Brain, Behavior, & Immunity - Health 9 (2020) 100176

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Full Length Article

IL-6 and hsCRP in Somatic Symptom Disorders and related disorders

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ARTICLE INFO

Keywords:
Somatic Symptom Disorder and related disorders (SSRD)
interleukin-6 (IL-6)
high-sensitive C-reactive protein (hsCRP)
biomarkers
systemic low grade inflammation (SLI)
childhood sexual abuse

ABSTRACT

Background: Interleukin 6 (IL-6) and high-sensitivity C-reactive protein (hsCRP) are biomarkers of systemic low-grade inflammation (SLI) in depression and anxiety. The question if SLI in those conditions is related to comorbid chronic medical conditions has not been resolved. DSM-5 Somatic symptom disorders and related disorders (SSRD) are conditions with serious distress related to physical symptoms as main criterion. They can occur in patients with medically unexplained symptoms (MUS) and in patients with known comorbid chronic medical conditions. Often, comorbid depression and anxiety are present. SSRDs offer the opportunity to explore the role of SLI in relation to mental distress, including trauma, MUS, chronic medical conditions and comorbid mental disorder. AIM: We hypothesized that increased IL-6 and hsCRP may be directly linked to SLI in SSRD, and that comorbid chronic medical conditions, childhood trauma, current stress and comorbid depression and anxiety may be risk factors that account for some of the variance of SLI in SSRD. METHODS: We explored these relationships in a large sample of 241 consecutive outpatients with SSRD. RESULTS: Mean hsCRP level was 3.66 mg/l, and mean IL-6 level was 3.58 pg/ml. IL-6 and hsCRP levels were associated with each other: $\tau = 0.249$, $p < .001$; a medium size correlation. Comorbid chronic medical conditions, adverse childhood events other than sexual trauma, and current stress levels were not associated with IL-6 or hsCRP levels. CONCLUSION: IL-6 and hsCRP are elevated in SSRD, indicating SLI in SSRD independently of comorbid chronic medical conditions. In clinical research, elevated IL-6 and hsCRP can be used as biomarkers of SLI and can indicate risk for childhood sexual abuse in SSRD. Elevated hsCRP may be a biomarker indicating risk for comorbid depression or high pain levels in SSRD as well.

1. Introduction

Research concerning Systemic Low-grade Inflammation (SLI) in mental disorders is gaining ground (Miller et al., 2003; Rief et al., 2010). Prolonged SLI activity, resulting in sickness behaviour (fatigue, pain, mood and cognitive symptoms), may provoke mental disorders (Viljoen, Pantzer, 2005) such as depression (Dantzer et al., 2008; Del Grande da Silva et al., 2016; Simon et al., 2008), Post Traumatic Stress Disorders (PTSD) (Lindqvist et al., 2017) and anxiety disorders (Del Grande da Silva et al., 2016; Kovacs et al., 2016; Vogelzangs et al., 2016). Associations with cytokines such as interleukin-6 (IL-6) have been explored mostly in depressive disorder (Dowlati et al., 2010; Simon et al., 2008) with inconsistent results (Einvik et al., 2012) which might be explained by possible confounding by comorbid chronic medical conditions such as cardiovascular disorders (Howren et al., 2009). IL-6 plays a role in both innate and adaptive immunity (Scheller et al., 2011). Within the adaptive immune response, IL-6 plays a crucial role in activating antibody-producing B cells to proliferate, leading to an enhanced antibody response. Concentrations of IL-6 are elevated in patients with acute and severe infection (Tsalik et al., 2012) but also in chronic inflammatory disorders such as rheumatoid arthritis and inflammatory bowel disease (Gabay, 2006). Normal concentrations of IL-6 range between 2 and 10 pg/ml. Although IL-6 levels in the normal range do not exclude the possibility of an ongoing inflammatory process such as SLI, it is unclear what might be an indicative IL-6 level for

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https://doi.org/10.1016/j.bbih.2020.100176
Received 11 August 2020; Received in revised form 16 October 2020; Accepted 28 October 2020
Available online 17 November 2020

SLI in mental disorders.

As part of the innate immune system, IL-6 acts on hepatocytes to induce expression of C-reactive protein (CRP), in what is known as the acute phase response. Depending on lab procedures, normal values for CRP range between 2 and 10 mg/l, and a level of 10 mg or higher is an indicator of a serious infection, trauma or inflammatory condition. (Mayo Clinic, 2020) However, despite a level of <10 being in the normal range, epidemiological and intervention studies found a level of 3–10 mg/l on minor CRP elevation, defined as high-sensitivity CRP (hsCRP), to be prospectively associated with an increased cardiovascular risk (Pfützner, Forst, 2006). A level of 3.0 mg/l or higher is considered to indicate at least in part an inflammatory process, or SLI (Ridker, 2016).

Adverse childhood experiences (ACE) occur in mental disorders such as depressive and anxiety disorders (Van der Feltz-Cornelis et al., 2019). Cytokine levels in depressive disorder may differ between depressed patients who experienced ACE and patients who did not; (Pedrotti Moreira et al., 2018); however, the literature is ambiguous (Grosse, 2016) (Pasco et al., 2010; Powers et al., 2019) as another study found that an association between ACE and hsCRP in depressed individuals disappeared after controlling for socioeconomic factors and health behaviours (Gouin et al., 2017). A meta-analysis revealed an association between CRP but not IL-6 with childhood trauma with larger effect sizes for clinical samples with chronic medical conditions such as cancer compared to general population samples (Baumeister et al., 2016). Based upon the literature, whether current or childhood traumatization is associated with IL-6 and hsCRP and what role chronic medical conditions might play in this link, remains unclear. A group of mental disorders that may be of particular interest for exploring the questions above are Somatic Symptom and Related Disorders (SSRD). They are characterized by physical symptoms that are associated with significant distress and impairment (American Psychiatric Association, 2013). SSRD are a group of conditions that include Somatic Symptom Disorders (SSD), SSD with pain, conversion disorder/functional neurological disorder (CD/FND), and health anxiety and can occur in patients with known chronic medical conditions as well as in patients with medically unexplained symptoms (MUS).

