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Original article

Assessment of functional respiratory complaints and related factors in people with hypermobile Ehlers-Danlos syndrome: Cross-sectional study

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ABSTRACT

Background: Hypermobile Ehlers-Danlos Syndrome (hEDS) is the most common type of EDS. Apart from joint symptoms, people with hEDS have systemic manifestations as a chronic modification of the breathing pattern (functional respiratory complaints (FRCs)) and mental disorders. However, the prevalence of FRCs, and its relationship with mental disorders, have not yet been estimated for this population.
Objectives: To assess the FRCs, central sensitization, disease perception, depression, and anxiety in people with hEDS from Belgium; and to identify the clustering of FRCs and determine any association with the characteristics assessed for this sample.
Methods: This cross-sectional study assessed socio-demographic characteristics, Nijmegen questionnaire (NQ), Central Sensitization Inventory (CSI), Brief Illness Perception Questionnaire, and the Hospital Anxiety and Depression Scale (HADS) in people with hEDS from Belgium. A two-step cluster analysis was performed to identify clusters according to NQ, and to understand how the other questionnaires are grouped among these clusters.
Results: The Spearman correlation coefficients showed that all the outcomes were significantly and positively correlated with each other ($p<0.05$). Furthermore, 84.9% of the sample had symptoms suggestive of FRCs, and 54.3% had probable anxiety. Three clusters were grouped (no FRCs, mild FRCs, and severe FRCs), with NQ, HADS-D and CSI-part A being the variables that contributed the most. People from cluster of severe FRCs got the worst scores for all the questionnaires.
Conclusion: FRCs, central sensitization, depression, and anxiety are prevalent comorbidities in people with hEDS. Moreover, those people with FRCs had worse results in the investigated parameters, with depression being the variable that contributed the most to the clusters of FRCs. Consequently, investigating mechanisms for these co-occurring symptom profiles may improve our understanding of pathogenesis and indicate new management strategies to alleviate these symptoms and lead to the development of more effective care for persons with hEDS.

Introduction

The Ehlers-Danlos syndrome (EDS) is an inherited clinically and genetically heterogeneous group of disorders of the connective tissue [1]. The main feature is abnormal collagen synthesis, leading to joint hypermobility, tissue fragility and skin hyperextensibility [1]. However, although the main clinical presentations are skin and musculoskeletal disorders, there could also be multisystem involvement [2] such as gastrointestinal dysfunction [3], respiratory [4] or neurological manifestations [5].

The International EDS Consortium proposed in 2017 a classification of 13 subtypes [6], each with a different phenotype, and with hypermobile EDS (hEDS) being the most common (80–90% of all EDS) [7]. The clinical features of hEDS are sometimes indistinguishable from other hypermobility spectrum disorders (HSD) [8].

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Due to joint abnormalities, persistent nociceptive input triggers central sensitization in people with hEDS, resulting in widespread pain [9]. Apart from joint symptoms, people with hEDS also have systemic manifestations such as exercise limitation, fatigue, dysautonomia, sleep disturbance, anxiety and depression [6,10]. The unpredictable and diverse nature of the symptoms exacerbates the misunderstanding of the syndrome [11], with a low understanding of their illness [12].

According to previous evidence, people with hEDS have a 2-fold higher incidence of cough, a 2.5-fold higher sputum production and a 3-fold higher prevalence of nocturnal cough and wheeze compared to controls [13]. Sometimes, when the breathing pattern is chronically altered, a dysfunctional breathing occurs, resulting in dyspnea [14,15]. To our knowledge, the prevalence of functional respiratory complaints (FRCs) in people with hEDS has not yet been estimated, which would be important for public health in treatment planning.

Apart from physical symptoms, mental disorders are also common in people with hEDS. A previous study reported that depression and anxiety were significantly higher in hEDS than in a healthy group [16]. The association of anxiety with other variables, such as pain and depression, has been described in people with hEDS [17]. In addition, anxiety has previously been associated with dysfunctional breathing and was considered an influential factor [18]. However, to our knowledge, these different conditions have never been assessed together and the relationship between mental health and FRCs remains unknown in hEDS.

Thus, the aims of this cross-sectional study were: 1) to assess FRCs, central sensitization, disease perception, depression and anxiety in people with Ehlers-Danlos syndrome from Belgium; 2) to identify the clustering of FRCs and to determine any association with the characteristics assessed for this sample.

