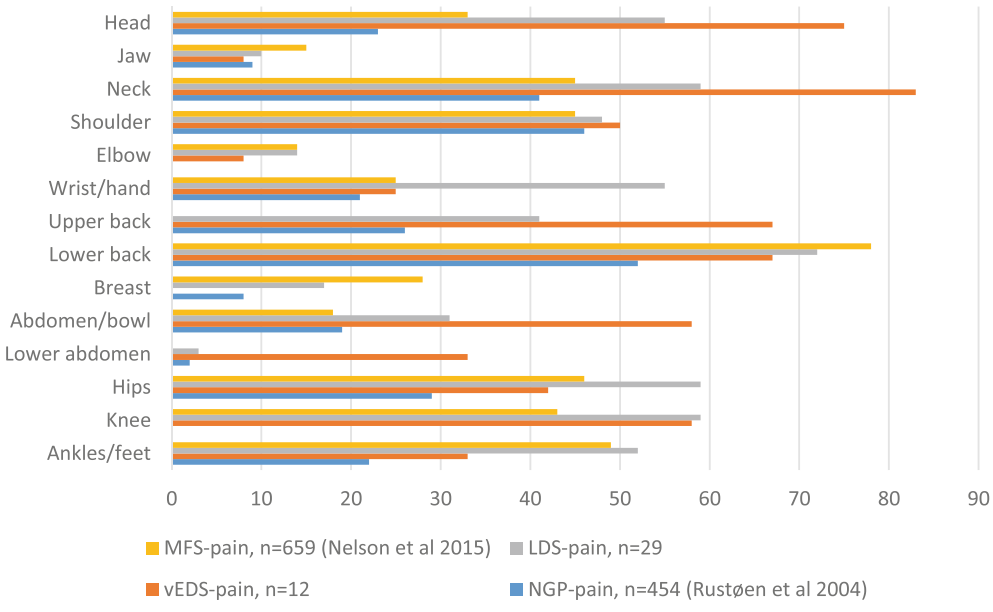

FIGURE 1 The distribution of chronic pain locations in LDS- and vEDS patients ($n = 41$), patients with chronic pain from an US MFS population and a Norwegian general population

Compared to the pain patients among NGP (Rustøen et al., 2004), the LDS, vEDS and MFS (Nelson et al., 2015) groups reported pain in the head, neck, lower back, and knees more frequently. Many in the LDS and MFS (Nelson et al., 2015) groups also reported pain in the hips and ankles/feet, and many in the vEDS group reported pain in the upper back, abdomen/bowel, and lower abdomen.

In the bivariate regression analyses, we found that perceived sleep problems ($p = 0.004$), higher level of fatigue symptoms ($p = 0.002$), and higher level of multi-organ burden ($p = 0.014$) were statistically significantly associated with chronic pain (Table 3).

3.3 | Fatigue

The distribution of the categories of FSS severity and the mean FSS scores for the study sample are shown in Table 4. In total, 58% reported high levels of fatigue symptoms. The FSS results did not differ statistically significantly between male and female participants ($p = 0.116$) or between those with LDS versus vEDS ($p = 0.079$). The mean FSS scores did not increase with higher age ($p = 0.669$).

Table 5 shows associations between demographic and clinical factors and the levels of fatigue. In the bivariate regression analyses, low PA level ($p = 0.014$), sleeping problems ($p < 0.001$), chronic musculoskeletal pain ($p < 0.001$), high level of cardiovascular ($p = 0.025$) and multi-organ burden ($p < 0.001$), and high level of HADS-A ($p = 0.001$) were found to be statistically significantly associated with fatigue scores.

Thirty-five (67%) participants perceived sleep problems, and most of them 24/35 (69%) reported problems with falling asleep, followed by sleeping coherently (66%), staying awake during the day (54%), and early wake up (40%).