We hypothesize that increased IL-6 and hsCRP may indicate SLI in SSRD, and that comorbid chronic medical conditions, trauma and stress, and comorbid depression and anxiety may be risk factors that account for some of the variance in SLI in SSRD.

Our objectives are to:

1 Describe IL-6 and hsCRP levels and clinical characteristics in patients with SSRD in relation to comorbid chronic medical conditions; ACE, AAE, childhood and adult sexual abuse; current stressful life events (LCU); and comorbid mental disorders
2. Explore if IL-6 and hsCRP levels are associated with each other. Explore which one is better to use as biomarker for SLI in SSRD in clinical research. Explore if there is scope to establish cut-off scores for use as a biomarker for SLI in SSRD in clinical research.

2. Methods

This is a cross-sectional observational study. The study sample contains patients with comorbid medical conditions, and patients without comorbid medical conditions. Also, it contains patients with trauma and stress, and patients without, as well as patients with and without comorbid depression and anxiety. This diversity in the sample enables us to evaluate our hypothesis. The Scientific Institutional Review Board of GGz Breburg approved the study protocol.

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.

The standard intake procedure has been described elsewhere (Van Eck van der Sluijs et al., 2017) and is summarized below. Medical examination by a physician involved assessment of somatic symptoms by medical history taking; a questionnaire measuring somatic symptoms; physical examination; neurological examination; laboratory assessments; 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. 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, Poole, 1993; Whicher, 1998). labs. 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.

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 (American Psychiatric Association, 2013). Psycho-diagnostic questionnaire assessment of psychological symptoms, ACE, AAE, and stressful life events were performed by questionnaires and Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Patient files and the data-warehouse were assessed for the variables described in Table 1.

Supervision and checks by two supervisors (JvE and CFC) secured the standardization of the intake procedure, the reporting in the electronic patient files, and the data extraction and data-entry by trained assistants.

2.1. Statistical analysis

Variables explored were IL-6 and hsCRP, SSRD categories, pain, somatic symptoms and functioning. Elevated hsCRP was defined by a level of 3 mg/L or higher. Elevated IL-6 was established as described in the methods. Covariates were ACE, childhood sexual abuse, current daily life stress measured as Holmes and Rahe life events score (LCU), current trauma measured by AAE, as well as comorbid chronic medical conditions, comorbid mental disorders, age, gender, and marital status.

Regarding the description of clinical characteristics, for the continuous variables, means, SD, medians and range were calculated. For the categorical variables, frequencies and percentages were calculated. This was done for all participants together and for each SSRD category separately. Whether IL-6, hsCRP and clinical characteristics differed between SSRD categories (Table 2) and between patients with and without comorbid chronic medical conditions (Table 3) was explored with a robust one-way ANOVA (SSRD categories) or the non-parametric Wilcoxon-Mann-Whitney test (comorbid chronic medical conditions) if the variable was continuous, and with a chi-square test if the variable was categorical, and p-values reported. To test whether IL-6 and hsCRP levels were associated with any of the clinical characteristics, Kendall's correlation test was performed. Kendall's τ is a non-parametric correlation and was chosen because of the skewed distribution of IL-6 and hsCRP in the sample. For categorical characteristics, such as gender and comorbidity, Kendall's τ is similar to Wilcoxon-Mann-Whitney test, a non-parametric variant of the independent t-test (Table 4). We used non-parametric tests to take into account the skewed distribution of IL-6 and hsCRP values and the presence of outliers. We performed a sensitivity analysis to deal with outliers for IL-6 and hsCRP values as follows. First, we performed log transformation of IL-6 and hsCRP and all IL-6 and hsCRP values of > 3SD above the mean were taken out of the sample. Then, the

Table 1
Data sources/measurement.

Factors	Classification	Based on
Diagnostic classification		
Type of SSRD	Type	Patient file: intake letter and DSM classification (American Psychiatric Association, 2013)
Psychiatric comorbidity	Yes/No	Patient file: DSM classification (if unclear, also MINI) (Sheehan et al., 1998)
Personality disorder	Yes/No	Patient file: DSM classification and SCID-2 (Spitzer et al., 1990)
Anxiety disorder	Yes/No	Patient file: DSM classification (if unclear, also MINI)
Depressive disorder	Yes/No	Patient file: DSM classification (if unclear, also MINI)
Developmental disorder	Yes/No	Patient file: DSM classification (if unclear, also MINI)
Comorbid CMC	Yes/No	Patient file: DSM classification, intake report (if needed also ICD classification) (WHO, 2016)
Psychosocial factors		
Relationship status	Single/Living together or Married/Living apart together/Other	Patient file: intake or registration form Or Psychodiagnostic examination: INTERMED (Huyse et al., 1999)
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 (Anda et al., 1998), 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.(van der Feltz-Cornelis et al., 2019a)
Recent trauma and recent life stress	Yes/No Score	Patient file: AAE, LCU (Holmes and Rahe, 1967), 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		
Scores: PSQ51 = PHQ15 = PHQ9 = GAD7 = SF36 = BPI =	Physical symptoms were measured using the PSQ51 (Van Hemert, 2003), 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.(De Waal et al., 2004) They were also measured by the PHQ15.(Kroenke et al., 2002) Higher scores indicated a higher symptom burden. 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 (Kroenke et al., 2009). 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.(Kroenke et al., 2010) 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.(Spitzer et al., 2006) We used the SF-36 general health domain score to assess general functioning. Studies confirmed the SF-36's validity and reliability.(Ware and Sherbourne, 1992) 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. It was validated in the US and in the Netherlands.(Ware et al., 1994; Aaronson et al., 1998) It is responsive to change.(McHorney et al., 1993) Normative data are available.(Garrat et al., 1994) Chronic non-malignant pain was measured by the Brief Pain Inventory (BPI).(Tan et al., 2004) Higher scores indicated a higher symptom burden.	
Lab at intake		
Venepuncture	Biochemical, Haematological and immunological lab protocol including hsCRP (immunoturbidimetry) and ELISA for IL-6	