Methods

Study population and design

The cross-sectional study was approved by the Ethics Committee of Cliniques Universitaires St Luc (No. B403201525660) and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Table S1 in the supplementary material). Participants were recruited from the patients list of the Ehlers-Danlos Syndrome Study and Research Group (GERSED) from Belgium.

All 389 people with hEDS from GERSED Belgium were invited to participate in the study. To be included in this study, people had to be over 18 years of age and French-speaking. They were excluded if they could not read or understand the questionnaires.

Once informed in writing, participants were asked to sign a consent form as a condition of participation in the study. An electronic survey including questions on functional breathing, central sensitization, disease perception, depression, and anxiety was emailed to participants between May and June 2018. They had to answer within the next 6 weeks. After all surveys were received, the data were backup from the platform, and organised for analysis.

Variables

The survey consisted of five parts and assessed:

- Socio-demographic characteristics: gender, age, marital status, employment situation, emotional traumas (separation, bereavement, or childhood abuse), and whether they practiced physical activity.
- Nijmegen questionnaire (NQ): this questionnaire is the most common method for screening dysfunctional breathing [19]. It consists of 16 items related to symptoms of daily life. Each item is scored on a 5-point graded scale, from 0 “never” to 4 “very often”. The total score is calculated by cumulating the scores for each question, with higher scores indicating a higher risk of FRCs [20]. A cut-off score of 22 is considered indicative of FRCs [21]. The content validity of this questionnaire has been supported by a good correlation with patients’ symptoms [22].
- Central Sensitization Inventory (CSI): this questionnaire identifies and quantifies the degree of the most important symptoms related to Central Sensitivity Syndrome (CSS). It consists of two parts (A and B). Part A contains 25 items related to current health symptoms. Each is rated on a five-point Likert scale as never (0), rarely (1), sometimes (2), often (3), and always (4). The total score for part A ranges from 0 to 100, with higher scores indicating worse CSS. A cut-off score of 40 is considered to discriminate between patients with and without CSS [23]. Different levels of CSS severity can be classified (subclinical, 0–29; mild, 30–39; moderate, 40–49; severe, 50–59; and extreme, 60–100) [24]. In part B, previously diagnosed CSS and related conditions (i.e. chronic fatigue syndrome, fibromyalgia, temporomandibular joint disorder, migraine or tension headaches, restless legs syndrome, irritable bowel syndrome, multiple chemical sensitivity, neck injury, anxiety disorders or panic attacks, or depression) are collected [25,26]. The score for part B was calculated by summing the number of comorbidities. The quality of evidence for the CSI questionnaire has been rated as good to excellent, being an easily explainable method with a high degree of construct validity [26].
- Brief Illness Perception Questionnaire (B-IPQ): the IPQ assesses items from the five components (illness identity, cause, time-line, consequences, and control/cure) underlying cognitive representations of illness on a 5-point Likert scale [27]. However, the B-IPQ summarizes the most important items of the IPQ, consisting of a 9-item scale, which is rated on a 0–10 response scale for the first 8 items [28]. It has been widely used and has good psychometric properties [29]. Higher scores indicate a more threatening view of illness [29].
- Hospital Anxiety and Depression Scale (HADS): the HADS is a 14-item scale that aims to identify possible or probable cases of anxiety and depression among patients in non-psychiatric hospital clinics. For this purpose, the scale is divided into anxiety (HADS-A) and depression (HADS-D) subscales, each with 7 questions. Each item is scored on a 4-point scale (0, never; 1, often; 2, very often; and 3, most of the time), with higher scores indicating worse anxiety or depression. The cut-off points for identifying possible and probable cases of anxiety or depression are: 0–7 no cases; 8–10 doubtful cases, and 11–21 probable cases [30].

The questionnaires are available in Table S2 in the supplementary material.

Statistical analyses

The normality of the distribution of continuous variables was tested with the Kolmogorov–Smirnov test. Parametric or non-parametric tests were used for the analysis as appropriate.

Socio-demographic characteristics and questionnaire results for the total population were calculated as mean and standard deviation following the law of large numbers, and the proportion of participants in each category was also reported.

Spearman correlation coefficients were then used to examine the relationship between the total score of the ordinal results of the following questionnaires: NQ, CSI (parts A and B), B-IPQ, and HADS (total, HADS-A and HADS-D).

Differences in characteristics or scores for FRCs, CSS and type of emotional trauma were calculated using the U-Mann Whitney test. Kruskall Wallis was used to test for differences by severity levels of CSI and by no-cases, doubtful and probable cases of anxiety and

depression. Bonferroni correction for multiple comparisons was used to test post-hoc pairwise hypotheses.