TABLE 3 The associations (OR; 95% CI) between demographic and clinical factors and *chronic musculoskeletal pain* in 52 adults with Loeys–Dietz syndrome or vascular Ehlers–Danlos syndrome

	Chronic musculoskeletal pain		Crude effect estimates[a]		
Independent variables	**Yes(n)**	**No(n)**	**cOR**	**95%CI for cOR**	***p* cOR**
Diagnose, LDS					
Yes (n)	29	5	0.4	0.1 to 1.4	0.126
No(n)	12	6	Ref		
Gender, women					
Yes(n)	25	4	0.2	0.1 to 1.0	0.057
No(n)	16	7	Ref		
Education ≥13 years					
Yes(n)	16	5	1.3	0.3 to 5.0	0.700
No(n)	25	6	Ref		
Working full time					
Yes(n)	11	3	1.0	0.2 to 4.4	0.977
No(n)	30	8	Ref		
Sleep problems					
Yes(n)	32	3	0.1	0.02 to 0.5	0.004
No(n)	9	8	Ref		
Age (years)			1.0	1.0 to 1.0	0.700
Physical activity level			0.5	0.1 to2.8	0.418
Time since diagnose confirmation (year)			1.0	0.9 to 1.2	0.534
Level of fatigue			2.4	1.4 to 4.0	0.002
Cardiovascular burden (0–7)			1.0	0.7 to 1.4	0.928
Multi-organ burden (0–11)			1.8	1.1 to 3.0	0.014
Anxiety level (HADS-A)			0.9	0.6 to1.1	0.256
Depression level (HADS-D)			0.9	0.6 to 1.4	0.711

Note: Dichotomous variables: Diagnose, LDS yes = 1, no = 0; gender, women yes = 1, no = 0; education level ≥ 13 years yes = 1, no = 0; working full time yes = 1, no = 0; sleeping problems yes = 1, no = 0. Continuous variables: age, physical activity level, time since diagnose confirmation, cardiovascular burden (0–7), multi-organ burden (0–11), level of fatigue (FSS), anxiety level (HADS-A), depression level (HADS-D).

Abbreviations: aOR, adjusted odds ratio; cOR, Crude odds ratio; CI, confidence interval; LDS, Loeys–Dietz syndrome; Ref, reference category.

*Statistically significant associations $p \leq 0.05$.

[a]Crude effect estimates: logistic regression analysis.

TABLE 4 *Fatigue* mean (*SD*) and *fatigue severity groups* in 52 adults with Loeys–Dietz syndrome and vascular Ehlers–Danlos syndrome

Fatigue characteristics	Total study sample, $n = 52$	LDS, $n = 34$	vEDS, $n = 18$
[a]FSS, (range 1–7), mean (*SD*) ($n = 52$)	4.8 (1.6)	5.1 (1.5)	4.3 (1.6)
No fatigue (score ≤4), *n*(%)	15 (29)	8 (24)	7 (39)
Borderline (score >4 ≤ 5), *n*(%)	7 (14)	4 (12)	3 (17)
High fatigue (score >5), *n*(%)	30 (58)	22 (64)	8 (44)

Abbreviations: LDS, Loeys–Dietz syndrome; vEDS, vascular Ehlers–Danlos syndrome.
[a]FSS, Fatigue severity scale.

TABLE 5 Self-reported symptoms of *fatigue* (*FSS*) in relation to demographic and clinical factors among 52 adults with Loeys–Dietz syndrome or vascular Ehlers–Danlos syndrome

	LDS and vEDS	Bivariate linear regression crude regression coefficients		
Independent variables	***n***	**cB**	**95% CI cB**	***p* cB**
Diagnose, LDS	51	0.8	−0.1 to 1.7	0.079
Gender, women	52	−0.7	−1.6 to0.2	0.116
Educational level ≥ 13 years	51	−0.3	−1.2 to 0.6	0.560
Working full time	51	−0.3	−1.3 to 0.7	0.555
Time since diagnose confirmation (years)	47	0.04	−0.03 to0.1	0.303
Physical activity level	50	−1.3	−2.3 to −0.3	0.014
Sleep problems	51	2.2	1.4 to 2.9	<0.001
Chronic musculoskeletal pain	51	1.9	1.0 to 2.8	<0.001
Age (years)	52	0.01	−0.02 to 0.03	0.666
[b]Cardiovascular burden (0–7)	51	0.2	0.03 to 0.4	0.025
[c]Multi-organ burden (0–11)	50	0.4	0.2 to 0.6	<0.001
HADS-A	51	−0.3	−0.4 to −0.1	0.001
HADS-D	50	0.01	−0.3 to 0.3	0.946

