Four Clinical Profiles of adult outpatients with Somatic Symptom Disorders and Related Disorders (SSRD). A latent class analysis.

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Running head: Clinical Profiles in Somatic Symptom Disorders and Related Disorders (SSRD).

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Number of Tables: 4

Number of Figures: 1

Word count: 3367

Keywords: Somatic Symptom Disorders and Related Disorders (SSRD), Trauma, Pain, Biomarkers, Systemic Low-grade Inflammation, personalized medicine

Abstract

Objective: To obtain more insight into the patterns of co-occurring symptoms, biomarkers and predictors in Somatic Symptom Disorders and Related Disorders (SSRD) and to identify subgroups with profiles that might allow for personalised treatment.

Methods: Cross-sectional study design with Latent class analysis (LCA) to determine different subgroups in a cohort of 239 outpatients with SSRD in 3 steps: 1) building a latent class model; 2) assigning subjects to the latent classes that suited them best based on their posterior probability; 3) investigating the associations between these classes and personal characteristics such as age, gender, somatic comorbidity and general health perception.

Results: Four classes with clinically relevant profiles were found. One with trauma plus elevated inflammation biomarkers, high somatic symptom levels, pain and comorbid depression and anxiety. One with pain plus elevated biomarkers, depression and anxiety. One with low IL-6 and hsCRP, mostly linked to Illness Anxiety. And one with high pain and high elevated biomarkers, but less probability of other factors, that occurred mostly in men. General health perception was lower in classes with elevated inflammation biomarkers.

Conclusions: The findings of this first study exploring latent classes in an SSRD sample corroborate the current DSM-5 SSD subclassification for pain and Illness Anxiety Disorder. There is scope to extend the current DSM-5 classification with a subclassification of SSD with trauma, and a subclassification with elevated IL6 or hsCRP, as relevant for developing new personalised treatments addressing trauma or SLI in SSRD. Further research is needed to explore this.

Introduction

Somatic Symptom Disorders and Related Disorders (SSRD) replaced the DSM-IV somatoform disorders [1] in the DSM-5. The main criterion for classification as in Somatic Symptom Disorder (SSD) is to have a physical symptom that causes significant distress, as expressed in emotions, cognitions, and behavior, that leads to substantial impairment in role functioning and disability. The classification can occur both in patients with such distress related to a known medical condition, and in patients without a known medical condition. Pain can be the main bodily symptom, in which the condition is classified as SSD with predominant pain. Other, related conditions in the SSRD classifications are conversion disorder/functional neurological disorder(CD/FND) and Illness Anxiety disorder [2]. Illness Anxiety disorder has as focus a preoccupation with having or getting a serious illness, however, physical symptoms may not be present, or only to a small degree; and this involves a high degree of anxiety and excessive health-related behavior. Hence, when we consider that based upon the criteria only, SSRD are a heterogeneous group of disorders.

The criteria to establish these classifications have been shifting over time as they move from DSM-IV to DSM-5 and beyond, from ICD-10 to ICD-11 [3, 4]. For example, CD/FND only applies in case of symptoms that mimic neurological symptoms but that are not compatible with a neurological condition; so, actually, this is the only condition in the SSRD classifications where lack of explanation of the physical symptom is still a criterion. However, efforts are underway to establish this diagnosis based upon positive rather than negative criteria by establishing certain signs during neurological examination [5] such as the Hoover sign [6]. Also, DSM-IV hypochondriasis evolved to illness anxiety disorder with slightly differing criteria [1]. Hence, there is a large amount of fluidity in the criteria over time that can affect research and clinical work.

Currently, pain is the main characteristic that has been taken into account in the DSM-5 classification for SSD [2]. Relevant factors in the diagnosis and treatment approach that so far have not been taken into account as criteria for classification are symptomatology that may influence the clinical picture of these patients in the context of comorbidity with chronic medical conditions, [7] or with depressive disorder or anxiety disorder [8]. Furthermore, early childhood or current traumatization, especially childhood sexual trauma [9] have been suggested as predictors. In addition, biomarkers for systemic low-grade inflammation (SLI) have been explored in SSRD, and have been found to be elevated compared to levels in the general population [7]. Another study exploring biomarkers for SLI more extensively in CD/FND, a subclassification of SSRD, found several cytokines to be elevated compared

to levels of healthy people [10]. This finding is intriguing. There may be a possible link with childhood traumatization [9]; furthermore, childhood trauma has been found to have a negative association with treatment outcome in CD/FND as well [11]. Hence, research is needed to establish if such factors would be relevant as diagnostic criteria for treatment implications, and what domains they potentially would cover.

We identified symptomatology, biomarkers for SLI and predictors as possible relevant domains for this study. What role different characteristics in such domains may play in relation to the different classifications in patients with SSRD has not been the subject of research so far, although this may be relevant for adaptation of future research classifications, but also clinically for treatment indications in SSRD.

