



Establishing central sensitization inventory cut-off values in Dutch-speaking patients with chronic low back pain by unsupervised machine learning

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ABSTRACT

Background: Human Assumed Central Sensitization (HACS) is involved in the development and maintenance of chronic low back pain (CLBP). The Central Sensitization Inventory (CSI) was developed to evaluate the presence of HACS, with a cut-off value of 40/100. However, various factors including pain conditions (e.g., CLBP), contexts, and gender may influence this cut-off value. Unsupervised clustering approaches can address these complexities by considering diverse factors and exploring possible HACS-related subgroups. Therefore, this study aimed to determine the cut-off values for a Dutch-speaking population with CLBP based on unsupervised machine learning.

Methods: Questionnaire data covering pain, physical, and psychological aspects were collected from patients with CLBP and aged-matched healthy controls (HC). Four clustering approaches were applied to identify HACS-related subgroups based on the questionnaire data and gender. The clustering performance was assessed using internal and external indicators. Subsequently, receiver operating characteristic (ROC) analysis was conducted on the best clustering results to determine the optimal cut-off values.

Results: The study included 63 HCs and 88 patients with CLBP. Hierarchical clustering yielded the best results, identifying three clusters: healthy group, CLBP with low HACS level, and CLBP with high HACS level groups. The cut-off value for the overall groups were 35 (sensitivity 0.76, specificity 0.76).

Conclusion: This study found distinct patient subgroups. An overall CSI cut-off value of 35 was suggested. This study may provide new insights into identifying HACS-related patterns and contributes to establishing accurate cut-off values.

1. Introduction

Central Sensitization (CS) refers to an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input [1]. However, due to the inability to measure the mechanisms related to CS in individual humans [2], it has been proposed to refer to CS as Human Assumed Central Sensitization (HACS) [2–4]. HACS has been implicated in the development and maintenance of various chronic pain conditions, such as Chronic Low Back Pain (CLBP), fibromyalgia, and osteoarthritis [5]. CLBP is a leading contributor to global disability [6]. While the overall efficacy of rehabilitation

for patients with CLBP is generally positive, the average effect sizes are modest [7]. The possible presence of HACS is one of the key factors contributing to the complexity of CLBP [8] which could be among the factors responsible for the modest treatment effects [9]. Recognizing HACS in individuals with CLBP is crucial for tailoring appropriate treatment strategies, as interventions targeting CS may differ from those addressing peripheral mechanisms [10,11].

Despite its importance in recognizing HACS in CLBP, there is currently no universally accepted gold standard for diagnosing HACS [2]. The Central Sensitization Inventory (CSI) questionnaire was developed as a self-report questionnaire to screen for the presence and

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severity of HACS in individuals experiencing musculoskeletal pain [12]. The CSI has demonstrated good psychometric properties in various pain conditions [13]. A cut-off value of 40 out of 100 was established to indicate the presence of CS syndromes ((CSS), e.g., fibromyalgia, chronic fatigue syndrome, etc.). This cut-off value was determined based on a study involving patients with chronic pain, and it has demonstrated good sensitivity (81 %) and specificity (75 %) [14]. However, it has been observed that the cut-off values for CSI vary across different types of musculoskeletal pain, ranging from 11 to 40 [14–17], as well as across different cultural and national contexts [18]. This variability highlights the need for establishing context-specific cut-off values to improve the utility of the CSI in diverse populations. Furthermore, along with social and psychological factors, gender can affect pain perception. This might influence the presentation and severity of HACS, and ultimately determine the cut-off value [19,20]. To the best of our knowledge, there is no cut-off value established for Dutch-speaking patients with CLBP. Because of the lack of gold standard, the relationship between the CSI and HACS remains ambiguous. It is uncertain whether the CSI indicates enhanced nociceptive responses or also a psychological hypervigilance [21,22].

To establish an accurate cut-off value for CSI in Dutch-speaking patients with CLBP, the main challenge lies in accurately identifying the HACS-related subgroup. To address these challenges, unsupervised machine learning, especially clustering [23–25] may be a possible approach. Clustering approaches are proven successful in identifying patient subgroups, such as cancer subtypes, facilitating the development of personalized treatments. One study proposed a latent subspace learning clustering approach based on multiple components and high-dimensional input data (RNA and protein) to identify cancer subtypes efficiently and effectively [23]. Another study employed a deep clustering approach to identify cancer subtypes specifically based on RNA data [24]. The deep clustering approach has shown impressive performance; however, it relies on large datasets for model training. Additionally, the deep structure of the models introduces complexity, which can reduce transparency and may not align with legal requirements. For instance, the European General Data Protection Regulation (GDPR, EU 2016/679) mandates the explanation of the underlying logic behind any automated decision-making process that significantly impacts individuals [26]. Considering the relatively small data size in this study and the importance of transparency, four different clustering approaches will be explored: K-means, Hierarchical clustering, Self-organizing map, and Density-based spatial clustering of applications with noise. These clustering approaches are data-driven and offer ante-hoc explainability. They can automatically learn the relationships between variables and explore the possible HACS-related subgroups based on the questionnaire data that reflect pain, physical functioning, psychological factors, and HACS. These clustering approaches do not rely on prior knowledge or assumptions about the underlying structure of the data and can identify distinct groups within the data based on patterns of HACS. Based on the clustering results, researchers can uncover the optimal cut-off value that best differentiates individuals with low and high levels of HACS in a data-driven and context-specific manner. Apart from this, these approaches are flexible and can be applied to various types of data [27], such as demographic, cultural, and psychosocial factors, making them suitable for analyzing the complex and multidimensional nature of HACS. Additionally, the good scalability [27] of these approaches makes them easily scalable to accommodate large datasets, such as electronic health record system. In the future, by collecting more diverse and representative samples of the Dutch-speaking patients with CLBP, this scalability ensures that the established cut-off value is robust and generalizable to the broader population with CLBP.