Note: Dichotomous variables: Diagnose, LDS yes = 1, no = 0; gender, women: yes = 1, no = 0; education level ≥ 13 years yes = 1, no = 0; working full time yes = 1, no = 0; sleeping problems yes = 1, no = 0; chronic musculoskeletal pain yes = 1, no = 0. Continuous variables: age, physical activity level, time since diagnosis confirmation, cardiovascular burden (0–7), multi-organ burden (0–11), anxiety level (HADS-A), depression level (HADS-D).
Abbreviations: B, unstandardized regression coefficient; LDS, Loeys–Dietz syndrome; cB, crude B.
*Statistically significant associations $p \leq 0.05$.

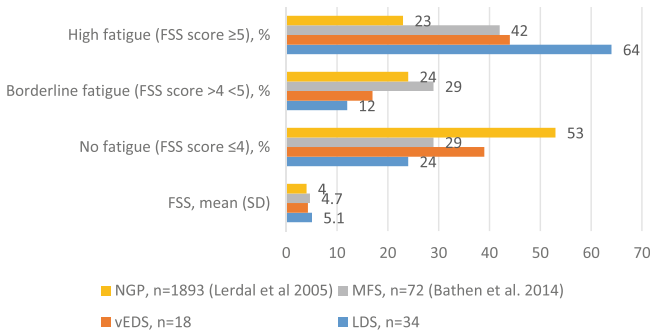

FIGURE 2 The proportions assessed to have no fatigue, borderline fatigue, and high level of fatigue symptomatology among the LDS- and vEDS patients compared with a Norwegian MFS population and a Norwegian general population

Figure 2 shows the FSS results for the studied LDS- and vEDS individuals, a Norwegian MFS group (Bathen et al., 2014) and for the NGP (Lerdal et al., 2005). Of these, the LDS group had the highest mean FSS score and the highest proportion with high fatigue scores.

4 | DISCUSSION

4.1 | Main findings

To the best of our knowledge, this is the first study investigating self-reports on chronic musculoskeletal pain and fatigue symptomatology in adults with molecularly confirmed LDS and vEDS.

The main findings were high prevalence of pain and fatigue symptoms, reports of multiple pain locations, and that pain symptoms influenced participation in housekeeping, work and leisure activities in the study population. Common pain locations were in the head, neck, lower back, and knees. Overall, LDS participants reported higher pain intensity compared to those with vEDS. More than half of the study population developed pain during childhood or adolescence. Participants with sleep problems and/or high multi-organ burden tended to

report *both chronic pain* and *high levels of fatigue symptoms*, those with *chronic pain* tended to report high levels of fatigue, and those with high levels of *fatigue* tended to report low levels of PA, high cardiovascular burden and high HADS-A scores.

4.2 | Chronic musculoskeletal pain

Chronic pain is a significant problem in the NGP; and women, low educational level, being frequently ill, or having a chronic illness are important variables predicting chronic pain (Rustøen et al., 2004; Svebak et al., 2006). In our study, the prevalence of chronic musculoskeletal pain was extremely high (79%), much higher than in the NGP (24%) (Rustøen et al., 2004), and higher than in an US MFS population (67%) (Nelson et al., 2015). The reported pain prevalence in MFS patients varies from 47% to 92% between studies (Velvin et al., 2016) and is highlighted as a dominant and presenting symptom of MFS (von Kodolitsch et al., 2019). Schubart et al. (2019), found less symptom burden and pain in a vEDS group, compared to classical and hypermobile EDS patients.