Finally, a two-step cluster analysis was used as an exploratory tool to identify clusters of FRCs based on the results of the different questionnaires: CSI (Part A), CSI (Part B), B-IPQ, HADS-A and HADS-D. This method for cluster analysis uses a distance measure to separate groups and then a probabilistic approach to choose the optimal subgroup model [31]. The optimal number of clusters was based on the log-likelihood distance and the Schwarz Bayesian criterion [32]. NQ was used as categorical variable (FRCs or no FRCs), and the total score of CSI-part A, CSI-part B, B-IPQ, HADS-A and HADS-D were entered as continuous variables. The silhouette coefficient, which compares the average within cluster cohesion with the average between-cluster separation, was examined to assess the goodness-of-fit of the cluster solution. Values between 0.20 and 0.50 indicate a fair fit, and values of 0.50 or more a good fit [33]. The percentage of contribution of each variable to such a clustering solution will be represented as a relative importance index.

All analyses were performed with SPSS-IBM (Version 25.0. IBM Corp), and the significance level was set at a *p*-value of less than 0.05.

Results

The socio-demographic characteristics of the study sample are shown in Table 1. Of the 186 participants who responded to the survey (47.8%), 159 were women (85.5%), with more people in the 46−55 age group (n = 68; 36.6%). All of them self-reported to meet the new hEDS clinical diagnostic criteria [6]. Many of them were married (47.3%) and unemployed and not looking for a job (31.7%). Regarding emotional trauma, 41.9% suffered a separation, 69.4% bereavement, 21.5% childhood abuse, and 39.8% other types of traumas.

The results of the questionnaires are shown in Table 2. Regarding NQ, the mean was 34.9 ± 11.6, and most participants had a positive score (n = 158; 84.9%). When analysing the CSI scores, the mean score was 61.7 ± 16.4, and 165 participants (88.7%) had CSS. The most frequent type was the extreme (n = 116; 62.4%). Ninety-one participants had been diagnosed with depression (48.9%), and the mean total B-IPQ score was 53.67. Finally, the mean total HADS-A and HADS-D scores were 11.3 ± 4.1 and 7.8 ± 4.4, with 101 (54.3%) and 57 (30.6%) probable cases of anxiety and depression, respectively.

Table 1
Socio-demographic characteristics of the study sample.

	Total (n = 186)
Sex	
Male (n;%)	27 (14.5%)
Female (n;%)	159 (85.5%)
Age	
18−25 (n;%)	12 (6.5%)
26−35 (n;%)	25 (13.4%)
36−45 (n;%)	38 (20.4%)
46−55 (n;%)	68 (36.6%)
56−65 (n;%)	25 (13.4%)
65−75 (n;%)	15 (8.1%)
>75 (n;%)	3 (1.6%)
Marital status	
Married (n;%)	88 (47.3%)
Living with a partner (n;%)	40 (21.5%)
Separated or divorced (n;%)	33 (17.7%)
Never married (n;%)	25 (13.4%)
Employment situation	
Full time (n;%)	57 (30.6%)
Part-time (n;%)	33 (17.7%)
Unemployed and looking for a job (n;%)	9 (4.8%)
Unemployed and not looking for a job (n;%)	59 (31.7%)
Retired (n;%)	28 (15.1%)
Emotional trauma	
Separation (n;%)	78 (41.9%)
Bereavement (n;%)	129 (69.4%)
Childhood abuse (n;%)	40 (21.5%)
Other (n;%)	74 (39.8%)
Practice physical activity (n;%)	85 (45.7%)

Notes: Data presented as n (sample size) and percentage over the total.

Table 2
Questionnaires results of the study sample.