In this study, by using questionnaires which provide information about pain, physical, and psychological aspects, we aim to 1) explore the HACS-related subgroups based on unsupervised clustering approaches; 2) establish the optimal cut-off values of CSI within Dutch-speaking

population with CLBP based on the clustering results; and examine gender differences in optimal cut-off values.

2. Methods

2.1. Participants

The data of Dutch-speaking patients with CLBP utilized in the present study was extracted from an existing dataset of a broader study [28]. Data collection took place from September 2017 to September 2019, and comprehensive protocol details have been previously documented [28]. The entire protocol aims to explore various instruments for investigating symptoms related to HACS in patients with CLBP [28]. The aged-matched Dutch-speaking healthy controls (HC) were recruited by advertisements on social media and flyers.

The patients with CLBP were recruited from the outpatient Pain Rehabilitation Department at the Center for Rehabilitation of the University Medical Center Groningen (CvR-UMCG). CLBP is characterized by recurring pain in the lower back lasting for over 3 months. This pain is associated with emotional distress and/or functional disability and is not caused by any other diagnosis [29]. Inclusion criteria were as follows: 1) age ≥ 18 years; 2) admission to the interdisciplinary pain rehabilitation program; 3) ability to follow instructions; 4) signed informed consent. Patients were excluded if they: 1) had a specific diagnosis that better accounted for their CLBP symptoms (e.g., cancer, inflammatory diseases, or spinal fractures); 2) experienced neuralgia and/or radicular pain in the legs (examination by physiatrist); 3) were pregnant. The presence of comorbidities related to HACS (e.g., fibromyalgia, osteoarthritis or chronic fatigue syndrome) are no reason for exclusion from the study. The HCs were included if they: 1) were aged ≥ 18 years; 2) could follow instructions; 3) provided signed informed consent. Exclusion criteria for healthy controls: 1) report more than mild pain (evaluated by Visual Analogue Scale, see below); 2) use of anti-depressant or antiepileptic drugs at the time of completing the questionnaire.

The Dutch-speaking patients with CLBP were collected with the approval of the Medical Research Ethics Committee of the University Medical Center Groningen (METc 2016/702). All procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

2.2. Measures

In this study, eight questionnaires, all validated in Dutch, were employed to evaluate HACS-related factors, including pain, physical functioning, psychological aspects, and HACS.

Pain was measured by Visual Analogue Scale (VAS), with values ranging from 0 to 100 mm. Values below 44 mm represent mild pain, 45–74 mm indicate moderate pain, and above 75 mm signify severe pain [30].

Functioning was evaluated using the Pain Disability Index (PDI) [31], the physical functioning subscale of the Rand36 questionnaire (Rand36-PF) [32], and the Work Ability Score (WAS) [33]. Higher PDI values (0–70) reflect greater pain interference with daily activities, while higher Rand36-PF values (0–100) indicate lower disability. WAS assessed self-reported workability, with higher values representing better workability.

Psychological Aspects were measured using the Pain Catastrophizing Scale (PCS, 0–52) [34], the Injustice Experience Questionnaire (IEQ, 0–48) [35], and the Brief Symptom Inventory (BSI global severity index t-score). PCS and IEQ values over 30 are clinically relevant, and higher BSI values denote more severe psychological symptoms.

HACS was evaluated by the CSI part A. CSI values can range from 0 to 100, with higher values assuming a higher level of CS [36]. Only section A was utilized in this study.

The data processing pipeline is depicted in Fig. 1. Initially,

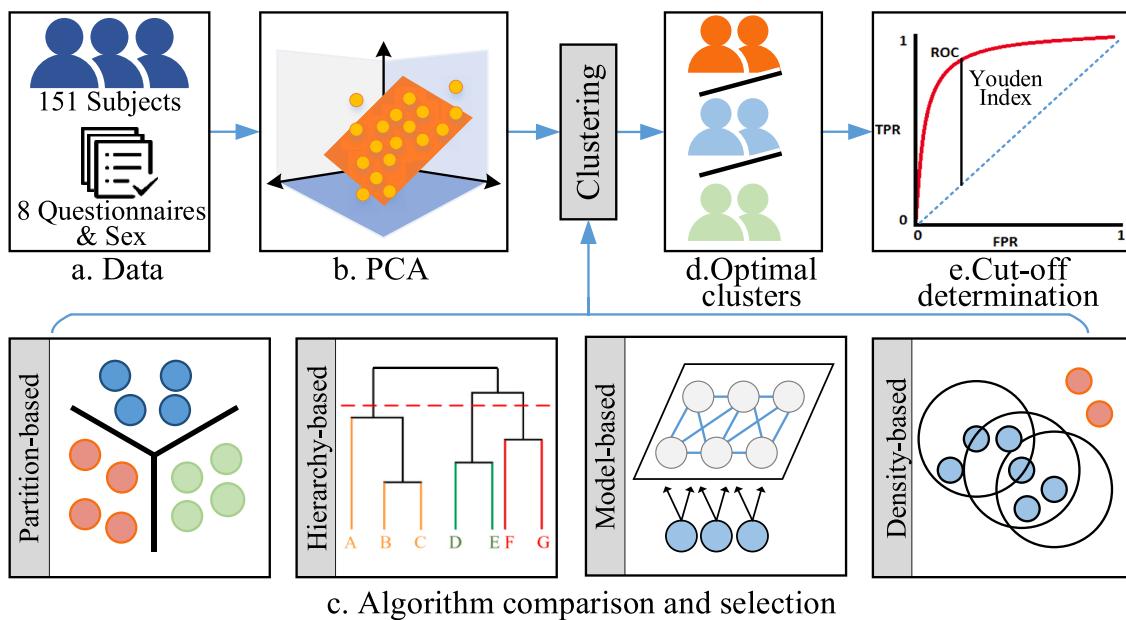


Fig. 1. The data processing and analysis pipeline: (a) data collection; (b) PCA; (c) Clustering algorithms comparison and selection; (d) Optimal clusters; (e) Cut-off determination.

questionnaire data and gender information were got from 151 subjects (Fig. 1a). Subsequently, the data were standardized using the Z-score approach, and Principal Component Analysis (PCA) was employed to reduce dimensionality (Fig. 1b). The first four components, accounting for 80 % of the variance, were utilized. At the end, the features in each data sample which represents each subject were reduced from 9 to 4. Four kinds of clustering approaches were applied (Fig. 1c) to identify potential HACS-related groups. The optimal clusters were determined based on the most effective clustering results (Fig. 1d). Lastly, ROC analysis was conducted on these clusters to ascertain the best cut-off values for CSI (Fig. 1e).