Only a fifth (21%) of our study group reported no pain problems, 15% of those with LDS and 33% of those with vEDS. It is likely that future studies also will find variations in pain prevalence between LDS subgroups and vEDS groups, but there is no doubt that pain seems to be a problem for a huge proportion of these patients. In participants with pain, we found higher pain scores during activity and lower at rest compared to those reporting pain from the NGP (4.5 and 3.0 vs 3.9) (Rustøen et al., 2004). Similar to those reporting pain in NGP (Rustøen et al., 2004), widespread pain was common among our study participants. A smaller proportion of our participants reported four or more bodily pain locations compared to persons reporting pain among the NGP (53% vs 71%). However, pains located to the head, abdomen/bowel, upper-, and lower extremities were more frequent among patients with LDS and vEDS compared to those in the NGP.

Several authors claim that pain burden in HTADs is connected to joint problems, skeletal deformities, and hypermobility followed by risk of dislocations and/or subluxations (MacCarrick et al., 2014; Meester et al., 2017; Schubart et al., 2019). In LDS patients, pain may also be connected to joint contractures and osteoarthritis (*SMAD3*) (Meester et al., 2017; MacCarrick et al., 2014). The fact that almost everyone with LDS reported chronic pain in our study may be due to their mixed joint problems with both hypermobility, joint contractures, and osteoarthritis.

Pain limited most participants in leisure activities, fewer in housekeeping and in work life. This is consistent with findings on life satisfaction reported in an earlier article on the same study population (Johansen et al., 2021) which showed low satisfaction with the leisure domain. These findings might indicate that adaptation to leisure and housekeeping is more difficult than customizing employment. One might speculate that those who still work probably prioritize using their efforts to manage the job at the expense of reduced participation in leisure activities.

We found no association between age and chronic pain. However, more than half of the participants reported that pain problems occurred during childhood and adolescence, which is a considerably higher proportion than reported among those reporting pain among NGP (Rustoen et al., 2005). Warnink-Kavelaars et al. (2021)) also found significant pain problems in a mixed group of children with HTAD. HTAD's are congenital disorders commonly presenting with symptoms such as hypermobility and contractures that may cause pain at a young age. Developing chronic pain at a young age is a negative predictor for curing the pain (Landmark et al., 2018) and might influence participation and social life for many years (Breivik et al., 2006; Landmark et al., 2013).

Among persons with pain problems in the NGP, the most common pain managements reported were usage of analgesics (43.0%), physiotherapy (31.9%), acupuncture/ transcutaneous nerve stimulation (5.9%), and relaxation (3.1%) (Rustoen et al., 2005). Among our participants, PA, rest, and cooling were mentioned as pain relieving by some patients, while others found these interventions to increase the pain. Heating and analgesics were mentioned as reducing pain, and stress and static work situations increased pain. Several studies documented that MFS patients have low satisfaction with pain treatment (Nelson et al., 2015; Velvin et al., 2016; von Kodolitsch et al., 2019), as also reported in pain populations in general (Breivik et al., 2006). As highlighted by von Kodolitsch et al. (2019), the pain is chronic and should focus on management with low risk of developing addiction to medications; cognitive therapy, mental and physical activities, and transcutaneous nerve stimulation should be considered.

4.3 | Fatigue

Fatigue scores above 5 (i.e., high levels of fatigue symptoms) were more common in our study population (58%) compared to Norwegian MFS patients (42%)(Bathen et al., 2014) and the NGP (23%) (Lerdal et al., 2005). We found the prevalence of high level of fatigue to be higher among LDS patients (64%) than among those with vEDS (44%), and also compared with MFS (42%) (Bathen et al., 2014). Fatigue symptoms among people with chronic illness are common (Lerdal et al., 2005). Interestingly, Schubart et al. (2019)) found higher mental fatigue symptoms among vEDS compared to other EDS subgroups. Unfortunately, the FSS do not differ between mental and physical fatigue, but this should be investigated in future studies of vEDS. We found no association between age and fatigue. However, clinical experience and findings from a study on children with HTAD (Warnink-Kavelaars et al., 2021) show that fatigue problems also in children with these diagnoses can be common.