associations between IL-6 and hsCRP and the characteristics in Tables 2 and 3 were recalculated. If any differences were found in the statistical conclusions, this was reported in the Tables. A regression coefficient for age and IL-6 was obtained by a robust regression analysis to take violations of the normality assumption into account. A chi-square test was used to explore sexual revictimization in patients reporting childhood sexual abuse. We explored if IL-6 and hsCRP levels (continuous) were associated using a Kendalls τ correlation. A sensitivity analysis was performed by excluding the outliers.

In order to establish cut-off scores for use in clinical research as a biomarker for SLI in SSRD, several steps were undertaken. As first step, a score of 3.0 mg/l or higher was used as a cut-off score for elevated hsCRP, assuming that a hsCRP score of 3.0 mg/l or higher is an indicator of inflammation(Ridker, 2016). We then checked which IL-6 value corresponded with the percentage of patients having 3.0 mg/l or higher for hsCRP in our sample, a method used elsewhere (Cho et al., 2013). As a second step, we took out all outlying values of IL-6 and performed a regression analysis with hsCRP as the predictor and IL-6 levels as the dependent variable to explore which IL-6 value corresponds to a hsCRP level of 3.0 mg/l. We then explored if elevated levels of hsCRP and of IL-6, as established by the method described above, were associated with particular clinical characteristics for which they could be used as biomarker, by comparing patient with and without elevated IL-6 levels (Table 5) and patient with and without elevated hsCRP levels (Table 6). Means, median, SD and range are given for the continuous variables and frequencies and percentages for the categorical variables. The non-parametric Wilcoxon-Mann-Whitney test was used to test whether patients with and without elevated levels differed significantly on these variables if the variable was continuous, and with a chi-square test if the

Table 2
Clinical and demographic characteristics and p-values for the whole sample and SSRD categories. Percentages are based upon the N per variable.

IL-6 M (SD) Median [Range]	IL-6 without outliers M(SD) Median [Range]	hsCRP M (SD) Median [Range]	Age M (SD)	Gender Male N (%)	LCU M (SD)	AAE M (SD) N (%) N = 233	ACE M (SD) N (%) N = 233	Childhood sexual abuse N (%)	Adult sexual abuse	PHQ9 M (SD)	GAD7 M (SD)	BPI M (SD)	PSQ51 M (SD)	PHQ15 M (SD)	SF36 M (SD)	Somatic comorbidity N (%)
SSRD Classification N (%)																
SSRD Total group 241 (100)																
3.58 (16.03) **1.65** **[0.62–226]**	2.12 (1.4) 1.65 [0.62–9.65]	3.66 (4.54) 2.17 [0.2–31.14]	42.31 (13.43)	97 (40.2%)	92.38 (93.19)	**1.46 (1.72)** 140 (60.1%)	1.75 (2.09) 144 (61.8%)	**53 (22.2%)**	16 (8.2%)	14.29 (6.13)	11.6 (5.39)	**5.65 (2.5)**	16.35 (8.93)	15.52 (5.57)	18.82 (3.32)	142 (58.9%)
Somatic Symptom Disorder (SSD) 176(73%)																
2.16 (1.82) **1.63** **[0.62–16.5]**	2.06 (1.4) 1.63 [0.62–9.65]	3.61 (4.57) 1.99 [0.2–31.14]	42.36 (41.5)	74 (42%)	95.6 (95.95)	1.49 (1.70) 104 (61.5%)	1.65 (1.97) 105 (62.1%)	33 (18.9%)	10 (7.2%)	14.36 (6)	11.62 (5.51)	5.42 (2.49)	16.16 (8.9)	15.57 (5.55)	18.71 (3.24)	107 (60.8%)
SSD with pain 36(15%)																
10.7 (41.55) **2.01** **[1.07–226]**	2.41 (1.44) 1.96 [1.07–7.08]	4.24 (4.9) 2.55 [0.2–23.41]	42.78 (14.28)	13 (36.1)	85.84 (94.56)	**1.81 (2.05)** 23 (63.9%)	2.17 (2.32) 24 (66.7%)	**13 (36.1%)**	5 (14.7%)	15.56 (5.93)	12.59 (5.19)	**7.25 (1.86)**	19.06 (8.04)	16.97 (5.28)	20.11 (2.42)	20 (55.6%)
Illness anxiety 15(6%)																
2.22 (1.5) **1.93** **[0.62–5.24]**	2.22 (1.5) 1.93 [0.62–5.24]	2.59 (3.18) 1.74 [0.2–1.72]	43.6 (14.01)	7 (46.7)	92.27 (91.59)	**0.36 (0.63)** 4 (28.6%)	1.14 (1.41) 7 (50%)	**1 (7.1%)**	0 (0%)	11.17 (6.1)	9.92 (4.35)	**4.31 (2.36)**	12.46 (7.4)	13 (4.51)	18.07 (3.75)	7 (46.7%)
Conversion Disorder (CD) 14(6%)																
5.88 (13.32) **1.71 [0.87–48]**	2.05 (1.32) 1.52 [0.87–4.58]	3.98 (4.64) 2.71 [0.23–17.15]	39 (14.43)	3 (21.4%)	71.92 (59.37)	1.43 (1.4) 9 (64.3%)	2.5 (3.13) 8 (57.1%)	**6 (42.9%)**	1 (9.1%)	12.83 (7.8)	10.57 (5.18)	5.54 (2.76)	15.21 (11.52)	13.64 (6.62)	17.57 (4.89)	8 (57.1%)
p-value for variable differences between the SSRD categories																
0.315	0.556	0.585	0.808	0.422	0.799	**0.004**	0.566	**0.015**	0.368	0.221	0.373	**0.001**	0.071	0.185	0.157	0.712

Table 3
Clinical characteristics in SSRD patients with comorbid CMC versus no comorbid CMC.