	Total (n = 186)
Nijmegen questionnaire total score	34.89 ± 11.57
No FRCs (n;%)	28; 15.1%
FRCs (n;%)	158; 84.9%
CSI- part A total score	61.74 ± 16.37
No central sensitisation syndrome (n;%)	21; 11.3%
Central sensitisation syndrome (n;%)	165; 88.7%
Subclinical (n;%)	10; 5.4%
Mild (n;%)	9; 4.8%
Moderate (n;%)	19; 10.2%
Severe (n;%)	32; 17.2%
Extreme (n;%)	116; 62.4%
CSI- part B total score	3.98 ± 2.31
Chronic fatigue syndrome (n;%)	69 (37.1%)
Fibromyalgia (n;%)	56 (30.1%)
Temporomandibular joint disorder (n;%)	54 (29%)
Migraine or tension headaches (n;%)	89 (47.8%)
Restless legs syndrome (n;%)	46 (24.7%)
Irritable bowel syndrome (n;%)	71 (38.2%)
Multiple chemical sensitivity (n;%)	35 (18.8%)
Neck injury (n;%)	49 (26.3%)
Anxiety disorders or panic attacks (n;%)	72 (38.7%)
Depression (n;%)	91 (48.9%)
B-IPQ total score	53.67 ± 9.14
HADS total score	19.09 ± 7.58
HADS-A total score	11.27 ± 4.10
HADS-A no anxiety (n;%)	31 (16.7%)
HADS-A doubtful cases (n;%)	54 (29%)
HADS-A probable cases (n;%)	101 (54.3%)
HADS-D total score	7.82 ± 4.40
HADS-D no depression (n;%)	93 (50%)
HADS-D doubtful cases (n;%)	36 (19.4%)
HADS-D probable cases (n;%)	57 (30.6%)

Notes: Data presented as mean ± standard deviation for the total scores, and n (sample size) with percentage over the total for the categorical variables.
Abbreviations: CSI = Central Sensitization Inventory; B-IPQ = Brief Illness Perception Questionnaire; FRCs = Functional Respiratory Complaints; HADS = Hospital Anxiety and Depression Scale; HADS-A = Hospital Anxiety and Depression Scale - Anxiety; HADS-D = Hospital Anxiety and Depression Scale – Depression.

Relationship between study variables

Table 3 shows the Spearman correlation coefficients between NQ, CSI-part A, CSI-part B, B-IPQ, and HADS scores (total, HADS-A and HADS-D). All of them were significantly and positively correlated with each other (p<0.05). The strongest correlations were between CSI-part A and NQ (0.791), HADS total (0.678), HADS-A (0.580), and HADS-D scores (0.619).

Questionnaires results by FRCs, central sensitization score, anxiety, and depression

Table 4 shows the results of the questionnaires by the different categories.

Participants who scored more than 22 on the NQ scale (n = 158), scored higher on all questionnaires than the others (p<0.011).

When comparing the questionnaire results of the participants who scored more than 40 in CSI (n = 165), all the results were worse for them compared to those who scored less than 40 (p<0.002). Scores on the other questionnaires were worse as the level of CSI was more severe. However, when doing Bonferroni analyses, not all pairwise comparisons reached statistically significant differences, but

Table 3
Correlation coefficients among Nijmegen questionnaire, CSI, B-IPQ and HADS.

	Nijmegen total score		CSI- part A total score		CSI- part B total score		B-IPQ total score		HADS total score		HADS-A	
		p-value		*p*-value		*p*-value		*p*-value		*p*-value		*p*-value
CSI- part A total score	0.791	0.001										
CSI- part B total score	0.479	0.001	0.535	0.001								
B-IPQ total score	0.468	0.001	0.538	0.001	0.286	0.001						
HADS total score	0.605	0.001	0.678	0.001	0.440	0.001	0.552	0.001				
HADS-A	0.540	0.001	0.580	0.001	0.363	0.001	0.454	0.001	0.875	0.001		
HADS-D	0.520	0.001	0.619	0.001	0.430	0.001	0.532	0.001	0.894	0.001	0.577	0.001

Results indicate Spearman correlation coefficients.
Abbreviations: CSI = Central Sensitization Inventory; B-IPQ = Brief Illness Perception Questionnaire; HADS = Hospital Anxiety and Depression Scale; HADS-*A* = Hospital Anxiety and Depression Scale - Anxiety; HADS-*D* = Hospital Anxiety and Depression Scale – Depression.

those with extreme CSS showed significant differences with all other CSS levels for all questionnaires.

Finally, when comparing the median of NQ, CSI, and total B-IPQ, by those participants with no-cases, doubtful cases and probable cases of anxiety and depression, all of them were significant. Overall, post hoc pairwise Bonferroni tests showed that participants with probable cases had significantly higher scores than those classified as no-cases or doubtful cases.

Questionnaires results by type of emotional trauma

Participants who had experienced separation, bereavement or childhood abuse scored higher on all questionnaires than those who had not experienced the corresponding type of emotional trauma ($p<0.05$), except for bereavement in B-IPQ score (Table S3 in the supplementary material).