Therefore, the aim of this study was to examine whether subgroups could be identified to obtain more insight into the patterns of co-occurring symptoms, biomarkers and predictors in a heterogeneous population of adult outpatients with SSRD. And if such subgroups would have profiles other than the already existing DSM-5 classifications, that might allow for personalised treatment.

Based on the results of prior studies, [11, 12] we expect at least one subgroup with many trauma-related predictors and one subgroup with biomarkers for SLI [7].

Methods

Clinical cross-sectional study, establishing classes related to clinical symptoms and possible predictors in SSRD, following the methodology of a profiling study [13]. The Scientific Institutional Review Board of GGz Breburg approved the study protocol.(2019-01).

Eligibility criteria

Consecutive outpatients diagnosed with SSRD at the Clinical Centre of Excellence for SSRD (CLGG), Tilburg, the Netherlands, from September 2016 until September 2018 were eligible after diagnosis at intake. Patients were excluded if they were < 18 years old, did not complete any questionnaires during intake, had IQ < 80 or had substance dependency.

Assessments

The standard intake procedure has been described elsewhere [14]. Medical examination by a physician involved assessment of somatic symptoms by medical history taking; a questionnaire measuring

somatic symptoms; physical examination; neurological examination; and venipuncture according to a biochemical, haematological and immunological lab protocol, including the measurement of hsCRP and IL-6 (ELISA). Immunological lab was taken if physical examination did not suggest an active transient infection. Details are provided elsewhere [7]. Psychiatric evaluation including exploration of sexual trauma was performed by semi-structured interview to provide SSRD DSM-5 classification and other comorbid DSM-5 classifications [2]. Psycho-diagnostic questionnaire assessment of psychological symptoms, adverse childhood experiences (ACE), adverse adult experiences (AAE), and stressful life events (LCU) were performed by questionnaires and Mini-International Neuropsychiatric Interview (MINI) [15]. Cases of discrepancy between MINI and psychiatric examination were discussed in the multidisciplinary team and resolved in the DSM-5 diagnostic classification, that was used for this study. Assessments at intake were done in a highly structured and supervised way by trained psychology assistants, supervised by psychologists, and by trained physicians, supervised by psychiatrists. Psychiatric examinations results would be discussed weekly between team psychiatrists to reach consensus on the DSM-5 classification.

Data sources

Patient files and the data-warehouse were assessed for the variables described in Table 1 in the Appendix.

- Table 1. Data sources/measurement in the Supplementary material –

Variables

We performed the analysis on a selection of these variables, that indicated dichotomously if a certain variable was present, informed by an earlier study, [7] as follows: elevated IL6 score ((≥2.056 pg/ml), elevated hsCRP score ((≥3.0 mg/l), presence of childhood trauma (ACE ≥1), adult trauma (AAE ≥1), childhood sexual abuse, adult sexual abuse, diagnosed CD/FND, Illness Anxiety, probable comorbid depressive disorder (PHQ9 ≥10), probable anxiety disorder (GAD7 ≥10), physical symptoms load (PSQ-51), clinically relevant pain (BPI ≥3). We also explored levels of the general health perception as measured by the SF36.

Analysis

Latent class analysis (LCA) was used to determine different subgroups of SSRD patients based on the variables mentioned above, except general health perception. For the analyses, Latent GOLD 6.0 was used [16, 17]. We used a three step approach.

The first step consists of establishing the number of classes. Several indices of model fit were used to determine the number of latent classes, namely the Bayesian information criterion (BIC), the Aikake information criterion (AIC), and the Aikake information criterion 3 (AIC3), which weight the fit and parsimony of the model. Furthermore, a bootstrap likelihood ratio test (BLRT; [18,17] was used to compare the different models. Lastly, the class sizes (i.e., smallest class needs to contain more than 5% of the sample) [19] and the clinical interpretation of the different classes were taken into account when determining the number of classes.

In the second step, subjects are assigned to the latent classes that suited them best based on their posterior probability.

Third, to characterize the different classes, we investigated the associations between these classes and personal characteristics such as age, gender, somatic comorbidity and general health perception.

Results

Table 2 shows the descriptives of the variables in the sample.

- Insert Table 2 Sample characteristics -

Table 3 shows the model fit indices for models with one to eight classes. The different fit indices suggested different models. The BIC was lowest for the 2-class model, the AIC was lowest for the 7-class model, and AIC3, which is a preferred criterion when sample sizes are small [20], was lowest for the 3-class model and 4-class model. The p values of the BLRT were significant up to and including the 5-class model, indicating that a 5-class model was preferred.