Comorbid CMC N = 142				No Comorbid CMC N = 99				p-value
Variable N	M(SD) Median	Range	N (%)	Variable N	M(SD) Median	Range	N (%)	
IL-6	2.4 (2.47)	0.62–19.4	Elevated*	IL-6	5.33 (25.07)	0.82–226	Elevated*	0.842
123	1.64		43 (35%)	83	1.77		29 (34.9%)	
IL-6 with outliers removed	2.14 (1.43)	0.62–8.46	41 (33.9%)	IL-6 with outliers removed	2.08 (1.36)	0.82–9.65	27	0.758
121	1.63			81	1.76		(33.3%)	
hsCRP	3.81 (4.91)	0.2–31.14	49 (36.3%)	hsCRP	3.45 (3.97)	0.2–22.11	38 (39.2%)	0.784
135	2.22			97	1.99			
Age	**44.8 (13.12)**	**18–80**	**NA**	**Age**	**38.73 (13.12)**	**15–78**	**NA**	**< 0.001**
142	**44**			**99**	**35**			
Gender	NA	NA	58 (40.8%)	Gender	NA	NA	39 (39.4%)	0.821
142				99				
Male N (%)								
LCU	96.09 (103.07)	0–545	NA	LCU	87.31 (78.02)	0–374	NA	0.993
116	67.5			85	72			
PHQ9	14.33 (6.21)	0–27	NA	PHQ9	14.24 (6.04)	0–27	NA	0.866
135	14			92	14			
GAD7	11.4 (5.54)	0–21	NA	GAD7	11.9 (5.17)	1–21	NA	0.567
136	11			94	11			
BPI	5.84 (2.45)	0–10	121 (87.7%)	BPI	5.36 (2.58)	0–10	74 (82.2%)	0.116
138	6.5			90	6			
PSQ51	17.02 (9.28)	1–45	NA	PSQ51	15.37 (8.35)	0–42	NA	0.186
136	17			93	14			
PHQ15	15.51 (5.59)	5–28	NA	PHQ15	15.54 (5.57)	0–30	NA	0.958
137	15			93	15			
SF36	**19.27 (3.45)**	**8–25**	**NA**	**SF36**	**18.15 (3.01)**	**6–24**	**NA**	**0.002**
140	**20**			**94**	**18**			
Childhood Sexual Abuse	NA	NA	34 (23.9%)	Childhood sexual abuse	NA	NA	19 (19.6%)	0.426
142				97				
Adult sexual Abuse	NA	NA	8 (7.1%)	Adult sexual abuse 82	NA	NA	8 (9.8)	0.501
113								
ACE	1.6 (1.88)	0–8	85 (61.2%)	ACE	1.98 (2.36)	0–10	59 (62.8%)	0.379
139	1			94	1			
AAE	1.35 (1.6)	0–7	82 (59%)	AAE	1.64 (1.88)	0–8	58 (61.7%)	0.335
139	1			94	1			

* Elevated IL-6 score = score 2.056 or higher as indicated in results section 4.4.

variable was categorical. We dealt with missing data by using pairwise deletion.

3. Results

Table 2 shows the clinical and demographic characteristics and p-values for the sample as a whole and for the different SSRD classifications.

The mean level of IL-6 in the total sample was 3.58 (16.03) with median 1.65 pg/ml and range 0.62–226. Seventy-two (35%) of the patients had elevated IL-6. After outlier removal (4 IL-6 values), mean IL-6 level was 2.12 (1.4) pg/ml, median remained the same, 1.65 pg/ml, and the range was 0.62–9.65 pg/ml. Mean hsCRP level was 3.66 (4.54) mg/l; median 2.17, range 0.2–31.14.37.5% of the patients have an hsCRP level higher than 3.0 mg/l. No outliers in hsCRP level were detected. There were no significantly different levels of IL-6 or hsCRP, prevalence of comorbid chronic medical conditions, or ACE in the different SSRD classifications. However, adult traumatic experiences (AAE) occurred in over 60% of all SSRD categories, except illness anxiety, which had significantly less AAE (28.6%; p = .004). Childhood sexual abuse occurred in only 7.1% of patients with illness anxiety, but significantly more often in SSD with pain (36.1%) and with CD/FND (42.9%) (p = .015). Expectedly, high pain score (BPI) occurred significantly more often in SSD with pain. Regarding sexual revictimization, childhood sexual abuse was reported in 53 (22.2%) of the sample. In patients with childhood sexual abuse, 21.4% reported adult sexual abuse versus 4.6% in patients without childhood sexual abuse (χ^2 (1) = 12.427, p = .001, phi = .252).

Table 3 shows the clinical and demographic characteristics of the sample divided as SSRD with comorbid chronic medical conditions versus without comorbid chronic medical conditions.