Cluster analysis

Subjects were grouped into three clusters: no FRCs (n = 28; 15.05%); mild FRCs (n = 88; 47.31%); and severe FRCs (n = 70; 37.64%). The distribution, median and quartiles of the results assessed according to the clusters obtained are shown in Fig. 1. Cluster of people with no FRCs got the lowest values for all the questionnaires, and cluster of people with severe FRCs got the highest ones. Variables such as NQ, HADS-D and CSI-part A, presented higher importance to discriminate the clusters. Conversely, HADS-A, B-IPQ and CSI-part B revealed less influence in distinguishing the clusters (Fig. 2).

Discussion

This large cohort study shows that people with hEDS have a high rate of comorbidities, studied through the questionnaires: FRCs (84.9% of the sample); central sensitization (88.7%); depression (30.6%); and anxiety (54.3%); and a low illness perception. Furthermore, when analysing the results by clusters of FRCs, those with severe FRCs got worse scores for all the questionnaires than those with no FRCs, with depression being the variable that contributed the most to these clusters.

In our Belgium cohort of people with hEDS, 84.9% had a score of more than 22 on the NQ, indicative of FRCs. To our knowledge, this is the first study estimating the prevalence of FRCs in people with hEDS. Previous studies have estimated the prevalence of FRCs in other populations, such as people with and without asthma, with a prevalence of 29–36% [34–36] and 8% [37], respectively. Recently, FRCs was shown to be particularly prevalent in post-COVID patients (29.4%) and warranted specific attention, although most of these patients did not have hyperventilation syndrome [38]. In contrast, in another study of survivors after hospitalization for COVID-19, similar results were found when assessing FRCs (21%), but in this case, 57% of patients with FRCs also had hyperventilation syndrome confirmed by a positive hyperventilation provocation test [39].

According to this evidence, the prevalence of FRCs is higher in people with hEDS than in the general population and the most impacted diseases. Moreover, the prevalence of FRCs in our study was higher than that shown by the study of Legander et al. for other expected comorbidities such as pain, sprains, contusion, or skin injuries [40]. Nevertheless, these data should be considered with caution, as there are many methods of diagnosing FRCs [19] and, due to the multidimensionality of breathing, a multi-component assessment is recommended [21]. The most common method relies on a positive NQ score, which is useful for quantifying and assessing subjective sensations; but other methods include ventilatory parameters such as end-tidal carbon dioxide measurement and breath holding time, and other subjective variables as the Self Evaluation of Breathing Questionnaire, or the Manual Assessment of Respiratory Motion [41,42]. Currently, there is no gold standard diagnostic method for FRCs, dysfunctional breathing or hyperventilation syndrome. Thus, in line with the COVID-19 studies discussed above, the prevalence of FRCs is not always related to hyperventilation syndrome, so the prevalence of FRCs assessed with NQ in our study has no specific relationship with hyperventilation syndrome.

Clinical manifestations in people with hEDS include those related to the rib cage, such as pectus excavatum, thin ribs, straight back syndrome, or scoliosis [4,43]. These deformities, with reduced respiratory muscle strength and even producing pain, result in an altered breathing pattern in patients with scoliosis [44]. Previous evidence has shown an association between abnormal dominance in upper rib cage motion in breathing and FRCs in patients with unexplained complaints [45]. Thus, the resulting altered breathing pattern in people with hEDS could explain why these people have more FRCs than patients with asthma or the general population.

The prevalence of anxiety in the general population in Central Europe was estimated at 3.6–7.0% [46], and the prevalence of depression in a cohort from United States was 8.5% before COVID-19 and 27.8% during the pandemic [47]. Similar to FRCs, our results in people with hEDS showed that 54.3% have anxiety and 30.6% depression, which is higher than the most expected comorbidities [40]. This findings are consistent with that of a previous study in which the prevalence of anxiety and depression was 45.7% and 37.1%, respectively, in a small sample of women with hEDS [48]. This population often reports problems in performing activities of daily living due to pain and fear of skin breakdown [49]. In addition, people with higher anxiety also have more fatigue, somatosensory amplification, and poorer social functioning [17], which is in line with our findings, showing that people with more anxiety had more depression, CSS and FRCs. Given that pain has been associated with central sensitisation in people with hEDS [9,50], if they have impaired CSS, their pain would also increase, and influence mental health. However, there is no set of consensual criteria defining CSS in the literature, and many items on the CSI are common elements of depression and anxiety disorders, so

Table 4
Questionnaire results by categories of the different questionnaires.