2.3. Clustering approach

After the pre-processing, to find the most suitable clustering approach for this study, 4 kinds of clustering approaches were included: K-means (partition based), Hierarchical clustering (hierarchy based), Self-organizing map (model-based), and Density-based spatial clustering of applications with noise (DBSCAN) (Density-based), see Fig. 1 c. The details of each clustering approach can be found in Appendix A.

2.4. Clustering performance evaluation

To evaluate the clustering results of the unsupervised clustering approaches, the internal and external validation measures were used. Internal validation measures, including the silhouette coefficient, Davies-Bouldin index, and Calinski-Harabasz index, evaluate cluster quality based on clustering results. For external validation, clustering results were compared with known labels (HC). External validation assists in determining clustering accuracy and ensuring the meaningfulness of clustering outcomes. The definitions of the internal validation measures are presented in Appendix B.

2.5. Statistical analyses

In this study, the Mann-Whitney U test was applied to examine the differences in demographic characteristics. Based on the optimal clusters, the receiver operating characteristic (ROC) curve analysis [37] was used to suggest an optimal CSI cut-off value (shown in Fig. 1 e.). The area under the ROC curve (AUC) represents the harmonic ratio of

sensitivity and specificity. The Youden index was calculated to evaluate the performance of the accuracy of a diagnostic test. Positive predictive values (PPV) and negative predictive values (NPV) serve as valuable indicators of diagnostic accuracy, reflecting the proportion of true positives (corresponding to high level of HACS) and true negatives (corresponding with low level of HACS) among all positive and negative findings, respectively. These metrics contribute to a comprehensive understanding of the diagnostic performance. In addition to PPV and NPV, likelihood ratios are employed as critical statistical measures to assess the diagnostic efficacy of tests. The positive likelihood ratio (PLR) is calculated by dividing the true positive rate by the false positive rate. Similarly, the negative likelihood ratio (NLR) is determined by dividing the false negative rate by the true negative rate. These ratios provide insights into the ability of diagnostic tests to discriminate between individuals with different CS levels.

As a whole, the combined utilization of AUC, Youden-index, sensitivity, specificity, predictive values, and likelihood ratios was used to determine the optimal CSI cut-off values. For clinical use, the cut-off value should have a sensitivity plus specificity of at least 1.5, which is halfway between 1 (useless) and 2 (perfect) [38].

To ensure transparency and reproducibility of the findings, we have made the project repository publicly accessible at https://github.com/xzheng93/CSI_cutoff_establishment.

3. Results

3.1. Demography

In this study, 296 subjects were included, while 139 subjects were excluded due to the incomplete questionnaires data, 6 subjects in HC group were excluded since they reported moderate pain. Therefore, 151 subjects (63 HC and 88 CLBP) were included in the data analysis. Table 1 shows the characteristics. The HC and CLBP groups are age-matched and were significantly different in BMI, but not in height and weight. The HC group reported less pain, better physical functioning, better psychological status, and lower CSI values. In terms of gender, females and males have matched BMI. Females are younger and smaller, and reported more pain, more disability, worse psychological status (e.g., depression, anxiety, distress, and pain catastrophising), and higher CSI values compared to male.

Table 1
Demography of participants.

	HC (n = 63)	CLBP (n = 88)	p-value	F(n = 74)	M(n = 77)	p-value
Gender	23F/40M	51F/37M	–	–	–	–
Age, years	40.9 ± 13.5	41.4 ± 12.3	= 0.988	37.5 ± 13.7	44.7 ± 10.7	<0.001
Height, cm	160.5 ± 56.7	175.2 ± 10.1	= 0.085	158.6 ± 42.7	179.1 ± 29.9	<0.001
Weight, kg	83.6 ± 17.0	86.6 ± 16.9	= 0.131	79.1 ± 16.3	91.3 ± 15.4	<0.001
BMI, kg/m ²	25.8 ± 3.9	28.3 ± 5.6	= 0.003	27.5 ± 6.2	27.0 ± 3.8	= 0.64
VAS (0–10)	0.5 ± 0.7	4.2 ± 2.3	<0.001	3.3 ± 2.8	2.1 ± 2.3	0.008
PDI (0–70)	5.1 ± 7.4	29.8 ± 14.4	<0.001	22.8 ± 16.1	16.3 ± 17.4	= 0.009
WAS (0–10)	8.5 ± 1.3	4.9 ± 2.4	<0.001	5.9 ± 2.9	6.8 ± 2.3	= 0.088
Rand36-PF (0–100)	28.4 ± 2.4	56.2 ± 21.4	<0.001	45.3 ± 20.4	44.0 ± 22.3	= 0.39
PCS (0–52)	4.3 ± 4.8	15.5 ± 10.5	<0.001	13.6 ± 9.8	8.2 ± 9.9	<0.001
IEQ (0–48)	3.4 ± 5.5	14.1 ± 8.2	<0.001	12.5 ± 9.1	7.0 ± 7.8	<0.001
BSI (t-score)	32.5 ± 5.3	36.6 ± 9.4	<0.001	36.4 ± 8.4	33.5 ± 7.7	= 0.004
CSI (0–100)	22.1 ± 9.7	38.1 ± 12.5	<0.001	34.5 ± 12.6	28.5 ± 14.4	= 0.004

HC: Healthy Controls; CLBP: Chronic Low Back Pain; F: Female; M: Male; VAS: Visual Analogue Scale. BMI: Body mass index. PDI: Pain Disability Index. WAS: Work Ability Score. Rand36-PF: Rand 36-Physical Functioning subscale. PCS: Pain Catastrophizing Scale. IEQ: Injustice Experience Questionnaire. BSI: Brief Symptom Inventory, CSI: Central Sensitization Inventory.