- Insert Table 3 Model fit -

From a statistical viewpoint, 2 - 5 class models were all acceptable solutions. Inspection of the classes of the different models showed that the classes of the 4-class model had the best clinical interpretation and class sizes of more than 10%. Therefore, the 4-class solution was chosen.

Class description

The probability of heightened scores on the different variables (left axis) and the average physical symptom load (right axis) for the different classes is shown in Figure 1.

- Insert Figure 1: Profiles based on the 4-class solution -

The 4 classes are labeled as follows:

1) Class 1 (trauma) (42.6% of the sample) represents patients with a high probability of having childhood and adult trauma and heightened scores on depression, anxiety, and pain.
2) Patients in class 2 (complex pain) (22.9%) had high probability of high scores on pain, but also heightened scores on depression, anxiety, but they do not have a very high probability of having experienced a trauma; they had the lowest probabilities of having childhood and adult trauma and low probabilities of childhood and adult sexual trauma.
3) The classes as a whole do not significantly differ on IL6 and hsCRP, however, pairwise comparisons show differences between IL6 and hsCRP between class 3 and the other classes (p values range between .018 and .023), that all have elevated IL-6 and hsCRP scores. Patients in class 3 (Low SLI) (20.0%) have almost never an elevated IL6 or hsCRP score, and have relatively low probabilities of having heightened scores on depression, anxiety, and pain. They have the lowest probabilities of having sexual trauma, and intermediate probabilities of having depression and pain.
4) Lastly, class 4 (14.5%) represents patients with a high probability of heightened pain, but no higher probability of heightened scores on the other variables (simple pain).

Table 4 shows the proportions of people with the clinical characteristics per class.

- Insert Table 4 Proportions of people with the characteristic per class (N=239) -

Table 4 shows significant differences between the classes on trauma as a child, recent trauma, sexual trauma as a child, depression, anxiety, pain, and physical symptom load. To further describe the four classes, differences between the classes concerning the demographic

characteristics, somatic comorbidity and general health perception were studied. They are shown in Table 5.

- Insert Table 5. Proportions and means of personal characteristics per class (N=239) –

Age and whether participants had a somatic comorbidity did not differ between the classes. Gender differed significantly between the classes (Wald = 9.51, p = .023). The class with simple pain contained more males (63%) compared to the other classes (32%, 32%, and 42%, respectively). The general health perception was taken into account, not as a symptom characterizing the sample, as the other variables, but as a clinically relevant factor. The general health perception also differed between the classes (Wald = 21.68, p < .001). It was better in low SLI and simple pain; (estimated means are 17.15 and 16.83, respectively) than in trauma and complex pain; (estimated means are 20.50 and 19.51, respectively).

Discussion

Our sample as a whole has slightly more women (59%) than men and the average age is 49 years. More than half have a comorbid chronic medical condition, and over 60% have elevated hsCRP; the percentage with elevated IL6 is much lower but still more than one third. SSD with pain is the most common presentation with 85%, and two thirds suffer from comorbid depression or anxiety. Physical symptom load is high and general health perception is low. Childhood and adult trauma are reported in two-thirds of cases. Childhood sexual trauma occurs in more than 20% and adult sexual trauma in almost 10%. All in all, this is a relatively young sample with high morbidity and comorbidity, that carries a burden of childhood trauma in many cases.

We examined whether subgroups of SSRD can be identified among 239 outpatients, and what profiles they have that might allow for personalization of treatment. We expected at least one subgroup with many trauma-related predictors and one subgroup with biomarkers for SLI [7]. Indeed we found one class with high trauma levels. Of the four classes, this class is the largest

in the sample (42.6%), and represents patients with a high probability of having childhood and adult trauma, and heightened scores on depression, anxiety, and pain.

Regarding biomarkers for inflammation, we found that the absence of such elevated biomarkers (IL-6 and hsCRP) was related to one particular class, low SLI, (20.0%). Patients in this class have low probabilities of sexual trauma, depression, anxiety and a low physical symptom load. Furthermore, this class contained the lowest proportion of patients with pain, although still 61% have pain. Although this class has the highest, albeit still rather low, proportion of Illness Anxiety Disorders compared to the others, this is not a significant difference with the other classes. This is the only profile with low inflammation markers. The other classes have moderate to high proportions of elevated IL6 and hsCRP.

The classes complex pain (22.9%), simple pain (14.5%), and trauma have very high proportions of elevated pain (> .88), but the two pain classes have lower proportions of trauma. Furthermore, the complex pain class contains a higher proportion of people with depression and anxiety, and a higher physical symptom load, but a lower proportion of childhood sexual trauma, compared to the simple pain class. The simple pain class has the highest proportion of elevated IL-6 and hsCRP.