There were no significant differences in terms of IL-6 or hsCRP levels between patients with versus those without comorbid chronic medical conditions. The only significant differences concerned age (p < .0001) and perceived general health (p = .002). Patients with chronic medical conditions were on average six years older, with an average of 44.8 years compared to 38.7 (13.12) in the group without comorbid chronic medical conditions. The SF36 general health score was significantly higher in the patients with comorbid chronic medical conditions, with a score of 19.27 (3.45) versus 18.15 (3.01) in the patients with SSRD with unexplained medical symptoms.

Table 4 shows the associations between IL-6 and hsCRP levels (continuous) and clinical variables over the whole sample.

IL-6 was associated with age, but hsCRP was not. Robust regression analysis yielded a Beta of .022 (95%CI = 0.012–0.032), meaning that for every year of an increase in age, there was a predicted increase in IL-6 of 0.022 pg/ml. IL-6 and hsCRP were both associated with pain. hsCRP was associated with the number of somatic symptoms (PSQ51 and PHQ15) and was negatively associated with a comorbid autism spectrum disorder.

IL-6 and hsCRP levels (continuous) were associated (Kendall's τ = 0.223, p < .001). After the exclusion of the four outliers, the association between IL-6 and hsCRP levels (continuous) was Kendall's τ = 0.249, p < .001.

An IL-6 value of 2.01 pg/ml corresponded with the percentage of patients with a hsCRP level of 3.0 mg/l or higher. As the second step, assuming that a hsCRP of 3.0 mg/l or higher is an elevated hsCRP level (Ridker, 2016), and after removing the outliers, we found that a hsCRP level of 3 mg/l predicted an IL-6 level of 2.056 pg/ml in a regression analysis (95%CI around prediction: 1.864–2.249).

We then explored if levels of hsCRP ≥3.0 mg/l and IL-6 ≥ 2.056 pg/ml were associated with particular clinical characteristics for which they

Table 4
Associations between IL6 and hsCRP and comorbid CMCs, ACE and recent stress, and other clinical variables.

Variable	IL-6	hsCRP
Age	$\tau = .26, z = 5.53, p < .001$	$\tau = .04, z = 0.91$ $p = .364$
Gender	$\tau = .00, z = -0.03, p = .978$	$\tau = -.05, z = -1.00, p = .317$
LCU	$\tau = -.07, z = -1.38, p = .168$	$\tau = .06, z = 1.20, p = .232$
SSRDcat	p = 0.419	p = 0.579
Somatic	$\tau = .01, z = 0.20, p = .841$	$\tau = .01, z = 0.28, p = .783$
PHQ9	$\tau = .09, z = 1.91, p = .056$	$\tau = .07, z = 1.47, p = .143$
GAD7	$\tau = .03, z = 0.65, p = .514$	$\tau = .04, z = 0.80, p = .425$
BPI	$\tau = .11, z = 2.13, p = .033$	$\tau = .14, z = 2.87, p = .004$
PSQ51	$\tau = .08, z = 1.64, p = .102$	$\tau = .12, z = 2.54, p = .011$
PHQ15	$\tau = .04, z = 0.88, p = .379$	$\tau = .11, z = 2.46, p = .014$
SF36	$\tau = .04, z = 0.76, p = .449$	$\tau = .05, z = 1.04, p = .299$
Childhood Sexual Trauma	$\tau = .08, z = 1.45, p = .146$	$\tau = .09, z = 1.72, p = .085$
Adult sexual trauma	$\tau = .08, z = 1.20, p = .232$	$\tau = -.07, z = -1.21, p = .224$
ACE	$\tau = .05, z = 0.90, p = .370$	$\tau = .05, z = 1.09, p = .277$
AAE	$\tau = .05, z = 0.90, p = .370$	$\tau = .01, z = 0.26, p = .792$
Co_Dep	$\tau = .02, z = 0.28, p = .780$	$\tau = .06, z = 1.03, p = .305$
Co_GenAnx	$\tau = -.03, z = -0.55, p = .581$	$\tau = -.04, z = -0.78, p = .437$
Co_PanDis	$\tau = -.04, z = -0.72, p = .474$	$\tau = -.02, z = -0.44, p = .656$
Co_PTSS	$\tau = .05, z = 0.82, p = .414$	$\tau = .05, z = 0.84, p = .401$
Co_PersDis	$\tau = -.01, z = -0.17, p = .869$	$\tau = -.06, z = -1.14, p = .254$
Co_ADHD	$\tau = -.03, z = -0.46, p = .647$	$\tau = -.06, z = -1.20, p = .228$
Co_Aut	$\tau = -.06, z = -1.03, p = .303$	$\tau = -.14, z = -2.68, p = .007$
Co_OCD	$\tau = -.06, z = -1.04, p = .297$	$\tau = .05, z = 0.91, p = .365$
Co_Anx_comb*	$\tau = -.02, z = -0.27, p = .788$	$\tau = .01, z = 0.20, p = .839$

* General Anxiety disorder, Panic Disorder, PTSS, and/or OCD as comorbidity.

could be used as biomarkers. A sensitivity analysis removing the IL-6 outliers was performed and the p-values for differences between elevated and non-elevated IL-6 levels are shown in Table 5.

Patients with elevated IL-6, i.e. levels of 2.056 pg/ml or higher, had significantly higher hsCRP: 4.87 (5.2) mg/l in the elevated IL-6 group versus 2.88 (3.86) mg/l in the non-elevated IL-6 group (p < .001). The mean age was 47.14 (11.5) in the elevated IL6 group versus 39.68 (13.61) in the non-elevated IL6 group, a difference of 8 years (p < .001). The elevated IL-6 group also showed significantly higher somatic symptom levels (PSQ51 mean 18.81 (9.09) versus 15.55 (8.85), p = .016.