3.2. Clustering results

After conducting 4 clustering approaches, their performance was compared and summarized in Table 2. With respect to internal indicators, hierarchical clustering, K-Means, and SOM demonstrated similar optimal values for Silhouette, Calinski-Harabasz, and Davies-Bouldin. In terms of external indicators, DBSCAN clustered all the HC subjects (n = 63) in the same cluster, but incorrectly classified 6 CLBP subjects within this cluster. Hierarchical clustering yielded a balanced outcome, clustering 62 HC subjects in the same cluster while misclassifying 3 CLBP subjects in the same cluster. Thus, hierarchical clustering may be considered the most suitable trade-off approach. Therefore, the results obtained from hierarchical clustering will be further analyzed to determine the optimal cut-off values of CSI.

Fig. 2 graphically demonstrates the clustering results of hierarchical clustering. The various colored blocks along the x-axis represent individuals from different groups, with red indicating HC and blue indicating CLBP. The y-axis represents distances, and therefore, the vertical lines depict the distances between distinct subjects or clusters. This figure clearly shows a distinct separation between HC and CLBP. Within

the CLBP cluster, two primary subgroups can be distinguished, represented by the colors grey and green. If the grey and green clusters are treated as one cluster, the distance between it and the orange cluster is 100.7. If the grey and green clusters are treated as two separate clusters, the smallest distance between them and the orange cluster is 123.2. Consequently, this dendrogram suggests the presence of three main clusters.

The CSI values for the three clusters identified by hierarchical clustering are depicted in Fig. 3 using a box plot. In this figure, red dots correspond to subjects from the HC group, while blue dots denote subjects from the CLBP group. Females are represented by round dots, while males are indicated by star dots. The box plot figures for other clustering approaches can be found in Appendix Figure C1, C2, and C3.

Fig. 3 evidently shows that cluster A predominantly comprises most of the red dots (HC, N = 62 out of 63) and a small number of blue dots (CLBP, N = 3), indicating that cluster A may represent the healthy group. To understand the meaning of cluster B and C, the demographic characteristics of the hierarchical clustering results are displayed in Table 3. In comparison to cluster B, cluster C exhibited significantly higher levels of pain (VAS) and disability (PDI), lower work ability (WAS) and physical functioning (Rand36-PF), higher pain catastrophizing (PCS), injustice (IEQ), distress (BSI), and CSI values. Consequently, cluster C is characterized as patients with high HACS level, while cluster B represents patients with low HACS level. Hence, cluster A, B, and C represent the healthy, patients with low HACS levels, and patients with high CS levels groups.

3.3. Cut-off value establishment

To establish the cut-off value for CSI to distinguish low and high levels of HACS, cluster A and B were combined to represent the low HACS levels population and cluster C was used to represent high HACS levels population. The demographic comparison of the overall low HACS and high HACS groups is presented in Table 4. Furthermore, to establish the cut-off values for females and males respectively, the females and males in the low HACS and high HACS groups were extracted for analysis, and the corresponding demographics are provided in Appendix Tables D1 and D2.

Based on the low and high levels HACS groups of overall, females, and males, ROC analysis was performed respectively, and the cut-off values for CSI, along with corresponding AUC, Youden Index, sensitivity, specificity, predictive values and likelihood ratio are presented in Table 5. In the table, the darker red colour represents better performance. By taken all the metrics into consideration, especially AUC and YI, the optimal cut-off value for the overall group is 35. Although cut-off values 34 and 35 for overall yielded the same AUC (=0.76) and YI (=0.52), but the cut-off value of 35 showed a more balance sensitivity and specificity. Therefore, the optimal cut-off value for the overall group is 35, with a AUC of 0.76, Youden Index of 0.52, sensitivity of 0.76, specificity of 0.76, PPV of 0.52, NPV of 0.91, PLR of 3.19, and NLR of 0.31. For females, the cut-off value is 34 (AUC = 0.71, Youden index = 0.41, sensitivity = 0.72, specificity = 0.69, PPV = 0.55, NPV = 0.83, PLR = 2.35, and NLR = 0.4), while for males, the cut-off is 34 (AUC = 0.87, Youden index = 0.74, sensitivity = 0.92, specificity = 0.81, PPV = 0.5, NPV = 0.98, PLR = 4.92, and NLR = 0.09).

4. Discussion

The aim of the present study was to explore HACS-related subgroups via unsupervised clustering approaches based on questionnaires data and establish CSI cut-off values for Dutch-speaking population with CLBP. The clustering results showed three distinct clusters: healthy group, patients with low HACS levels, and patients with high HACS levels. These clusters exhibited variations in pain intensity, disability levels, and psychological status. By comparing the low HACS level individuals (including healthy group), ROC analysis indicated the optimal

Table 2
Clustering performance evaluation.

Indicators	Approaches	Hierarchical Clustering	K-Means	DBSCAN	SOM
Internal	Silhouette	0.47	0.48	0.34	0.47
	Calinski-Harabasz	145.66	154.44	62.46	153.44
	Davies-Bouldin	0.91	0.89	3.89	0.90
External	True HC/ Predicted HC	62/65	60/65	63/69	60/63

DBSCAN: Density-based Spatial Clustering of Applications with Noise; SOM: Self-Organizing Map; HC: healthy controls.

Table 3

Demography of different clustering groups.