So, four classes with clinically relevant profiles were found. The class trauma with the highest proportion of trauma, combined with a high proportion of high somatic symptom levels, pain and comorbid depression and anxiety. Complex pain with pain, combined with depression and anxiety. Low SLI with low IL-6 and hsCRP, combined with less depression, anxiety, pain, and somatic symptom levels. And simple pain with high pain, but less probability of other factors, except childhood sexual trauma. All classes except low SLI have elevated IL6 and hsCRP and those all have a higher proportion of pain.

Regarding gender, simple pain, with highest pain scores and highest biomarker scores, contained significantly more males compared to the other classes. Although pain occurred in several classes, the link with biomarkers associated with systemic low-grade inflammation was most outspoken in males. General health perception was lowest in this class and in the class trauma that has high SLI, which might suggest that high inflammation markers are associated with lower general health perception.

The findings in this study are different from a latent class analysis that was performed in a general population sample in Denmark that did not focus on predictors or markers, but rather focused on the kind of symptoms experienced by people in the community. They found eight classes with pain, fatigue, gastrointestinal symptoms and general symptoms in varying levels of severity and complexity; the classes in their study showed overlap [21, 22]. Compared to that study, this study differs as it is a clinical SSRD sample that explores characteristics that may be relevant for diagnostic profiling and provide guidance for treatment. As this is the first study attempting such subtyping of SSRD, this is an innovative approach and we present novel findings with implications for future research, clinical practice and guidelines.

Strengths and limitations of the study

This is the first study exploring latent classes in an SSRD sample that may be relevant for diagnostic profiling and personalization of treatment. The sample size is large and the latent class analysis is a sophisticated approach. This is a new, exciting research development. Another strength of the study is the systematic data collection by trained assistants who were supervised regularly.

A limitation is that the sample existed of outpatients visiting the Clinical Centre of Excellence for Body Mind and Health, which is one of a limited number of Clinical Centers providing diagnosis and treatment to the top 5% complex cases of SSRD in the Netherlands [14]. Hence the findings in this study may not be generalizable to the general population but apply to complex cases of SSRD in specialised mental health settings in the Netherlands. Another limitation is that the statistically generated categories allowed for several classes and hence the number of classes was also informed by clinical considerations.

Implications of the findings

Replication studies will be needed to confirm the latent classes identified in this sample in other settings. Longitudinal studies are needed to explore if the identified classes differ in terms of treatment outcome if unpersonalised treatment is offered. Also, research should explore if personalization of treatment according to the classes identified in this study would have better outcomes than a one size fits all approach with an emphasis on CBT, that is currently recommended in several medical guidelines for SSRD.

If these classes would be used for clinical profiling to personalize treatment, [13] whilst taking existing evidence into account, most evidence exists regarding pain. Given the importance of illness perceptions in the course of chronic pain [23], research concerning simple pain, with highest pain scores and highest biomarker scores, could explore the effect of Cognitive Behavioural Treatment (CBT) to address illness perceptions [23], combined with advice regarding the use of anti inflammatory drugs such as paracetamol and NSAIDs to support optimal functioning [24], in patients with this profile. Treatments for patients with the complex pain profile could have a focus on combined treatment for depression and pain, with Problem Solving Treatment (PST), antidepressants and painkillers according to an algorithm avoiding opiates that are currenly commonly suggested in the WHO pain ladder, which has been shown to have potential [24, 25].

Treatment of patients with the profile of low IL6 or hsCRP with illness anxiety and generally low comorbidity would focus on treatment of illness anxiety with CBT, as has been common practice in hypochondriasis. Furthermore, research evaluating the effect of anti- inflammatory drugs such as cytokine blockers in patients with pain and high IL6 or hsCRP may be warranted, given the high proportion of elevated IL6 and hsCRP in patients with the pain profile identified in this study.

Patients with a profile as in the class trauma would need treatment approaches not only for their distress related to their physical symptoms, but also for having to deal with complex comorbidity and high childhood and adult levels of trauma. The introduction of a trauma related subclassification in DSM-5 SSRD and exploring personalised treatment options for this category in future research seems warranted, even more so as somatoform dissociation seems to play a role in complex PTSD in the new ICD-11, and a recent study suggests that somatoform and psychoform manifestations of dissociation should be routinely assessed in patients with ICD-11 C-PTSD because such expressions may cover intense affects and painful relationship experiences [26]. Although trauma focused treatments certainly do exist in psychiatry, [27] and are often combined with antidepressants in case of comorbid depression, they mostly do not pay sufficient attention to pain, other physical symptoms and anti-inflammatory treatment. Given the findings in this study, research is warranted to explore this.

A requirement for diagnostic profiling, given the findings of this study, would be the introduction of routine hsCRP and IL-6 assessments at intake. A recent study showed the possible diagnostic cut-off points for IL-6 and hsCRP in SSRD [7] and CD/FND [10]. However, such assessments are currently not yet common practice in all mental health settings where SSRD patients present themselves.