Findings for hsCRP after sensitivity analysis with reported means and SDs of IL-6 without the outlying IL-6 values are presented in Table 6.

Patients with elevated hsCRP, i.e. a level of 3.0 mg/l or higher, had significantly higher IL-6 (2.52 (1.59) pg/ml) versus 1.89 (1.26) pg/ml in the non-elevated hsCRP group (p < .001). They scored (marginal) significantly higher on BPI (6.3 (2.24) versus 5.18 (2.59), p = .002) and on somatic symptoms (PSQ51 mean 18.27 (9.69) versus 15.38 (8.29), p = .038; PHQ15 mean 16.7 (5.63) versus 14.94 (5.41), p = 0.038). Elevated hsCRP was significantly associated with childhood sexual abuse: 31% of 87 patients with elevated hsCRP had a history of childhood sexual abuse, versus 18.1% with non-elevated hsCRP (p = .042).

4. Discussion

This study for the first time investigates IL-6 and hsCRP in a large sample of patients with SSRD and demonstrates high levels indicating SLI. It shows that IL-6 and hsCRP do not differentiate between SSRD subclassifications such as SSD with pain, CD/FND and illness anxiety. Also, its innovative design and abundance of data allows for establishing that comorbid chronic medical conditions, general adverse childhood events, and current stress are not associated with IL-6 and hsCRP levels. We suggest that in clinical research, elevated IL-6 and hsCRP ca be used as biomarkers for SLI and can indicate risk for childhood sexual abuse in SSRD. Elevated hsCRP may also indicate risk for comorbid depression or high pain levels in SSRD. We establish cut-off scores for the first time that may be used in future clinical research.

The results show a mean IL-6 level of 3.58 (16.03) pg/ml and with correction for outliers this is 2.12 (1.4) pg/ml. hsCRP mean is 3.66 (4.54) mg/l, which is above the cut-off recommended by the American Heart Association for increased risk of cardiovascular events and SLI. The mean IL-6 level is higher than the cut-off of 2.056 pg/ml predicted by a hsCRP of 3.0 mg/l in our study. These levels are higher than in a study in the Swedish general population (Garvin et al., 2016), higher than in a general population study in Manhattan (Luna et al., 2014) and much higher than in an elderly general population sample in rural Iowa although the mean age in the elderly sample is higher than in our study (Harris et al., 1999). Also, the median of IL-6 and hsCRP in our study is higher than the median in a UK study in civil servants in London (Cho et al., 2013). The high levels of hsCRP and IL-6 in our sample fit a clinical population rather than a general population sample and seem to be indicative of SLI in SSRD.

In this sample of patients with SSRD, 142 (58.9%) of the patients had

Table 5
Clinical characteristics in elevated IL-6 compared to not elevated IL-6 after sensitivity analysis.

Variable	High IL-6	N (%)	N	Low IL-6	N (%)	N	p value
hsCRP	**4.87** (5.2); 2.86; [0.2–31.14]	34 (48.6%)	70	**2.88** (3.86); 1.24; [0.2–23.41]	37 (28.2%)	131	**<0.001**
Age	**47.14** (11.5); 47; [19–78]	NA	72	**39.68** (13.61); 38; [15–78]	NA	134	**<0.001**
Gender	NA	28 (38.9%)	72	NA	55 (41%)	134	0.764
LCU	85.52 (91.12); 65.5; [0–501]	NA	58	96.95 (95.52); 78; [0–545]	NA	116	0.415
Somatic comorbidity	NA	43 (59.7%)	72	NA	80 (59.7%)	134	0.998
PHQ9	15.53 (6.45); 16; [0–27]	NA	70	13.74 (6.04); 14; [0–27]	NA	126	0.058
GAD7	12.3 (5.49); 13; [1–21]	NA	70	11.34 (5.31); 11; [1–21]	NA	128	0.220
BPI	6.11 (2.23); 6; [0–10]	64 (91.4%)	70	5.5 (2.54); 6; [0–10]	107 (84.3%)	127	0.146
PSQ51	**18.81 (9.09); 17; [4–45]**	NA	69	**15.55 (8.85); 15; [0–36]**	NA	128	**0.016**
PHQ15	16.29 (5.28); 16; [5–27]	NA	68	15.35 (5.81); 15; [0–30]	NA	130	0.236
SF36	19.41 (3.04); 20; [13–25]	NA	71	18.57 (3.47); 19; [6–25]	NA	129	0.170
Childhood Sexual_Trauma	NA	22 (30.6%)	72	NA	24 (18.2%)	132	0.112
Adult sexual Trauma	NA	8 (13.6%)	59	NA	8 (7.8%)	103	0.234
ACE	**2.23 (2.38); 1; [0–9]**	49 (70%)	70	**1.57 (1.91); 1; [0–10]**	79 (60.8%)	130	0.064
AAE	1.87 (2.12); 1; [0–8]	45 (64.3%)	70	1.35 (1.5); 1; [0–6]	80 (61.5%)	130	0.230

Table 6
Clinical characteristics elevated hsCRP versus non-elevated hsCRP after removal of IL-6 outliers.