		Nijmegen total score	CSI- part A total score	CSI- part B total score	B-IPQ total score	HADS total score	HADS-A	HADS-D
Nijmegen total score	No FRCs (n = 28)		40 (6–70)	1 (0–4)	45.5 (24–61)	10 (1–30)	6 (1–16)	3 (0–15)
	FRCs (n = 158)		66.5 (18–90)	4 (0–10)	55 (29–74)	21 (6–38)	12 (3–20)	8.5 (0–18)
	p-value		0.001	0.001	0.011	0.001	0.001	0.001
CSI part A score	No CSS (n = 21)	18 (4–28)		1 (0–3)	41 (24–61)	10 (1–16)	6 (1–12)	2 (0–10)
	CSS (n = 165)	39 (11–57)		4 (0–10)	55 (29–74)	21 (5–38)	12 (3–20)	8 (0–18)
	p-value	0.001		0.001	0.002	0.001	0.001	0.001
CSI part A score	Subclinical CSS [1] (n = 10)	15.5 (4–28) [5]		0.5 (0–29) [4,5]	39 (31–60) [5]	7.5 (1–16) [5]	5.5 (1–9) [5]	2 (0–10) [5]
	Mild CSS [2] (n = 9)	19 (10–24) [5]		1 (0–3) [5]	44 (24–61) [5]	10 (6–15) [5]	8 (4–12) [5]	3 (0–5) [5]
	Moderate CSS [3] (n = 19)	23 (11–39) [5]		1 (0–5) [5]	49 (37–61) [5]	12 (5–23) [5]	9 (3–15) [5]	4 (1–11) [5]
	Severe CSS [4] (n = 32)	30 (16–43) [5]		3 (0–7) [1]	51 (29–66) [5]	15 (5–32) [5]	9 (3–18) [5]	6 (0–15) [5]
	Extreme CSS [5] (n = 116)	42 (19–57) [1,2,3,4]		4 (0–10) [1,2,3]	57 (35–74) [1,2,3,4]	22 (7–38) [1,2,3,4]	13 (4–20) [1,2,3,4]	9 (1–18) [1,2,3,4]
	p-value	0.001		0.001	0.001	0.001	0.001	0.001
		Nijmegen total score	**CSI- part A total score**	**CSI- part B total score**	**B-IPQ total score**	**HADS total score**	**HADS-A**	**HADS-D**
HADS-A	No anxiety [1] (n = 31)	22 (4–44) [2,3]	45 (6–73) [2,3]	1 (0–6) [2,3]	49 (31–68)[3]	8 (1–19) [3]		3 (0–12) [2,3]
	Doubtful cases [2] (n = 54)	33 (16–52) [1,3]	60.50 (18–82) [1,3]	3 (0–7) [1,3]	52 (24–72)[3]	15 (8–24) [3]		6 (0–14) [1,3]
	Probable cases [3] (n = 101)	41 (10–57) [1,2]	72 (33–90) [1,2]	4 (0–10) [1,2]	56 (29–74)[1,2]	24 (14–38) [1,2]		10 (0–18) [1,2]
	p-value	0.001	0.001	0.001	0.001	0.001		0.001
HADS-D	No depression [1] (n = 93)	29 (4–57) [2,3]	58 (6–86) [2,3]	2 (0–9) [2,3]	51 (24–68)[3]	14 (1–24) [2,3]	9 (1–18) [2,3]	
	Doubtful cases [2] (n = 36)	40.50 (14–56) [1]	68.5 (24–85) [1]	3 (0–7) [1]	53.5 (31–74)[3]	22.5 (14–28) [1,3]	13.5 (5–19) [1]	
	Probable cases [3] (n = 57)	42 (18–55) [1]	75 (49–90) [1]	5 (0–10) [1]	60 (29–73) [1,2]	26 (19–38) [1,2]	13 (7–20) [1]	
	p-value	0.001	0.001	0.001	0.001	0.001	0.001	

Notes**:** Data presented as median (minimum-maximum). Superscript numbers indicate statistically significant differences between the category of the corresponding row and the category with the number in the left column. Abbreviations: B-IPQ = Brief Illness Perception Questionnaire; CSI = Central Sensitization Inventory; CSS = Central sensitisation syndrome; FRCs = Functional Respiratory Complaints; HADS = Hospital Anxiety and Depression Scale; HADS-A = Hospital Anxiety and Depression Scale - Anxiety; HADS-D = Hospital Anxiety and Depression Scale – Depression; n = sample size.