Implications for future revisions of the DSM-5

The current SSRD classification has many advantages, as it has an overarching focus on distress in relation to physical symptoms, and allows for addressing such distress both in the context of known chronic medical conditions, and in case of lack thereof. The current classification has a subclassification in SSD for pain, which is supported by the findings in this study given the prevalence of more than 85%, and as two classes have pain as main symptom. The classification Illness Anxiety Disorder is supported by this study as well, and has been found to have particular characteristics such as low comorbidity and low IL6 levels. However, there is scope to extend the current classification with a subclassification of SSD with trauma. In the current sample of patients visiting an outpatient specialised mental health institution for the top 5% complex cases of SSRD in the Netherlands, this was the largest class (42.6%). This raises the question whether more focus on diagnosing and treating of trauma among patients SSRD could improve their treatment perspectives. Also, there is scope to add a subclassification with elevated IL6 or hsCRP, as this may imply the need for treatment addressing SLI in SSRD. Further research is needed to explore this.

Statements

Acknowledgement

Dilana Ozgul performed data-entry for this study. SHL provided the labprotocol and arranged the lab assessments for this study. GGz Breburg supported the study in CLGG.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. No informed consent was required, as for the present research we used data that were collected for administrative purposes and monitoring of treatment

outcome by treatment providers. According to Dutch law on Medical Treatment Agreement Article 7: 458, in accordance with the Helsinki Declaration, and according to the Dutch Central Medical Ethical Committee, no explicit informed consent is required for the use of clinical or administrative data, collected in the context of treatment provision. At intake at CLGG, patients were informed that Patient Reported Outcome Measures (PROM) and medical data obtained during intake and treatment could be used for research evaluation on an anonymous basis, unless they indicated their dissent. In case of dissent, this was notified in the patient file. Patient files of dissenting patients were excluded from the study. Data were coded in order to create an anonymous dataset. The research protocol was approved by the scientific committee of GGz Breburg (2019-01).

Disclosure Statement

The authors have no competing interests to report.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions

CFC conceived the study design, acquired financial support for the study, oversaw the data collection and training of psychology assistants, arranged for the lab protocol, initiated design of the data analysis, contributed to interpretation of data analysis, and wrote the first draft of the article. MB designed and performed the data analysis and contributed to writing of the article. JvEvdS contributed to study design, supervision of data collection and training of psychology assistants, contributed to design of data analysis, interpretation of data analysis and to writing of the article. All authors approved the final version of the article.

Data availability statement

The data are owned by a third party, GGz Breburg, that does not publicly share data. However, interested parties will be able to obtain data upon request as follows. Researchers can submit a research plan, which describes the background and methods of a proposed research question, and a request for specific data of the database used for this study to answer the research question. After approval of the research plan by the principal investigator and the

director of GGz Breburg, a deidentified minimal dataset can be obtained. Information can be requested by contacting the principal investigator.

List of abbreviations

AAE; Adverse Adult Experiences

ACE; Adverse Childhood Experiences

ACE-IQ; ACE International Questionnaire

ADHD; Attention-Deficit Hyperactivity Disorder

BPI; Brief Pain Inventory

CD/FND; conversion disorder/functional neurological disorder

CLGG; Clinical Centre of Excellence for Body, Mind and Health

CRP; C-reactive protein

DSM; Diagnostic and Statistical Manual of Mental Disorders

ECBS; Expert Committee on Biological Standardization

ELISA; Enzyme-Linked Immunosorbent Assay

GAD-7; Generalized Anxiety Disorder Questionnaire 7 items for anxiety

hsCRP; high-sensitivity C-reactive protein

ICD-10; International Classification of Diseases 10th Edition

IL-6; interleukin 6

LCU; Life Change Units: Holmes and Rahe Scale for current stressful life events

MINI; Mini-International Neuropsychiatric Interview

MUS; Medically Unexplained Symptoms

PHQ-9; Patient Health Questionnaire 9 items for depression

PSQ-51, Physical Symptom Questionnaire – 51 items

PHQ-15; Patient Health Questionnaire – 15 items for physical symptoms

PROM; Patient Reported Outcome Measures

PTSD; Post Traumatic Stress Disorder

SCID-2; Structured Clinical Interview for DSM-IV Axis 2 Disorders

SF-36; Short Form 36 items for general functioning

SLI; Systemic Low-grade Inflammation

SSD; Somatic Symptom Disorders

SSRD; Somatic Symptom Disorder and related disorders

TNF alpha; Tumour Necrosis Factor alpha

WHO; World Health Organization

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Table 1 Data sources/measurement