	Cluster A	Cluster B	p-value of A & B	Cluster C	p-value of A & C	p-value of B & C
Gender	25F/40 M	24F/24 M	–	25F/13 M	–	–
Age, years	41.2 ± 13.6	39.4 ± 11.8	= 0.436	43.2 ± 12.3	= 0.77	= 0.155
Height, cm	160.7 ± 55.8	175.5 ± 8.9	= 0.232	175.4 ± 11.6	= 0.278	= 0.807
Weight, kg	84.5 ± 17.9	82.3 ± 13.1	= 0.9	90.5 ± 18.6	= 0.038	= 0.028
BMI, kg/m ²	26.3 ± 4.8	26.8 ± 4.1	= 0.216	29.5 ± 6.0	= 0.002	= 0.023
VAS (0–10)	0.5 ± 0.9	3.3 ± 1.9	<0.001	5.4 ± 2.4	<0.001	<0.001
PDI (0–70)	5.3 ± 7.2	22.9 ± 13.2	<0.001	39.3 ± 10.1	<0.001	<0.001
WAS (0–10)	8.4 ± 1.4	6.0 ± 2.0	<0.001	3.4 ± 2.0	<0.001	<0.001
Rand36-PF (0–100)	28.7 ± 2.6	71.1 ± 14.4	<0.001	38.4 ± 13.7	<0.001	<0.001
PCS (0–52)	4.5 ± 4.8	11.0 ± 8.1	<0.001	21.5 ± 10.6	<0.001	<0.001
IEQ (0–48)	3.5 ± 5.4	11.1 ± 6.4	<0.001	18.3 ± 8.5	<0.001	<0.001
BSI (t-score)	32.4 ± 5.2	33.9 ± 9.6	= 0.038	40.5 ± 8.0	<0.001	= 0.001
CSI (0–100)	22.1 ± 9.5	35.0 ± 11.5	<0.001	42.9 ± 12.2	<0.001	= 0.007

F: Female; M: Male; VAS: Visual Analogue Scale. BMI: Body mass index. PDI: Pain Disability Index. WAS: Work Ability Score. Rand36-PF: Rand 36-Physical Functioning subscale. PCS: Pain Catastrophizing Scale. IEQ: Injustice Experience Questionnaire. BSI: Brief Symptom Inventory, CSI: Central Sensitization Inventory.

Table 4

Demography of low and high HACS samples.

	Low HACS	High HACS	p-value
Gender	49F/64 M	25F/13 M	–
Age, years	40.5 ± 12.9	43.2 ± 12.3	= 0.357
Height, cm	167.0 ± 43.3	175.4 ± 11.6	= 0.422
Weight, kg	83.6 ± 16.1	90.5 ± 18.6	= 0.017
BMI, kg/m ²	26.5 ± 4.5	29.5 ± 6.0	= 0.002
VAS (0–10)	1.7 ± 2.0	5.4 ± 2.4	<0.001
PDI (0–70)	12.8 ± 13.4	39.3 ± 10.1	<0.001
WAS (0–10)	7.4 ± 2.0	3.4 ± 2.0	<0.001
Rand36-PF (0–100)	46.7 ± 23.1	38.4 ± 13.7	= 0.301
PCS (0–52)	7.3 ± 7.2	21.5 ± 10.6	<0.001
IEQ (0–48)	6.8 ± 6.9	18.3 ± 8.5	<0.001
BSI (t-score)	33.0 ± 7.4	40.5 ± 8.0	<0.001
CSI (0–100)	27.6 ± 12.2	42.9 ± 12.2	<0.001

HACS: Human assumed central sensitization; F: Female; M: Male; VAS: Visual Analogue Scale. BMI: Body mass index. PDI: Pain Disability Index. WAS: Work Ability Score. Rand36-PF: Rand 36-Physical Functioning subscale. PCS: Pain Catastrophizing Scale. IEQ: Injustice Experience Questionnaire. BSI: Brief Symptom Inventory, CSI: Central Sensitization Inventory.

cut-off values of 35 in the total group and for males, and 34 for females.

To evaluate the performance of the clustering algorithms, both external and internal metrics were utilized in the present study. The clustering outcomes demonstrated that, across all methods, the majority of HC subjects were grouped into the same cluster. It may suggest that the proposed clustering approaches were accurate to a certain degree. Internal metrics evaluate the separation and cohesion of clusters; and, the values of these indicators may not support that the result clusters were well-separated. This might be attributed to the inherent nature of HACS, which is not strictly binary in its essence. Rather, HACS likely exists along a continuum, spanning from absent to more pronounced degrees [39]. The demographics of the clustering results reveal that cluster C (high HACS level group) exhibited the most severe pain, greatest disability, and poorest psychological status (e.g., depression, anxiety, distress, and pain catastrophising). In contrast, cluster B (patients with CLBP and low HACS level) occupies the middle of the spectrum, while cluster A (healthy group) is situated at the opposite end.

The cut-off value for CSI in our study for Dutch-speaking patients with CLBP is established at 35, with an AUC of 0.76, Youden Index of 0.52, sensitivity of 0.76, and specificity of 0.76. Three other studies have established CSI cut-off values for Dutch-speaking patients with chronic pain [20,40,41]. Initially, the CSI was translated into Dutch, and the Dutch version demonstrated sufficient test-retest reliability (ICC = 0.88) internal consistency (Cronbach's alpha = 0.91), and appropriate structural validity [41]. This study recommended employing a cut-off value of 40 for identifying patients (not solely CLBP) at risk of exhibiting signs of HACS based on earlier research [14]. The determination of this cut-off