Variable	High hsCRP	N percentage	N	Low hsCRP	Low Percentage	N	p value
IL6_outliers removed	**2.52** (1.59); 1.98; [0.7–9.65]	33 (47.1%)	70	**1.89** (1.26); 1.48; [0.62–8.46]	33 (26%)	127	**< 0.001**
Age	41.31 (13.28); 41; [18–72]	NA	87	42.67 (13.27); 41; [15–78]	NA	145	0.563
Gender	NA	33 Male (37.9%)	87	NA	57 (39.3%)	145	0.835
LCU	102.04 (95.63); 80; [0–545]	NA	72	87.8 (93.76); 64.5; [0–501]	NA	122	0.132
Somatic comorbidity	NA	49 (56.3%)	87	NA	86 (59.3%)	145	0.655
PHQ9	**15.23** (5.74); 15; [4–27]	NA	83	**13.7** (6.16); 13; [0–27]	NA	135	**0.030**
GAD7	12.28 (5.27); 13; [0–21]	NA	82	11.23 (5.38); 11; [1–21]	NA	139	0.141
BPI	**6.3** (2.24); 7; [0–10]	77 elevated BPI(92.8%)	83	**5.18** (2.59); 5; [0–10]	110 (80.3%)	137	**0.002**
PSQ51	**18.27** (9.69); 16; [1–45]	NA	81	**15.38** (8.29); 15; [0–36]	NA	140	**0.038**
PHQ15	**16.7** (5.63); 18; [5–30]	NA	83	**14.94** (5.41); 14; [0–27]	NA	139	**0.038**
SF36	19.33 (3.2); 19.5; [10–25]	NA	84	18.47 (3.34); 19; [6–25]	NA	142	0.066
Childhood							
Sexual_Trauma	NA	**27 (31%)**	87	NA	**26 (18.1%)**	144	**0.042**
ACE	2.08 (2.35); 1; [0–9]	52 (62.7%)	83	1.64 (1.93); 1; [0–10]	91 (64.1%)	142	0.356
AAE	1.57 (1.88); 1; [0–8]	49 (59%)	83	1.46 (1.65); 1; [0–7]	88 (62%)	142	0.974
Co_Aut	NA	2 (2.3%)	87	NA	13 (9%)	145	0.116

comorbid chronic medical conditions. There were no significant differences between SSRD classifications or patients with and without comorbid chronic medical conditions in terms of IL-6 or hsCRP levels. This suggests that SLI, which is not related to comorbid chronic medical conditions, may be an underlying mechanism, and that IL-6 and hsCRP are indicators of a direct pathophysiologic mechanism related to SLI in SSRD. The finding that both IL-6 and hsCRP are not associated with comorbid chronic medical conditions suggest that both are biomarkers reflecting SLI in SSRD.

All SSRD classifications showed a mean pain level above the cut-off score of ≥3 for clinically relevant pain on the BPI (Brecht et al., 2007), ranging between 4.31 in Illness Anxiety and 7.25 in SSD with pain. The mean IL-6 level in SSD with pain in our sample is approximately twice as high than in a sample of fibromyalgia patients (Mendieta et al., 2016). As the association between IL-6 and level of pain that we found cannot be explained by comorbid chronic medical conditions, a logical explanation might be that pain is a cytokine-related effect, as our findings suggest a role of SLI in the pathogenesis of nonspecific pain in SSRD. This is in line with a number of studies suggesting IL-6 plays a role in pain disorders, including fibromyalgia (Andrés-Rodríguez et al., 2019; Uçeyler et al., 2011). The pathophysiological role of cytokines in fibromyalgia is still unclear. One mechanism might be that IL-6 sensitizes pain receptors, although that would be at the cellular level and would not concern IL-6 in the circulation (Atzeni et al., 2019). Other studies suggest that prolonged sickness behaviour could be the underlying mechanism in the association between hsCRP, pain and depression. Also, It could be that pain and sleep disturbance are mediators of increased inflammatory activity, rather than pain being a consequence of increased inflammatory activity(Allen et al., 2020; Haack et al., 2007; Quartana et al., 2015). Unfortunately, we do not have data on sleep patterns to explore that in this dataset.

The average ACE score is 1.75, and 61.8% of the patients report ACE, which is almost similar to the 64% reported in the original ACE field study amongst 17,000 people visiting a medical evaluation centre in the USA. (Desai et al., 2002) However, the ACE scores in our study are lower than the 77% prevalence of ACE reported in specialty mental health outpatients with anxiety and depressive disorders (van der Feltz-Cornelis et al., 2019a).

Childhood sexual abuse was reported in 22.2% of the whole sample. We found high AAE levels and high rates of childhood sexual abuse, especially in SSD with pain and in CD/FND. Childhood sexual abuse was associated with adult sexual abuse in 21.4% of cases; therefore, sexual revictimization occurred in one in 5 cases of childhood sexual abuse. This rate is lower than in Australian community studies reporting approximately 35% revictimization (Werner et al., 2016), and in a study in specialty mental health outpatients with anxiety and depressive disorder in the Netherlands reporting 42% sexual revictimization (van der Feltz-Cornelis et al., 2019a). Therefore, the question arises whether there might be a particular mechanism that sparks the development of SLI and CD/FND after experiencing childhood sexual abuse and whether that involves sexual revictimization.