Among our study participants, sleep problems were common and in agreement with findings in other HTAD conditions (Rybczynski et al., 2010), pain patients (Menefee et al., 2000), and in patients with high levels of anxiety symptoms (Cox & Olatunji, 2016). Sleep problems in MFS are often connected to obstructive sleep apnea (Rybczynski et al., 2010), and treatment of the latter has been found effective for lowering fatigue symptoms in a general population, as well (Chotinaiwattarakul et al., 2009). To what extent obstructive sleep apnea is present in people with LDS or vEDS, is unknown and should be investigated.

4.4 | Pain, fatigue, and associations with demographic and clinical factors

In contrast to the NGP, we did not find any associations between pain (Rustøen et al., 2004) or fatigue symptoms (Lerdal et al., 2005) and gender, age, or educational level. The lack of such correlations in our LDS and vEDS participants correspond with findings on MFS patients (Bathen et al., 2014). This is an interesting finding and may indicate that gender, age, and educational level are less important factors for pain and fatigue experiences in HTADs. These findings need to be confirmed in studies of larger HTAD populations. In our patient group, those with sleeping problems and high multi-organ burden tended to report both chronic pain and high level of fatigue symptoms. Additionally, those with chronic pain tended to report higher fatigue scores, and those with high fatigue scores tended to report lower levels of PA, high cardiovascular burden and high HADS-A scores.

Our findings indicated that the existence of chronic pain, fatigue symptoms, sleep problems, high HADS-A scores, and disease symptom burden seemed to be interconnected and thus factors that may affect each other mutually. Corresponding associations between pain, psychological distress and fatigue were also pointed out in a recently published study from the Norwegian Twin Registry (Løke et al., 2022).

PA and exercise have shown to be effective in reducing pain in the general population (Landmark et al., 2013) and for reducing fatigue symptoms among persons with certain chronic conditions (Neill et al., 2006). As we have pointed out in previous articles, it is important to keep in mind that balancing PA is challenging for HTAD groups (Johansen et al., 2020b). They are advised to limit their PA which may increase the risk of inactivity and a sedative life, and thus might aggravate fatigue and pain.

4.5 | Strength and limitations

The main strengths of this study were the high response rate, the inclusion of persons with a genetically verified LDS or vEDS, and the completeness of the data with very few missing variables. Due to the rarity of the diagnoses and no available national registry, we do not know the representativeness of the 52 participants from the total population of LDS or vEDS in Norway (general population of 5.3 million inhabitants). Nevertheless, the study group was residents from all over Norway. The National Resource Centre for Rare Disorders is a free of charge service for all citizens with HTADs. However, registration at the center is voluntary, and is not a registry covering the total population with HTADs in Norway. Furthermore, individuals were usually registered because of their need for services such as diagnosis information, advice on lifestyle changes, or counseling on welfare services. Persons choosing to register may therefore differ from those who do not.

The study questionnaire included instruments that are well proven and validated in several patient populations, however as far as we know, not among HTADs. The self-reports might have introduced recall bias to questions on retrospective information.

Worth noticing is the possibility of some study participants being relatives. We did not collect information on this, and might have recruited participants from the same families, thus causing a possible confounding factor.