Factors	Classification	Based on
Diagnostic classification		
Type of SSRD	Type	Patient file: intake letter and DSM classification [2]
Psychiatric comorbidity	Yes/ No	Patient file: DSM classification
Personality disorder	Yes/ No	Patient file: DSM classification and SCID-2 [28]
Anxiety disorder	Yes/ No	Patient file: DSM classification
Depressive disorder	Yes/ No	Patient file: DSM classification
Developmental disorder	Yes/ No	Patient file: DSM classification
Comorbid CMC	Yes/ No	Patient file: DSM classification, intake report (including ICD-10 classification) [4]
Psychosocial factors		
Relationship status	Single / Living together or Married/ Living apart together/ Other	Patient file: intake or registration form Or Psychodiagnostic examination: INTERMED [29]
Family composition	Single without children/ Single with children/ With a partner without children / With a partner with children	Patient file: intake or registration form Or Psychodiagnostic examination: INTERMED
Social safety net	Good (both contact with friends and family)/ Moderate (only a single family member or a single friend)/ Bad (no friends/family)	Patient file: intake or registration form Or Psychodiagnostic examination: INTERMED
Education level	Very low (prim. school)/Low (junior high school)/ Medium (High school 2,3,4) /High (bachelor)/ Very high (MSc, PG)	Patient file: intake or registration form Or Psychodiagnostic examination: INTERMED
Work	Employed/ Sickness Law / Unemployment benefits / Social benefits/ Disability benefits / Retired	Patient file: intake or registration form Or Psychodiagnostic examination: INTERMED
Trauma		
Early childhood trauma	Yes No Score	Patient file: ACE, [30] intake and Psychiatric evaluation. The ACE International Questionnaire (ACE-IQ) is developed by the WHO. Development has been ongoing and for this study, the available version in 2015 was used. This covers mostly ACE indicating family dysfunction, physical, sexual and emotional abuse and neglect by parents or caregivers. It was translated from English to Dutch and back-translated to provide the official Dutch version. [11]
Recent trauma and recent life stress	Yes/No Score	Patient file: AAE, [11] LCU [31], intake and Psychiatric evaluation
Childhood sexual abuse	Yes/No	Patient file: ACE, intake and Psychiatric evaluation
Adult sexual abuse	Yes/No	Patient file: AAE, intake and Psychiatric evaluation
Symptoms at intake		
Physical symptoms (PSQ51, PHQ15)	Physical symptoms were measured using the PSQ-51, which is a 51-item questionnaire. The total score on the PSQ ranges from 0 to 51 and represents the number of physical symptoms that were regularly or often present in the last week. Higher scores indicated a higher symptom burden. De Waal provided normative data. [32-33] They were also measured by the PHQ15. [34] Higher scores indicated a higher symptom burden.	
Depressive symptoms (PHQ9)	Depression was assessed using the PHQ-9. The PHQ-9 is a reliable 9-item self-report questionnaire, with higher scores indicating higher levels of depressive symptoms. [35] Item scores ranged from 0 (not at all) to 3 (nearly every day), and total scores ranged from 0 to 27. Cut-off points of 5, 10, 15, and 20 represent mild, moderate, moderately severe and severe levels of depression. [36]	

Anxiety symptoms (GAD7)	Anxiety was assessed using the GAD-7. The GAD-7 is a reliable 7-item self-report questionnaire that measures symptoms of anxiety during the last 2 weeks. Higher scores indicated a higher symptom burden. GAD-7 scores range from 0 to 21, and cut-off scores of 5, 10, and 15 represent mild, moderate and severe levels of anxiety. [37]
General functioning (SF36)	The RAND SF-36 general health domain score assessed general functioning. Studies confirmed the SF-36's validity and reliability. [38] The SF-36 is a self-report questionnaire that contains 36 items, which are distributed across eight scales. Scores range from 0 to 100, where higher scores indicate better general functioning. For the analysis, they are scored in such a way that a low score indicates better functioning. It was validated in the US and in the Netherlands.[39] It is responsive to change and normative data are available. [40-41] The RAND general health perception is a summary of 5 items reflecting subjective quality of life and general functioning. This is often used as an overal summary of the quality of life as measured by the 8 domains of the SF36.
Pain (BPI)	Chronic non-malignant pain was measured by the Brief Pain Inventory (BPI). Higher scores indicate a higher symptom burden. [42]
Lab at intake	
Venepuncture	Biochemical, Haematological and immunological lab protocol including hsCRP (immunoturbidimetry) and ELISA for IL-6 Standardised lab procedures for hsCRP and for IL-6, authorised by the Expert Committee on Biological Standardization (ECBS) of the World Health Organization (WHO), are available.(Gaines Das RE, 1993; JT., 1998) In this study, plasma levels of IL-6 were measured by high sensitivity enzyme linked immunosorbent assay (ELISA; Quantikine HS ELISA R&D systems HS600B) performed by DS2, Dynex Elisa robot automated analyzers. Intra assay precision CV% was in the interval 6.9–7.8; interassay precision CV% was in the interval 6.5-9.6. The detection range of this assay was 0.02-10 pg/mL. None of the respondents had IL-6 levels below the detection limit of 0.02 pg/mL and 4 had values above the reference value of 10 pg/ml, as delineated in the outlier analysis. For hsCRP, immunoturbidimetry by automated analyzers was performed. The declared detection limit was 0.20 mg/l. Specimens were drawn from participants and frozen at -80 C until thawed for assay.

