Childhood maltreatment severity is associated with elevated C-reactive protein and body mass index in adult with schizophrenia and bipolar diagnoses

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ABSTRACT

BACKGROUND: Several studies have described an association between childhood maltreatment and inflammatory markers in the psychotic disorders (schizophrenia [SZ] and bipolar disorder [BD]). Previous studies have been relatively small (<50 participants), and the severity of abuse and the putative influence of body mass index (BMI) have not been properly investigated.

METHODS: The combined effects of childhood abuse severity and clinical diagnosis on inflammatory markers were investigated in a large sample (n=483) of patients with a disorder on the psychosis spectrum and in healthy controls (HCs). Plasma levels of inflammatory markers (high-sensitivity C-reactive protein [hs-CRP], soluble tumor necrosis factor receptor type 1 [TNFR-R1], glycoprotein 130 [gp130]) were analyzed, and BMI and data on childhood trauma events, on the basis of the Childhood Trauma Questionnaire (CTQ), were obtained from all participants.

RESULTS: Patients had increased levels of hs-CRP (P<0.001, Cohens d=0.4), lower levels of gp130 (P<0.001, Cohens d=0.5), higher BMI (P<0.001, Cohens d=0.5) and reported more childhood maltreatment experiences (P<0.001, Cohens d=1.2) than the HC group. The severity of childhood abuse (up to three types of abuse: sexual abuse, physical abuse, and emotional abuse) was associated with elevated BMI (f=8.46, P<0.001, Cohen's d=0.5) and hs-CRP (f=5.47, P=0.001, Cohen's d=0.3). Combined effects of patient status and severity of childhood abuse were found for elevated hs-CRP (f=4.76, P<0.001, Cohen's d=0.4). Differences among the groups disappeared when BMI was added to the model.

DISCUSSION:

Trauma-altered immune activation via elevated hs-CRP in patients with SZ and BD may be mediated by higher BMI; however, the direction of this association needs further clarification.

1. INTRODUCTION

The immune system has been suggested to play a role in the pathophysiology of schizophrenia (SZ) and bipolar disorder (BD) (Leboyer *et al.*, 2016, Morch *et al.*, 2016), and we and others have shown that patients with SZ or BD show signs of an activated immune system, including increased levels of C-reactive protein (CRP) as well as more specific markers of the tumor necrosis factor (TNF), interleukin (IL)-1 and the IL-6 system (Dieset *et al.*, 2012b, Hope *et al.*, 2009).

Recent genome-wide association studies (GWAS) have indicated immune genes as susceptibility genes in individuals with SZ, including the major histocompatibility complex (MHC) (2014, Ripke *et al.*, 2011, Stefansson *et al.*, 2009). Regions and genes within the MHC region and the HLA locus, and upregulation of the NOTCH4 gene, have been implicated in individuals with SZ and BD (Dieset *et al.*, 2012a, Leboyer *et al.*, 2016). Both SZ and BD are highly heritable polygenetic diseases on the opposite ends of the psychosis continuum spectrum (Craddock *et al.*, 2009, Craddock and Owen, 2010). Beyond genes in the MHC region, genes encoding innate immune system proteins, such as the toll-like receptors TLR-4 and TLR-2, have been suggested to be central markers of immune defense against diseases (Leboyer *et al.*, 2016).

The brain and the immune system are not fully developed at birth, and early experiences can shape the relationship between the immune system and the brain (Danese and S, 2016). In addition to genetic markers, environmental factors that affect the immune system have been associated with the development of SZ and BD, including obstetric complications, infection during pregnancy (Brown, 2011, 2015), and childhood maltreatment (Danese *et al.*, 2008, Danese *et al.*, 2007, Elenkov *et al.*, 1999). Recent meta-analyses have suggested that childhood maltreatment may trigger low-grade immune activation, as reflected by increased

circulating levels of CRP, TNF and IL-6 (Baumeister *et al.*, 2015, Coelho *et al.*, 2014). Several studies using limited sample sizes (n<50) have investigated childhood maltreatment and inflammation in individuals with SZ, and have found higher levels of IL-6, TNF and CRP in people with childhood maltreatment (Dennison *et al.*, 2012, Hepgul *et al.*, 2012), thus mirroring the observations in adult individuals with SZ and BD (Dieset *et al.*, 2012b, Hope *et al.*, 2009).