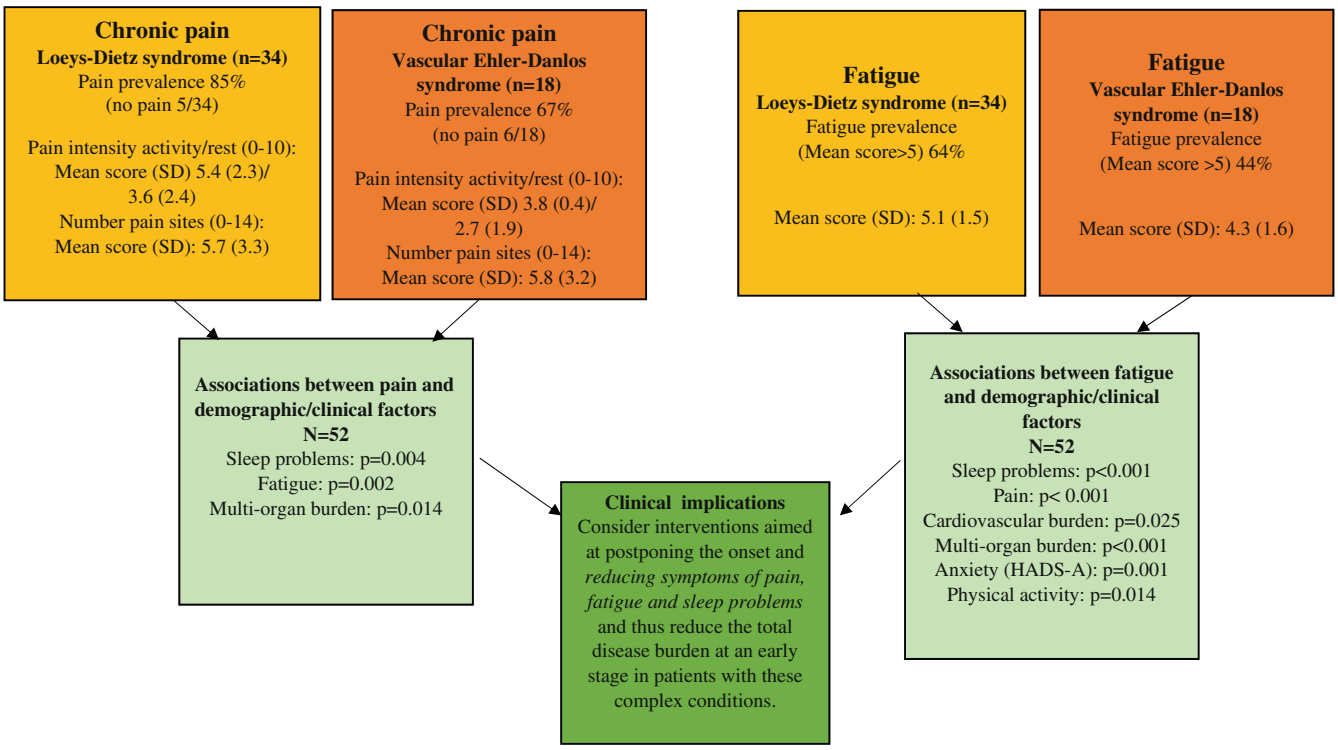

FIGURE 3 An overview, pain and fatigue in adults with LDS and vEDS, associations and implications

The relatively small sample size leads to low statistical power for several analyses. We are aware that we explored many associations, which may increase the possibility of statistically significant findings. The presence or lack of statistically significant findings in this small study sample do not allow for firm conclusions or generalizability to LDS or vEDS patients as such, and need more robust studies for confirmation. However, we recognize the high proportions of symptom profiles- and burdens in this study, and do especially welcome investigations of interventions aimed at reducing these.

5 | CONCLUSION

This study showed very high proportions with chronic musculoskeletal pain and clinically relevant fatigue symptoms among persons with LDS and vEDS. The symptom profiles were disabling as the participants reported high interference with housekeeping, work, and leisure activities. Multiple pain locations were common, especially in the head-, neck-, lower back-, and knee regions. According to our data and analyses, disease burden, sleep problems, anxiety, chronic pain, and fatigue symptoms seemed to mutually reinforce each other. We conclude that chronic pain and fatigue symptoms should be recognized as important features among patients with HTADs in the lifelong follow-up. Clinical and research initiatives should consider interventions aimed at postponing the onset and/or reducing symptoms of pain, fatigue, and sleep problems, and thus reduce the total disease burden at an early age in patients with these complex conditions.

Figure 3 shows an overview of the main findings in this study.

AUTHORS CONTRIBUTION

The authors state equal participation work on this article.

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CONFLICT OF INTEREST

The authors report no conflicting interests.

DATA AVAILABILITY STATEMENT

The data underlying this study is restricted by the Regional Committee for Medical and Health Research Ethics in South East Norway. Due to these ethical restrictions regarding potentially identifying patient information, data is not available.

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