Both elevated hsCRP and elevated IL-6 are associated with childhood sexual abuse. Childhood sexual abuse contributes to psychological trauma and its consequences. Maybe sexual abuse in a child would be associated with physical injury and the deposit of body material or other substances in the body of the child, and hypothetically this might induce immunological reactions that might have effects into adulthood. However, this has so far not been explored. We found that sexual revictimization occurs in 1 in 5 patients with childhood sexual abuse in this sample; however, the analysis showed no association between hsCRP and adult sexual abuse, so that would not be an explanation. Baumeister et al. found elevated IL-6 and hsCRP in childhood trauma (2016) and proposed that somatic comorbidity or comorbid depression or different kinds of trauma might play a role in this. However, we did not find an association with general childhood trauma other than sexual trauma, and not with comorbid chronic medical conditions. Also, although mean levels of anxiety are at the clinical level in our sample, the association between hsCRP ($p = .029$) or IL-6 ($p = .066$) and childhood sexual abuse remained significant after controlling for PTSD or GAD7. Hence our study does not support a role for anxiety or comorbid PTSD as explanation of elevated hsCRP or IL-6 in case of childhood sexual abuse by anxiety or comorbid PTSD in SSRD. Cellular pathways may be involved. T cell expression has been found to be elevated in women with PTSD who experienced childhood sexual abuse independently of norepinephrine or cortisol levels (Lemieux et al., 2008). Future research should explore this pathogenic mechanism further. IL-6 and hsCRP were associated with each other with a medium effect size. This leaves room for other mechanisms affecting their association. There may be several possible explanations for this. Research suggests that, although hsCRP is associated with IL-6 and can predict cardiovascular risk (Koenig et al., 1999), being an acute phase protein produced in the liver after activation by IL-6 (Volanakis, 2001), it might not be the most eligible biomarker for chronic SLI, whereas IL-6 plays a role in both acute phase and chronic inflammatory processes, as well as in autoimmunity, via various pathways (Tanaka et al., 2014). Another explanation might be that IL-6 and hsCRP might be biomarkers for SLI in slightly different patient profiles. Although the underlying mechanism needs to be elucidated further, this study suggests that elevated IL-6 and hsCRP can be used as biomarkers for SLI in SSRD independently of comorbid chronic medical conditions. They can also indicate risk for childhood sexual abuse in SSRD and elevated hsCRP can indicate risk for comorbid depression or high pain levels in SSRD as well. Both hsCRP and IL-6 have been identified as reliable biomarkers for inflammation, indicating different parts of the inflammation pathway, by the Centers for Disease Control and Prevention and the American Heart Association (Pearson et al., 2003), in a scientific statement in which they

guided the possibilities and pitfalls of clinical use as biomarkers. They also indicated which would be useful for use as cardiovascular clinical risk biomarker, and which for other conditions. In terms of cut-off levels, based upon the results, we found an IL-6 level of 2.056 pg/ml corresponding with a hsCRP level of 3.0 mg/l. To take lab variety into account, we suggest using a cut-off for IL-6 of 2.0 pg/ml. This would enable us to conduct future research applying and validating those cut-offs for profiling studies. (van der Feltz-Cornelis, 2020).

4.1. Strengths and limitations

This is an innovative study which attempted to approach the question of SLI in SSRD in a clinical sample and to explore clinical relevance and possible diagnostic value of IL-6 and hsCRP. The sample size was large and the wealth of systematically assessed clinical data enabled us to explore the influence of demographic and clinical characteristics, including several aspects of trauma and stress, as well as somatic and psychiatric comorbidity on the association between IL-6, hsCRP and several SSRD categories. We shed light on the extent to which SLI might play a role in SSD, SSD with pain, CD/FND and illness anxiety, and this opens avenues for further research. The finding that IL-6 and hsCRP levels were associated with pain and somatic symptoms but were not associated with comorbid chronic medical conditions is of high clinical relevance. The finding that hsCRP and IL-6 are associated with childhood sexual abuse in SSRD indicates the possibility to use both to discern a patient profile combining SLI and childhood sexual abuse in SSRD. Elevated hsCRP also seems to discern pain and comorbid depression states with SLI in SSRD. Furthermore, we were able to suggest a cut-off level for IL-6 to be used as a biomarker in SSRD, something that so far has not been done, that can be validated in further research, and that opens the avenue of conducting clinical profiling studies. All of these can be considered strengths of our study. There are, however, also limitations. The cross-sectional, observational design does not allow controlling for confounders for which data are not available, as could be done in an experimental randomised controlled design. Smoking (Zevin et al., 2001) and obesity (Yudkin et al., 1999) are known to be of influence on SLI, but we had no data on these variables available in this sample. Our study sample provides the opportunity to make an intragroup comparison only, as we cannot compare with healthy controls from the same region. The latter would be relevant in terms of generalisability of our findings, as there might be uncontrollable associations with local environmental factors, including water, food, pollution, and climate conditions, that might play a role in cytokine levels in a given population. Other limitations are that some of the SSRD types had rather small numbers of patients. Also, this is a sample of patients with longstanding SSRD symptoms who visited a clinical centre of excellence that provides treatment to the 5% most complex patients in the Netherlands (Van Eck van der Sluijs et al., 2017). Hence, this study provides us with knowledge about the levels of SLI and the use of IL-6 and hsCRP as clinical biomarkers in chronic long-term cases of SSRD; this cannot automatically be generalized to SSRD in general.

4.2. Recommendations for research

Longitudinal studies are needed that explore a possible temporal association between IL-6 or hsCRP, pain levels, childhood sexual abuse and treatment outcome in SSRD. This program of research should enable us to describe patient profiles (van der Feltz-Cornelis, 2020) that may benefit from different treatment provisions for SSRD, taking clinical characteristics and biomarkers into account. To this end, a personalised medicine approach for SSRD might be developed.

5. Conclusion

IL-6 and hsCRP levels are substantially higher in SSRD compared to the general population and to fibromyalgia patients. IL-6 and hsCRP indicate SLI in SSRD independently of comorbid chronic medical conditions. In terms of cut-off levels, based upon the results, we found an IL-6 level of 2.056 pg/ml corresponding with a hsCRP level of 3.0 mg/l. In clinical research, elevated IL-6 and hsCRP can be used as biomarkers for SLI and can indicate risk for childhood sexual abuse in SSRD. Elevated hsCRP may also be used as a biomarker indicating risk for comorbid depression or high pain levels in SSRD. Further high-quality longitudinal studies are needed to confirm these findings and to evaluate the magnitude of these associations.

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, 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).

Funding sources

GGz Breburg funded and supported the study. The funder had no influence on the design and conduct of the study, the preparation and analysis of the data and the interpretation and description of the results.

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.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Acknowledgement

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

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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