value of 40 was based solely on patients with chronic pain and CSS, as well as HCs, while patients without CSS were excluded [14]. It yielded a sensitivity of 0.81 and specificity of 0.75. A recent study established the cut-off values 30 for Dutch-speaking patients with chronic pain and at least one CSS, compared to HCs, reporting high sensitivity (0.85) and specificity (0.92) [20]. However, because patients with chronic pain and without CSS were excluded, the sensitivity and specificity scores of the cut-off values may not accurately reflect the discriminative ability between patients with or without CSS. A follow-up study [42] employed the cut-off value of 40 to distinguish between patients with chronic pain with or without CSS, showing similar sensitivity (0.83), but a notably decreased specificity of 0.55. As demonstrated in our study, there are distinct differences in pain intensity, disability levels, and psychological status between HCs and patients with chronic pain and high levels of HACS, whereas patients with chronic pain and low levels of HACS fall in the middle. In our study we conducted a sensitivity analysis by comparing cluster C (comprising patients with high HACS levels) exclusively with the HC group, as elaborated in Appendix E. Remarkably, the optimal cut-off values remained consistent, and, simultaneously, all metrics exhibited substantial improvements (AUC = 0.83, Youden Index = 0.65, sensitivity = 0.76, and specificity = 0.89). These results may suggest the need to include patients with low levels of HACS when determining and evaluating the cut-off values. Another research, which established cut-off values for Dutch-speaking patients with chronic pain, identified four clinically relevant categories: low (0–26), mild (27–39), moderate (40–52), and high (53+) [40]. However, this study only utilized the CSI value distribution of patients with chronic pain while excluding HCs. The distribution may change and vary based on the assessed population. Apart from this, this approach may lead to suboptimal cut-off values since it does not allow for discrimination between patients with HACS, as well as HCs. Therefore, in our study, the optimal cut-off values of CSI were determined based on high HACS levels and low HACS levels (with HC) groups.

Because no gold standard exists for assessing HACS, previous studies have employed various methods to indirectly determine the presence of HACS. Some studies assume that the presence of HACS can be indicated by one or several CSS [14,17,20]. The presence of CSS was assessed by a physician based on symptom complaints or thorough physical examination (e.g., tender-point evaluations fibromyalgia) [43] or self-reported questions (such as section B of the CSI which asks participants if they have been diagnosed with CSS) [14,20]. However, due to the lack of a gold standard, expert judgment may vary across clinicians, potentially introducing bias into the cut-off value [14]. Apart from this, HACS can exist even when a CSS is absent [8]. Some studies use quantitative sensory testing (QST) to evaluate the dynamic modulation of nociceptive signals [44] as an indicator for the presence of HACS based on pressure pain threshold, temporal summation, conditioned pain modulation, and thermal QST [16,45,46]. However, QST is

Table 5
CSI cut-off values.

CF	Overall						Females						Males											
	AUC	YI	Sen.	Spe.	PPV	NPV	PLR	NLR	AUC	YI	Sen.	Spe.	PPV	NPV	PLR	NLR	AUC	YI	Sen.	Spe.	PPV	NPV	PLR	NLR
20	0.63	0.27	1	0.27	0.31	1	1.36	0	0.58	0.16	1	0.16	0.38	1	1.2	0	0.67	0.34	1	0.34	0.24	1	1.52	0
21	0.65	0.29	1	0.29	0.32	1	1.41	0	0.59	0.18	1	0.18	0.38	1	1.22	0	0.69	0.38	1	0.38	0.25	1	1.6	0
22	0.64	0.28	0.97	0.31	0.32	0.97	1.41	0.08	0.58	0.16	0.96	0.2	0.38	0.91	1.21	0.2	0.7	0.39	1	0.39	0.25	1	1.64	0
23	0.66	0.32	0.97	0.35	0.33	0.98	1.49	0.08	0.6	0.2	0.96	0.24	0.39	0.92	1.27	0.16	0.71	0.42	1	0.42	0.26	1	1.73	0
24	0.67	0.35	0.97	0.37	0.34	0.98	1.55	0.07	0.6	0.2	0.96	0.24	0.39	0.92	1.27	0.16	0.73	0.47	1	0.47	0.28	1	1.88	0
25	0.69	0.39	0.97	0.42	0.36	0.98	1.67	0.06	0.61	0.23	0.96	0.27	0.4	0.93	1.31	0.15	0.77	0.53	1	0.53	0.3	1	2.13	0
26	0.71	0.42	0.97	0.44	0.37	0.98	1.75	0.06	0.61	0.23	0.96	0.27	0.4	0.93	1.31	0.15	0.79	0.58	1	0.58	0.32	1	2.37	0
27	0.7	0.41	0.92	0.49	0.38	0.95	1.79	0.16	0.59	0.19	0.88	0.31	0.39	0.83	1.27	0.39	0.81	0.62	1	0.62	0.35	1	2.67	0
28	0.71	0.42	0.89	0.52	0.39	0.94	1.87	0.2	0.63	0.27	0.88	0.39	0.42	0.86	1.44	0.31	0.77	0.55	0.92	0.62	0.33	0.98	2.46	0.12
29	0.71	0.43	0.87	0.56	0.4	0.93	1.96	0.24	0.63	0.27	0.84	0.43	0.43	0.84	1.47	0.37	0.79	0.58	0.92	0.66	0.35	0.98	2.69	0.12
30	0.72	0.43	0.87	0.57	0.4	0.93	2	0.23	0.63	0.27	0.84	0.43	0.43	0.84	1.47	0.37	0.8	0.59	0.92	0.67	0.36	0.98	2.81	0.11
31	0.71	0.43	0.82	0.61	0.41	0.91	2.1	0.3	0.61	0.23	0.76	0.47	0.42	0.79	1.43	0.51	0.82	0.64	0.92	0.72	0.4	0.98	3.28	0.11
32	0.73	0.46	0.82	0.65	0.44	0.91	2.3	0.29	0.64	0.27	0.76	0.51	0.44	0.81	1.55	0.47	0.84	0.67	0.92	0.75	0.43	0.98	3.69	0.1
33	0.74	0.49	0.79	0.7	0.47	0.91	2.62	0.3	0.68	0.35	0.72	0.63	0.5	0.82	1.96	0.44	0.84	0.67	0.92	0.75	0.43	0.98	3.69	0.1
34	0.76	0.52	0.79	0.73	0.5	0.91	2.97	0.29	0.71	0.41	0.72	0.69	0.55	0.83	2.35	0.4	0.84	0.69	0.92	0.77	0.44	0.98	3.94	0.1
35	0.76	0.52	0.76	0.76	0.52	0.91	3.19	0.31	0.69	0.37	0.68	0.69	0.53	0.81	2.22	0.46	0.87	0.74	0.92	0.81	0.5	0.98	4.92	0.09
36	0.74	0.47	0.71	0.76	0.5	0.89	2.97	0.38	0.67	0.33	0.64	0.69	0.52	0.79	2.09	0.52	0.83	0.66	0.85	0.81	0.48	0.96	4.51	0.19
37	0.7	0.39	0.61	0.79	0.49	0.86	2.85	0.5	0.65	0.29	0.56	0.73	0.52	0.77	2.11	0.6	0.76	0.52	0.69	0.83	0.45	0.93	4.03	0.37
38	0.7	0.4	0.61	0.8	0.5	0.86	2.97	0.5	0.65	0.29	0.56	0.73	0.52	0.77	2.11	0.6	0.77	0.54	0.69	0.84	0.47	0.93	4.43	0.36
39	0.71	0.41	0.61	0.81	0.51	0.86	3.11	0.49	0.65	0.29	0.56	0.73	0.52	0.77	2.11	0.6	0.78	0.55	0.69	0.86	0.5	0.93	4.92	0.36
40	0.7	0.39	0.58	0.81	0.51	0.85	3.12	0.52	0.66	0.32	0.56	0.76	0.54	0.77	2.29	0.58	0.74	0.47	0.62	0.86	0.47	0.92	4.38	0.45
41	0.7	0.39	0.55	0.84	0.54	0.85	3.47	0.53	0.68	0.36	0.56	0.8	0.58	0.78	2.74	0.55	0.71	0.41	0.54	0.88	0.47	0.9	4.31	0.53
42	0.67	0.35	0.5	0.85	0.53	0.83	3.32	0.59	0.69	0.38	0.56	0.82	0.61	0.78	3.05	0.54	0.63	0.26	0.38	0.88	0.38	0.88	3.08	0.7
43	0.67	0.35	0.47	0.88	0.56	0.83	3.82	0.6	0.7	0.4	0.52	0.88	0.68	0.78	4.25	0.55	0.63	0.26	0.38	0.88	0.38	0.88	3.08	0.7
44	0.67	0.34	0.45	0.89	0.59	0.83	4.21	0.62	0.68	0.36	0.48	0.88	0.67	0.77	3.92	0.59	0.65	0.29	0.38	0.91	0.45	0.88	4.1	0.68
45	0.67	0.34	0.45	0.89	0.59	0.83	4.21	0.62	0.68	0.36	0.48	0.88	0.67	0.77	3.92	0.59	0.65	0.29	0.38	0.91	0.45	0.88	4.1	0.68