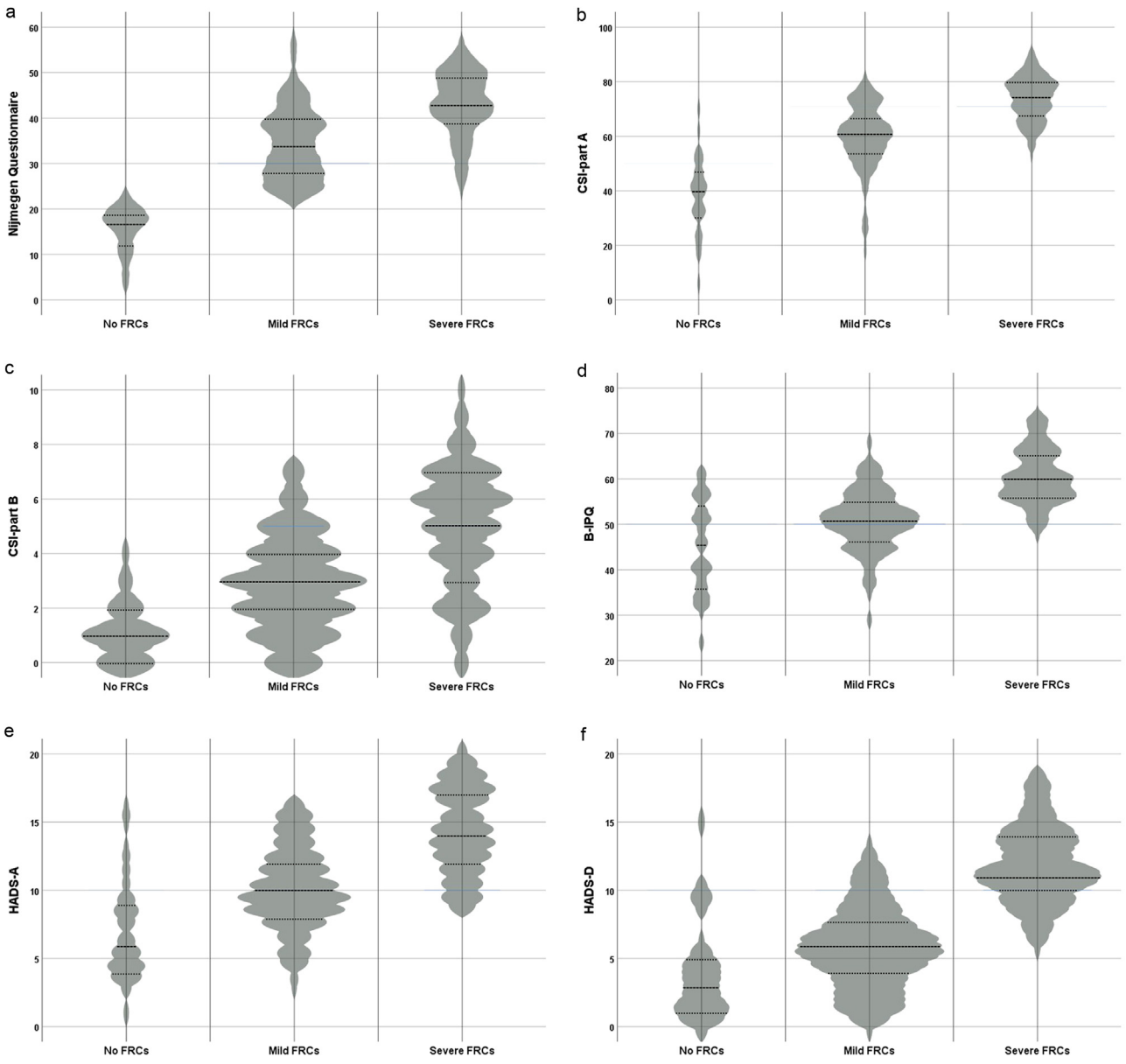

Fig. 1. Violin plots showing the distribution of the questionnaires according to the clusters obtained. The violin plots indicate the data distribution, the median and the first and third quartiles for each group. a) Nijmegen questionnaire; b) CSI-part A; c) CSI-part B; d) B-IPQ; e) HADS-A; f) HADS-D.

Abbreviations: B-IPQ = Brief Illness Perception Questionnaire; CSI = Central Sensitization Inventory; FRCs = Functional Respiratory Complaints; HADS = Hospital Anxiety and Depression Scale; HADS-*A* = Hospital Anxiety and Depression Scale - Anxiety; HADS-*D* = Hospital Anxiety and Depression Scale – Depression.