Childhood maltreatment is more frequent in patients with severe mental illness, including SZ and BD (Aas *et al.*, 2016, Etain *et al.*, 2008, Larsson *et al.*, 2013), and may contribute to disease development and disease severity at least partly through immune activation. A genetic overlap between inflammation and stress markers has been reported in patients within the psychosis spectrum (Fillman *et al.*, 2014), thus supporting the presence of a stress-immune vulnerability in this group. Furthermore, prenatal immune stimulation in mice interacts with peripubertal stress exposure and consequently increases the likelihood of developing neuroimmunological changes later in life, thus supporting a synergistic relationship between immune activation and early life stress (Giovanoli *et al.*, 2013).

In addition to early life stress, patients with SZ and BD present with an adverse metabolic profile, including a higher body mass index (BMI) (Coodin, 2001), which may contribute to systemic inflammation through production of inflammatory mediators by adipose tissue (Festa *et al.*, 2001). Interestingly, a history of childhood trauma has also been associated with higher BMI via emotional eating (Danese *et al.*, 2014). Together, these findings indicate that childhood maltreatment may interact with a genetic vulnerability to the disease, thus suggesting a double-hit model in which maltreatment subsequently causes elevated immune activation in individuals with SZ and BD.

Study hypotheses: First, we hypothesized that the number of childhood abuse events is associated with elevated inflammatory markers (i.e., the general inflammatory marker high-sensitivity [hs]-CRP and markers of activation of the TNF [soluble TNF receptor type 1 [sTNF-R1]] and IL-6 [gp130] system) and higher BMI levels. Second, owing to the suggested role of the immune system in the pathophysiology of SZ and BD (Leboyer *et al.*, 2016, Morch *et al.*, 2016), we hypothesized that patient status and the number of childhood abuse events have combined effects on the level of inflammation, such that patients who have experienced the most childhood abuse should have the most elevated inflammatory markers. Finally, owing to the roles of adipose tissue and BMI on inflammatory markers (Festa *et al.*, 2001), we hypothesized that differences in immune activation between groups are influenced by BMI.

2. MATERIALS AND METHODS

2.1 Participants

2.2. The participants were recruited consecutively from psychiatric units (outpatient and inpatient) in 4 major hospitals in Oslo, as part of the Thematically Organized Psychosis (TOP) Study. A total of 483 participants (with schizophrenia [n=148] or bipolar disorder [n=123]), and healthy individuals [n=212]) were recruited. Inclusion criteria for the healthy controls were the following: living in the same district as the patients, being between 18 and 65 years and having no lifetime diagnosis of any SCID 1 diagnoses. Exclusion criteria for all groups (patients and controls) included the following: organic psychosis, neurological disorder, intellectual disability (IQ under 70), autoimmune disease or cancer, unstable or uncontrolled medical conditions interfering with brain function, and age outside the range of 18–65 years. The Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate approved the study. All the participants gave

written informed consent. The participants were enrolled between 2007 and 2016.

Clinical Assessment

Trained physicians, psychiatrists and clinical psychologists performed clinical assessments. Diagnoses were based on the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I), chapters A-E. All clinical personnel completed a training program in diagnostics and symptom rating, which was based on the training program at UCLA (Los Angeles, California). The diagnostic reliability was found to be satisfactory with an overall agreement on DSM-IV diagnostic categories of 82% and an overall κ of 0.77 (95% CI: 0.60-0.94). The calculated Defined Daily Dosages (DDD) of antipsychotic medication was calculated in accordance with the guidelines from the World Health Organization Collaborating Center for Drug Statistics Methodology (http://www.whocc.no/atcdd).

2.3. Inflammatory and metabolic markers

BMI was calculated as the individual's body weight (in kilograms) divided by the square of their height (in meters). Blood sampling was performed between 8 am and 2 pm (in patients) and between 8 am and 5 pm (in healthy controls). The analysis of clinical chemistry parameters was performed at the Department of Clinical Chemistry, Oslo University Hospital, Oslo, Norway, on an Integra 800 from Roche Diagnostics (Basel, Switzerland), by using standard methods.

For the immunological analysis, blood was drawn into EDTA-containing vials, and plasma was extracted and stored at -80 °C. Plasma levels of hs-CRP, gp130, and sTNF-R1 were measured via enzyme immunoassay (EIA) kits obtained from R&D systems (Minneapolis MN, USA). Intra-and interassay coefficients of variance were less than 10%.