Table 2 Sample characteristics (N = 239)

	N (%)	M (SD) [range]	Total N
Female	143 (59.8%)		239
Age		42.5 (13.4) [15 – 80]	239
Comorbid chronic medical condition	142 (59.4%)		239
Elevated IL6	73 (35.8%)		204
Elevated hsCRP score	144 (62.3%)		231
Conversion Disorder	14 (5.9%)		239
Illness Anxiety Disorder	14 (5.9%)		239
Childhood Trauma	146 (62.9%)		232
Adult Trauma	140 (60.3%)		232
Childhood Sexual Trauma	53 (22.2%)		239
Adult Sexual Trauma	22 (9.5%)		232
Depressive Disorder	169 (74.8%)		226
Anxiety Disorder	146 (63.8%)		229
Pain	194 (85.5%)		227
Physical Symptom Load		16.4 (8.9) [0 – 45]	229
General Health Perception (SF36)		18.8 (3.3) [6 – 25]	234
PHQ9		14.3 (6.1) [0 – 27]	226
GAD7		11.6 (5.4) [0 – 21]	229
BPI		5.6 (2.5) [0 – 10]	227

Table 3 Model fit

Number of classes	**LL**	**BIC**	**AIC**	**AIC3**	**Npar**	**p-value BLRT**	**Entropy R^2**
1	-2098.20	4267.59	4222.39	4235.39	13		1
2	-2012.55	4172.96	4079.10	4106.10	27	<0.001	0.69
3	-1982.53	4189.60	4047.07	4088.07	41	<0.001	0.76
4	-1962.48	4226.17	4034.96	4089.96	55	0.002	0.78
5	-1943.99	4265.85	4025.98	4094.98	69	0.003	0.78
6	-1927.34	4309.22	4020.68	4103.68	83	0.198	0.79
7	-1909.70	4350.62	4013.40	4110.40	97	0.007	0.81
8	-1896.21	4400.31	4014.43	4125.43	111	0.007	0.83

LL log likelihood, BIC Bayesian information criterion, AIC Aikake information criterion, AIC3 Aikake information criterion 3, Npar numbers of para-meters, BLRT bootstrap likelihood ratio test

Table 4 Proportions and means of people with the characteristic per class (N=239)

Variable	Class 1: Trauma	Class 2: Complex Pain	Class 3: Low SLI	Class 4: Simple Pain	Wald	p	Post hoc
Elevated IL-6	0.39	0.41	0.13	0.51	6.60	0.086	3 < 1, 2, 4
Elevated hsCRP	0.43	0.44	0.11	0.49	6.03	0.110	3 < 1, 2, 4
Conversion Disorder	0.07	0.02	0.05	0.12	2.58	0.460	-
Illness Anxiety disorder	0.05	0.04	0.14	<0.01	3.99	0.260	-
Childhood Trauma	0.89	0.27	0.57	0.51	22.33	**< .001**	2, 4, 3 < 1; 2 < 3
Adult Trauma	0.99	0.08	0.59	0.29	8.31	**0.040**	2 < 1
Childhood Sexual Trauma	0.29	0.15	0.03	0.41	10.50	**0.015**	3 < 1, 4; 2 < 4
Adult Sexual Trauma	0.16	0.04	0.04	0.06	6.61	0.086	-
Depressive disorder	0.91	0.97	0.28	0.54	39.24	**< .001**	3, 4 < 1, 2
Anxiety disorder	0.93	0.91	0.16	0.02	33.74	**< .001**	4, 3 < 1, 2
Pain	0.91	0.88	0.61	1.00	13.35	**0.004**	3 < 2, 1
Physical Symptom Load*	20.62	18.95	7.12	12.92	165.66	**< .001**	3 < 4 < 2, 1