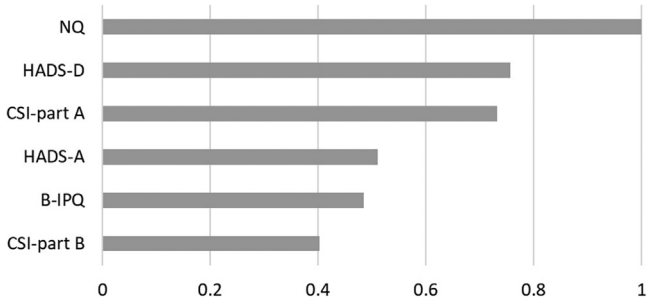

Fig. 2. Predictor importance for the different questionnaires to the obtained clusters.

Abbreviations: B-IPQ = Brief Illness Perception Questionnaire; CSI = Central Sensitization Inventory; HADS = Hospital Anxiety and Depression Scale; HADS-*A* = Hospital Anxiety and Depression Scale - Anxiety; HADS-*D* = Hospital Anxiety and Depression Scale – Depression; NQ = Nijmegen Questionnaire.

this association is to be expected due to the overlap of some symptoms [26].

In addition, when considering the NQ scores in our sample, people with FRCs had more CSS, disease perception, anxiety, and depression than those without FRCs. Hyperventilation results in increased minute ventilation with subsequent hypocapnia. Panic disorders, like anxiety and depression, often present with breathing disorders [51], with hyperventilation being the main factor producing increased blood alkalosis and triggering somatic events [52]. Furthermore, dyspnea and FRCs are prevalent when people experience anxiety or depression, which could explain the contribution of mental disorders to the FRCs distribution of our sample [53]. Finally, our sample showed a poor perception of illness with a total score of 53.67, which is similar to previous evidence with a score of 47.17 [12]. This could be explained by the high prevalence of the comorbidities assessed, as those with hEDS who had FRCs, central sensitization, anxiety or depression, also scored worse on illness perception.

When analysing whether our sample had suffered any emotional trauma, 41.9% had experienced separation, 69.4% had suffered bereavement, and 21.5% had been abused in childhood. In the case of separation, the process and symptoms of hEDS could influence the social aspects of these people, making it difficult for them to socialize in everyday life. Moreover, suffering from any of these emotional traumas may increase depression and anxiety, which could also imply a worsening of the other symptoms as discussed above, making a vicious cycle.

Our study should be interpreted considering several limitations. First, the cross-sectional design of the study prevents us from making cause-effect inferences. Indeed, we cannot know whether FRCs are producing mental disorders, or whether it is the mental disorders that are causing the FRCs. Furthermore, the similarity between the symptoms assessed in the NQ and the symptomatology of people with hEDS (such as abdominal bloating or palpitations), or the resemblance of NQ with the CSI part-A (stiffness, anxiety, tiredmess…), could explain the expected correlation between these, and we cannot confirm whether these symptoms are due to hEDS or to FRCs. Second, our study only included hEDS voluntary patients from GERSED Belgium with a participation rate of 47.8%. Probably only the most motivated individuals participated in the study, so caution is needed when inferring our data to the global hEDS population. However, e-mail response rates are around 25−30%, so our participation rate is above average [54], and is in line with the response rate of a recent study in people with Joint Hypermobility Syndrome/ hEDS (44.5% response rate for postal survey) [12]. On the other hand, 85.5% of our sample was female, but this percentage is similar to the prevalence from a recent hEDS cohort (81.2%) [55]. Moreover, the diagnosis of hEDS with new clinical diagnostic criteria was self-reported by patients and not based on clinical examination, and we only assessed outcomes with self-reported questionnaires, so the results could be overestimated. Third, we considered NQ as a diagnostic method for FRCs. Nijmegen questionnaire has been found to be reproducible as a patient reported outcome measure; nevertheless, the limitation of NQ is that the pathophysiology it is describing is not well understood. Moreover, as there is no gold standard method, our results could have differed if another method had been used. Finally, other outcomes that were not considered in our analyses, such as physical activity, quality of life or other respiratory conditions, could have influenced our results.

In conclusion, our findings show that FRCs, central sensitization, depression and anxiety are highly prevalent comorbidities in people with hEDS, and illness perception is poor in this population. Moreover, people with FRCs have worse scores in the investigated parameters, with depression being the variable that contributed the most to the clusters of FRCs. Consequently, it is important to consider FRCs in this population and observe whether there are associated symptoms, with further research to better examine the relationship between these manifestations. Finally, those with depression or anxiety also had worse results on all other parameters, so it is important to consider mental health in the management of people with hEDS.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.resmer.2023.101017.

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