2.4 Childhood Trauma Questionnaire (CTQ)

To measure childhood adverse events, we used the Childhood Trauma Questionnaire (CTQ), a retrospective questionnaire that assesses traumatic experiences in childhood. The CTQ has answers ranging from "never true", "rarely true", "sometimes true", "often true", to "very true", and it yields a total score as well as five sub-scores: physical, emotional and sexual abuse, physical and emotional neglect (Bernstein *et al.*, 1994). The reliability and validity of the CTQ have been demonstrated previously (Aas *et al.*, 2014b, Bernstein *et al.*, 1994). In this study, the short version (28-item version) of the CTQ was translated into Norwegian. A predefined cut-off score from Bernstein was used to divide into above or below the moderate severe cutoff score as a predefined measure of abuse (Bernstein *et al.*, 1994), see Supplementary Material Table 1.

2.5. Statistics

Data were analyzed with Predictive Analytic software, Version 22 (IBM Corp., USA). Continuous variables are presented as median, mean ± SD. For descriptive analyses (Tables 1), we used chi square tests and univariate ANOVAs. For data not normally distributed (BMI, hs-CRP, gp130, childhood trauma), Kruskal-Wallis tests, Mann–Whitney U tests, or Spearman's correlation tests were conducted.

Data that were not normally distributed (BMI, hs-CRP, gp130) were log transformed before the parametric analyses. To analyze the level/severity of abuse, trauma data were grouped on the basis of one or more CTQ abuse subtypes with scores above the predefined moderate to severe cutoff score of trauma by Bernstein (Bernstein *et al.*, 1994), divided into abuse groups similar to those described in Etain *et al*. (2013) and Aas *et al*. (2014a-b) For an overview of the distribution of the sample, see Supplementary Material Table 2. ANOVAs were performed to investigate group differences in inflammatory markers (hs-CRP, gp130).

The roles of group status (control/patient) and trauma on levels of inflammatory markers were analyzed. Owing to the high correlation between CTQ neglect items and minimization/denial (MD) score (MacDonald *et al.*, 2015, MacDonald *et al.*, 2016), we focused our main analyses (ANOVAs) on childhood abuse (sexual abuse, physical abuse, and emotional abuse). For the ANOVAs, immune markers were added as the dependent variable (one at a time), and group status (patient/control) and severity of abuse were divided into four groups (0, 1, 2, 3) as independent variables. For the multiple comparisons analyses (see Table 3 and Table 1), Bonferroni adjustment was performed. For Figure 2 and Figure 3, participants were divided into the following groups: "controls with no abuse", n=202, "controls with at least one type of abuse", n=8, "patients with no abuse", n=157, "patients with one type of abuse", n=54, "patients with two types of abuse", n=32, and "patients with three types of abuse", n=17. Because only 8 controls had abuse scores above moderate to severe levels and only one control had two types of abuse, abuse in controls was defined as "one or more types of abuse" (n=8). Because BMI may be a moderating factor between childhood maltreatment and inflammatory markers, ANCOVA was conducted with BMI as a covariate. Effect sizes were computed using Cohen's *d* (Cohen, 1977). Cohen's *d* was calculated to compare the mean and SD in the high-trauma group to the low-trauma group (Cohen's $d = M_1 - M_2 / s_{pooled}$, where $s_{pooled} = \sqrt{[(s_1^2 + s_2^2) / 2]}$). For the ANOVA/ANCOVA analyses, partial eta squared values were transformed into Cohen's *d* for consistency. Hs-CRP values greater than 20 mg/L were excluded to avoid those with possible acute inflammation due to infection or injury, and follow-up analyses were restricted to CRP < 10 mg/L.

To rule out that inclusion of the time of blood sampling might have influenced the results, follow-up analyses were conducted by adjusting for the time of the blood samples. The threshold for statistical significance was set at $p < 0.05$ with post hoc Bonferroni corrections.

3. RESULTS

3.1. Sample characteristics

Sample demographics and clinical characteristics are shown in Table 1. One hundred ninety-one (70.5%) patients were taking at least one type of antipsychotic medication; eighty (29.5%) patients used antidepressants. The mean age of the patients was 30.3±10.6 years, and 51% of the patients were males. Patients with SZ were younger than both patients with BD and the control group (Table 1). A significant difference among the three groups was also found for sex distribution (P=0.002): the BD group was almost 60% female, whereas the SZ and HC groups were 41% female. Patients reported more childhood maltreatment events than HC individuals (P<0.001). No differences in abuse illness/severity (sexual, physical or emotional abuse) were observed between SZ and BD (X^2 =5.11, df=3, P=0.16). SZ and BD individuals had higher hs-CRP levels (p<0.001) and BMI (p<0.001) as well as lower gp130 (P<0.001) than HCs. In contrast, no significant differences in sTNFR1 were observed between the patients (SZ and BD) and the controls (p>0.1). No associations were observed between defined daily dose (DDD) and immune markers (P>1.0) or DDD and diagnosis (P>1.0). The severity of childhood abuse (sexual abuse, physical abuse, and emotional abuse), which was divided into no abuse (n=358), one type of abuse (n=61), two types of abuse (n=33), and three types of abuse (n=17), was associated with elevated BMI (ANOVA: f=8.46, P<0.001, Cohen's d=0.5) and higher hs-CRP level (ANOVA: f=5.47, P=0.001, Cohen's d=0.3) (see Figure 1 and Figure 2). Bonferroni corrections for multiple comparisons were performed for post hoc tests.