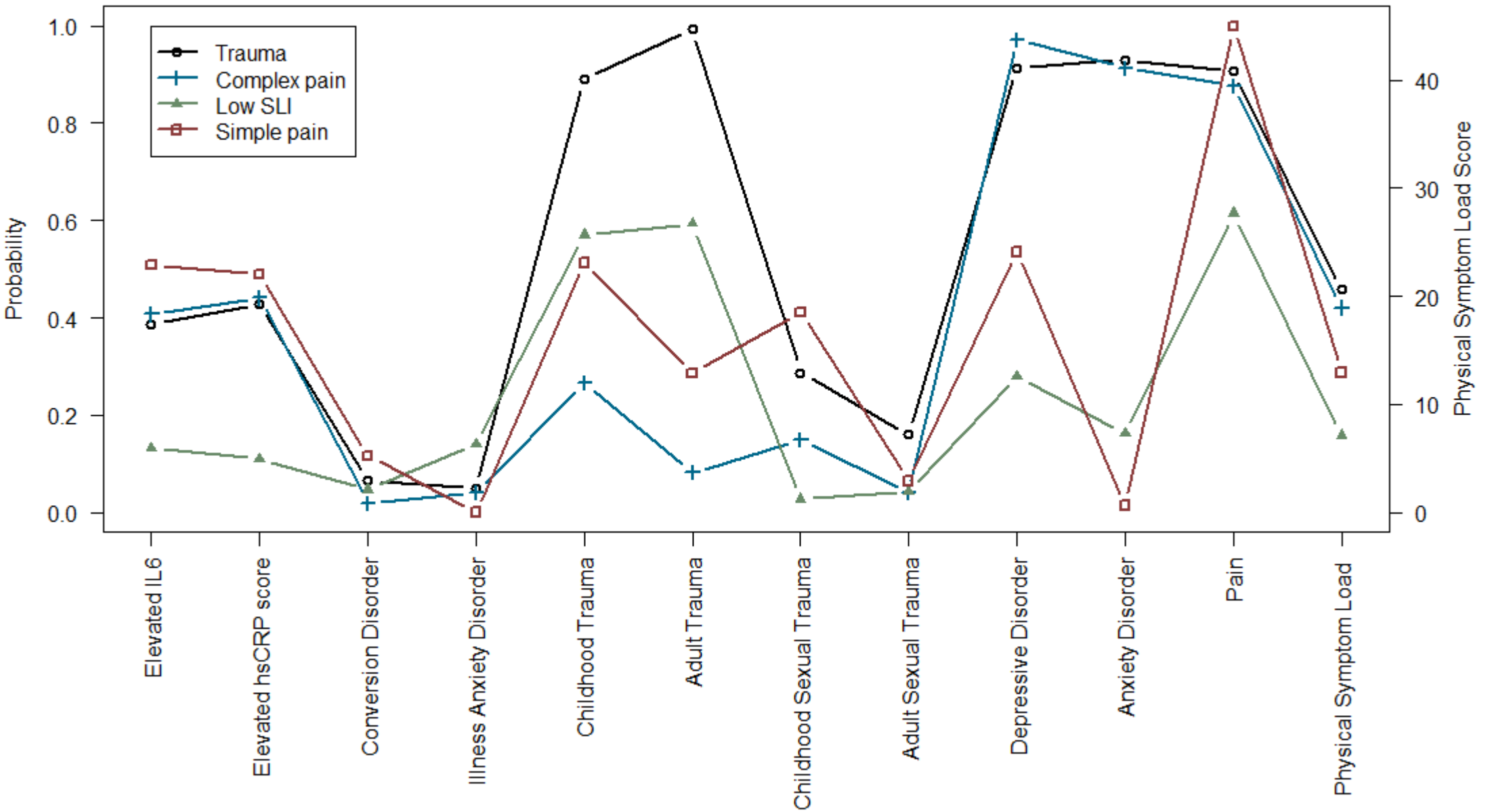
Significant p-values are in bold. IL-6 = interleukin 6; hsCRP = high-sensitivity C-reactive protein

SLI = Systemic Low-grade Inflammation; *means of Physical Symptom Load per class

Table 5 Proportions and means of personal characteristics per class (N=239)

Variable	Class 1: Trauma	Class 2: Complex Pain	Class 3: Low SLI	Class 4: Simple Pain	Wald	p	Post hoc
Gender (female)	0.68	0.68	0.58	0.37	9.51	**0.023**	3, 1, 2 > 4
Age*	40.40	44.84	44.59	40.44	5.25	0.150	-
Somatic comorbididty	0.67	0.43	0.45	0.45	0.90	0.830	-
General Health Perception*	20.51	19.50	17.14	16.82	21.68	**< .001**	1, 2 > 3, 4

*means of Age and General Health Perception per class


Trauma
Complex pain
Low SLI
Simple pain
Probability
1.0
0.8
0.6
0.4
0.2
0.0
Physical Symptom Load Score
40
30
20
10
0
Elevated IL6
Elevated hsCRP score
Conversion Disorder
Illness Anxiety Disorder
Childhood Trauma
Adult Trauma
Childhood Sexual Trauma
Adult Sexual Trauma
Depressive Disorder
Anxiety Disorder
Pain
Physical Symptom Load