CF: cut-off values; AUC: area under the curve; YI: Youden index; Spe: specificity; Sen: sensitivity; PPV: positive predictive values; NPV: negative predictive values; PLR: positive likelihood ratio; NLR: negative likelihood ratio. The optimal cut-off values are underlined. The darker red colour represents better performance.

time-consuming and requires specialized equipment and trained personnel, and does not take the physical functioning and psychosocial issues into consideration while HACS is also related to these factors [47, 48]. Moreover, there is an absence of established cut-off values for QST for the assessment of HACS [2]. Our study employed data-driven clustering approaches to automatically uncover potential patterns in individuals based on pain, physical functioning, and psychological factors. Through the examination of the interrelationships among these factors, the clustering results indicated the division of the CLBP group and HC group into three primary clusters (cluster A, B and C). In addition to this, our study, through the association of CSI values and psychological states across the three clusters, may corroborate the finding that CSI is associated with psychological constructs [21]. However, since no biological measures were included in our study, it is not possible to determine if CSI is exclusively associated with psychological constructs.

Literature indicates significant differences in pain perception between genders [49–51]. Females generally exhibit a higher prevalence of clinical pain disorders and lower pain thresholds compared to males [49–51]. Accordingly, it was expected that females would demonstrate higher cut-off values for CSI, indicating higher sensitivity to nociceptive stimuli. Several studies have provided evidence in support of this hypothesis [42, 52, 53]. In our study, females reported higher levels of pain, disability, CSI values, and worse psychological status. However, this could be confounded by the higher number of females in the CLBP group. Contrary to previous research [52, 53], our study did not find higher cut-off value for females compared to males (34 vs. 35), and the sum of our sensitivity and specificity for the females group was 1.41, below 1.5 [38]. Given the unequal distribution of male and female participants in both CLBP and HC groups, the distributions of their CSI values are also uneven. Hence, the gender-related cut-off values derived from this study should be interpreted cautiously.

Artificial intelligence has been successfully applied in the healthcare domain [54–57], as evidenced by its use in tasks such as exploring

patient subgroups [23, 24, 58]. In this study, facing the relatively small dataset and general features (questionnaires and demographic data), 4 unsupervised clustering approaches were employed. These approaches effectively identify distinct subgroups within the patients with CLBP and HACS, as illustrated in Fig. 2, and provided good explainability, as demonstrated in Appendix F, Fig. 1. Furthermore, the utilization of the proposed clustering approaches offers a flexible and adaptable methodology that can accommodate diverse data types, thereby providing valuable insights into the complex and multidimensional characteristics of HACS. As knowledge of HACS continues to expand, the methodology employed in this study can be applied to identify patterns associated with HACS, incorporating increasingly precise factors that accurately capture the essence of HACS. Furthermore, these clustering approaches can be implemented within the electronic health record system. As the system expands, the scalability of the clustering approaches allows for learning from each case, leading to the generation of increasingly robust cut-off values. This contributes to the advancement of “Data Driven Health Care”.