-Table 1, Figure 1-2 around here-

3.2. Investigating the effects of patient status and childhood abuse severity on hs-CRP levels

A significant difference in hs-CRP was observed among the groups: HCs without childhood abuse had the lowest hs-CRP, and patients with three types of abuse (sexual, physical, and emotional) had the highest hs-CRP (see Figure 3, Table 2). Post hoc tests showed that patients with three types of abuse had higher hs-CRP levels than patients with no childhood abuse (mean±SD=5.08±3.81 vs 3.12±3.09, P=0.007, Cohen's d=0.6). Patients without childhood abuse had higher hs-CRP than HCs without childhood abuse (mean±SD=3.12±3.09 vs 2.33±2.50, P=0.007, Cohen's d=0.3). These results remained the same when the time of blood sampling was added into the model. When BMI was added into the model, there was no longer a significant difference in hs-CRP levels across groups with different levels of severity of abuse ($P>0.1$).

-Table 2 and Figure 3 around here-

3.3 Investigating the effects of patient status and childhood abuse severity on gp130 levels

HCs without abuse had the highest gp130, and patients with three types of abuse had the lowest gp130 (see Figure 4). These results remained the same after the time of blood sampling and BMI were added into the models. No significant difference in gp130 and severity of abuse was observed (see Table S3).

-Figure 4 around here-

To rule out that acute inflammation might have been driving our results, follow-up analyses were conducted only in participants with hs-CRP < 10 mg/L (23 participants were

excluded), showing similar results. More trauma experiences were still associated with higher hs-CRP and higher BMI (data available on request). Finally, no associations were observed between sTNFR-1 and childhood abuse ($p<0.01$).

4. DISCUSSION

Our study is, to our knowledge, the largest study to show an association between childhood abuse and activation of immune markers in patients with SZ or BD (measured as one group) and HCs. Our study demonstrates combined effects of the level/severity of childhood maltreatment and a psychosis spectrum diagnosis on elevated immune activation. Participants who reported severe childhood abuse were also more likely to be obese, contributing to the elevated hs-CRP in the patient group. Our data also demonstrated lower levels of gp130, an antagonist for IL-6, in participants with childhood abuse, thus potentially suggesting increased IL-6 activity in trauma victims. In contrast to the studies by Dennison *et al.*, (2012) and Hepgul *et al.*, (2012), we also found significantly higher levels of immune markers in patients without childhood maltreatment than those found in HCs. Our study was larger than the two previous studies, and the differences between the studies may be related to the higher power in our study.

Our study supports the hypothesis that increased adiposity, as reflected by higher BMI, may mediate the effects of childhood maltreatment on CRP levels. Our finding that participants who had experienced childhood maltreatment were more likely to be obese is consistent with a recent meta-analysis by Danese *et al*. (2014) comprising 190,285 participants, which has suggested that childhood maltreatment is a risk factor for obesity over the course of life. In addition to emotional eating, elevated inflammation levels in maltreated individuals may induce fatigue and reduced activity (Dantzer *et al.*, 2008, Miller *et al.*, 2009),

thereby further contributing to obesity and increased inflammation in adulthood and potentially representing a pathogenic loop in these individuals. This possibility is consistent with an association between BMI and inflammatory markers, including CRP, both in childhood (Siervo *et al.*, 2012) and adulthood (Festa *et al.*, 2001). No association between inflammatory markers and medication (measured by DDD) was observed, thus indicating that changes in BMI were not related to medication in our sample. Notably, both obesity and hs-CRP are risk factors for the development of type 2 diabetes, cardiovascular disease and functional disability (Noble *et al.*, 2010, Ribeiro-Santos *et al.*, 2014, Van Gaal *et al.*, 2006), and comorbid general medical illnesses have been proposed to contribute to the reduced physical health observed in patients with SZ and BD (Kessing *et al.*, 2015). Hence, childhood maltreatment might have long-lasting effects that contribute to reduced physical health in individuals with SZ and BD via alterations in immune-inflammatory markers and obesity. Our study confirms this effect in the largest sample of SZ, BD, and HCs in the literature and includes levels of the severity of abuse in this context.