There were several limitations to the current study. Firstly, the data for our study were obtained from a larger study with different objectives. As a result, some critical information, such as part B of the CSI and objective measurements like QST, was absent. However, once we acquired these additional pieces of information, the flexibility and adaptability of the proposed approach enabled us to redo the analysis easily, thereby identifying patterns related to HACS and determining more accurate CSI cut-off values. Secondly, cluster C exhibited patterns associated with high levels of HACS, but it is important to note that individuals in cluster C should not be directly classified as patients with HACS. Instead, the clustering results provide insights into the severity of HACS levels among participants [36]. It is worth acknowledging that utilizing CSI as an input for identifying optimal clustering results and determining the best cut-off values for CSI introduces the potential risk of circular reasoning. However, the results of the feature importance

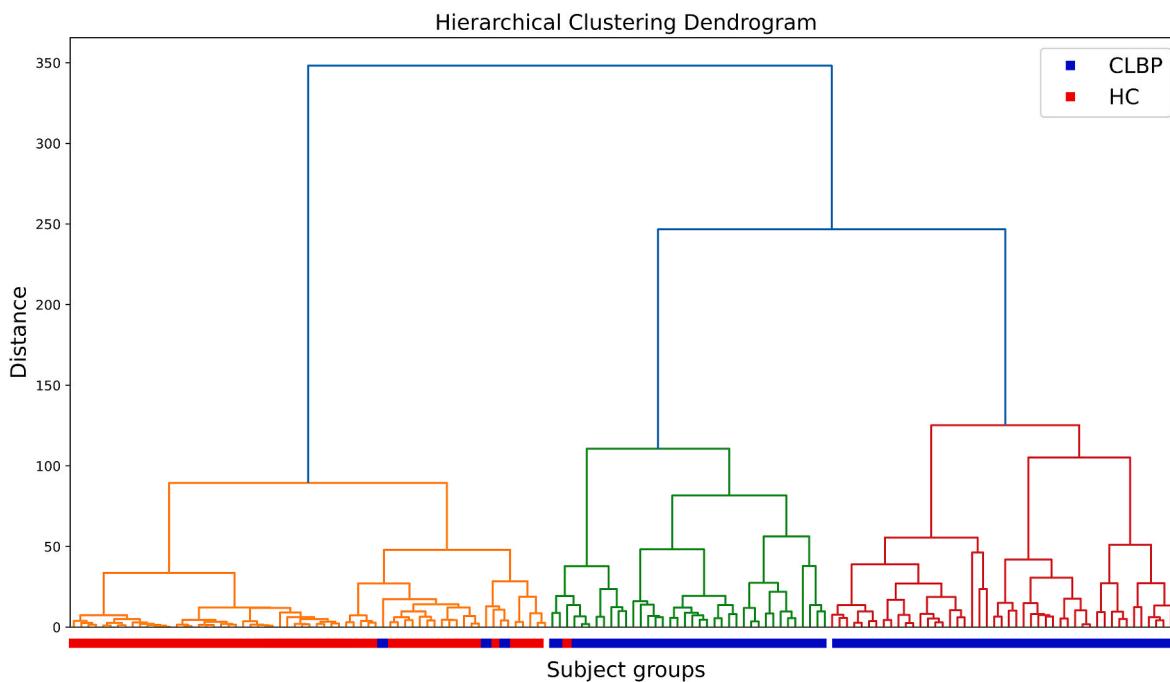


Fig. 2. Dendrogram result of hierarchical clustering: red and blue blocks mean subjects from HC and CLBP groups, trees colored in orange, grey, and green indicate the presence of three primary clusters. HC: Healthy Controls; CLBP: Chronic Low Back Pain.

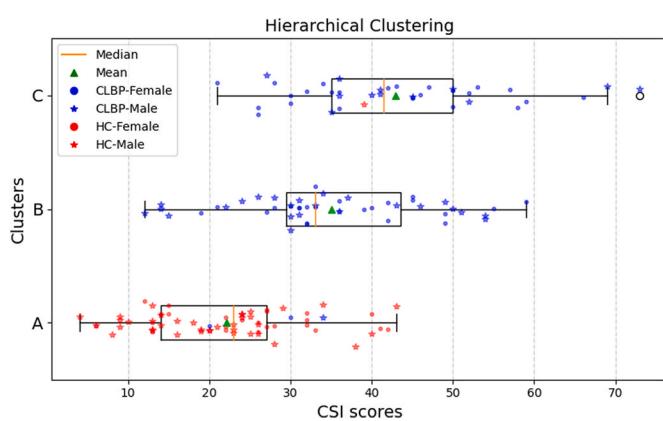


Fig. 3. CSI clustering results of Hierarchical clustering. HC: Healthy Controls; CLBP: Chronic Low Back Pain; CSI: Central Sensitization Inventory.

analysis using PCA (further details provided in Appendix F. Fig. 1) indicate that the clustering process primarily relied on information such as gender, Rand-36, and BSI, with CSI ranking 7 out of 9 variables. Consequently, the associated risk is minimal. Thirdly, the cut-off value for females may not be valid enough since the sensitivity plus specificity lower than 1.5. Apart from this, the distribution in gender was imbalanced between the CLBP and HC groups. Consequently, the proposed cut-off values for the genders separately should be interpreted with caution.

5. Conclusion

This study employed unsupervised machine learning approaches to investigate HACS-related clusters, taking into account pain intensity, disability levels, psychological status, and gender. Through these data-driven approaches, three distinct clusters emerged: the healthy group, patients with low HACS levels, and patients with high HACS levels. Demographic analysis revealed that patients with high HACS levels and the healthy group were situated at opposite ends of the spectrum, with

patients exhibiting low HACS levels positioned in the middle. Based on these clustering outcomes, a CSI cut-off value of 35 was established for the Dutch-speaking population with CLBP. CSI cut-off values of 34 and 35 were determined separately for females and males. However, these two cut-off values should be interpreted cautiously due to gender imbalances in the dataset.

The methodology employed in this study offers a data-driven means to identify subgroups, establish optimal diagnostic thresholds, and enriches the comprehension of this intricate HACS. Ultimately, this methodology empowers researchers and clinicians to craft more personalized and effective approaches for assessing and managing conditions associated with HACS and other diseases.

CRediT authorship contribution statement

Xiaoping Zheng: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Conceptualization. **Claudine JC. Lamoth:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Hans Timmerman:** Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization. **Egbert Otten:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Michiel F. Reneman:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

This manuscript did not use generative AI.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.combiomed.2024.108739>.

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