Our data suggest combined effects of childhood maltreatment (sexual abuse, emotional abuse, and physical abuse) and patient status on elevated hs-CRP levels. It is possible that these patients may be specifically vulnerable to the negative effects of childhood trauma, owing to increased exposure to trauma (Aas *et al.*, 2016, Mondelli *et al.*, 2010) and genetic makeup, which includes immune-related genes as risk genes for SZ and BD (Consortium., 2015, Consortium., 2014). Recent studies have shown that immune cells can cross the blood-brain barrier and that the blood-brain barrier becomes more "leaky" in these disease states (Banks and Erickson, 2010, Beumer *et al.*, 2012, Dieset *et al.*, 2016, Khandaker and Dantzer, 2016), thus potentially contributing to increased inflammation in the central nervous system. Prenatal and perinatal infections can also disrupt fetal neurodevelopmental processes and lead to long-lasting changes in the brain and an increased risk of psychotic disturbances in early

adulthood (Meyer *et al.*, 2009). However, owing to the cross-sectional design of our study, we cannot conclude whether the increased presence of immune markers in the patients was related to the development of the illness or was simply a secondary phenomenon resulting from the illness. Our study is the first to show that the number of different types of childhood abuse experiences is related to higher inflammatory markers in a dose-dependent fashion. This finding was made possible by our large sample size (N=483 participants: schizophrenia [n=148] or bipolar disorder [n=123]) and healthy individuals [n=212]). This effect has not been possible to investigate in the smaller, previously published schizophrenia studies with N<50 (Dennison *et al*., 2012, Hepgul *et al*., 2012). This study is also the first to demonstrate among those with bipolar disorder that elevated inflammatory markers are higher in patients with childhood abuse compared with patients without childhood abuse. Previous smaller studies have found that the presence of childhood abuse (without investigating the number of childhood abuse subtypes) is associated with elevated immune markers in the schizophrenia spectrum (Dennison *et al*., 2012, Hepgul *et al*., 2012), but no previous studies have included bipolar patients.

Strengths and limitations: The study included a large and well characterized sample size. However, blood samples were collected at different times, and not all of the subjects were fasting; however, the inclusion of the time of blood sampling into the model did not improve the model or change the findings. Furthermore, the data on childhood maltreatment were collected retrospectively, but the retrospective design has been found to be satisfactory in the collection of childhood maltreatment information in patients with severe mental disorders (Fisher *et al.*, 2011). Reports of childhood maltreatment have been found to be stable over time in addition to a large overlap of reports of childhood maltreatment across various sources (e.g., clinical case notes, questionnaires) (Fisher *et al*., 2011). We cannot rule out that our findings might be specific to schizophrenia or bipolar illness, because similar

findings are present in other mental disorders, such as in unipolar depression. Causality cannot be inferred, because this was a cross-sectional study and not a prospective long-term study. In this study, we investigated BMI levels as a measure of obesity and several immune markers, both being associated with poor physical heath (Noble *et al*., 2010, Ribeiro-Santos *et al*., 2014, Van Gaal *et al*., 2006). However, it should be noted that physical heath also includes parameters not measured in this study. Furthermore, gp130 receptor levels are not exclusive to IL-6 levels, because several other proteins might be associated with gp-130. It should also be noted that the control group with childhood abuse was small (n=8), and we were not able to investigate the severity of abuse in the control sample. Owing to the small number of controls with abuse, interaction analyses of group (control/patients) x trauma on inflammatory activation was not performed.

Our study supports a broader traumatic non-specific increase in immune activation via elevated hs-CRP in patients with SZ and BD. Participants who reported more types of childhood abuse were also more likely to be obese, thus potentially contributing to the elevated hs-CRP in the patient group.

Clinical relevance: Patients with an SZ or BD illness who report a history of childhood maltreatment are at risk of obesity and elevated immune system components (hs-CRP), both of which are risk factors for reduced physical health. Thus, in these patients, strategies to improve physical health behavior should be addressed in conjunction with regular treatment.

FIGURE LEGENDS

Figure 1: Participants with more types of childhood abuse have higher BMI levels.

Figure 2: Participants with more types of childhood abuse have higher hs-CRP.

Figure 3: Combined effects of patient status and childhood abuse severity on elevated hs-CRP.

Figure 4: Controls without abuse had the highest gp130.

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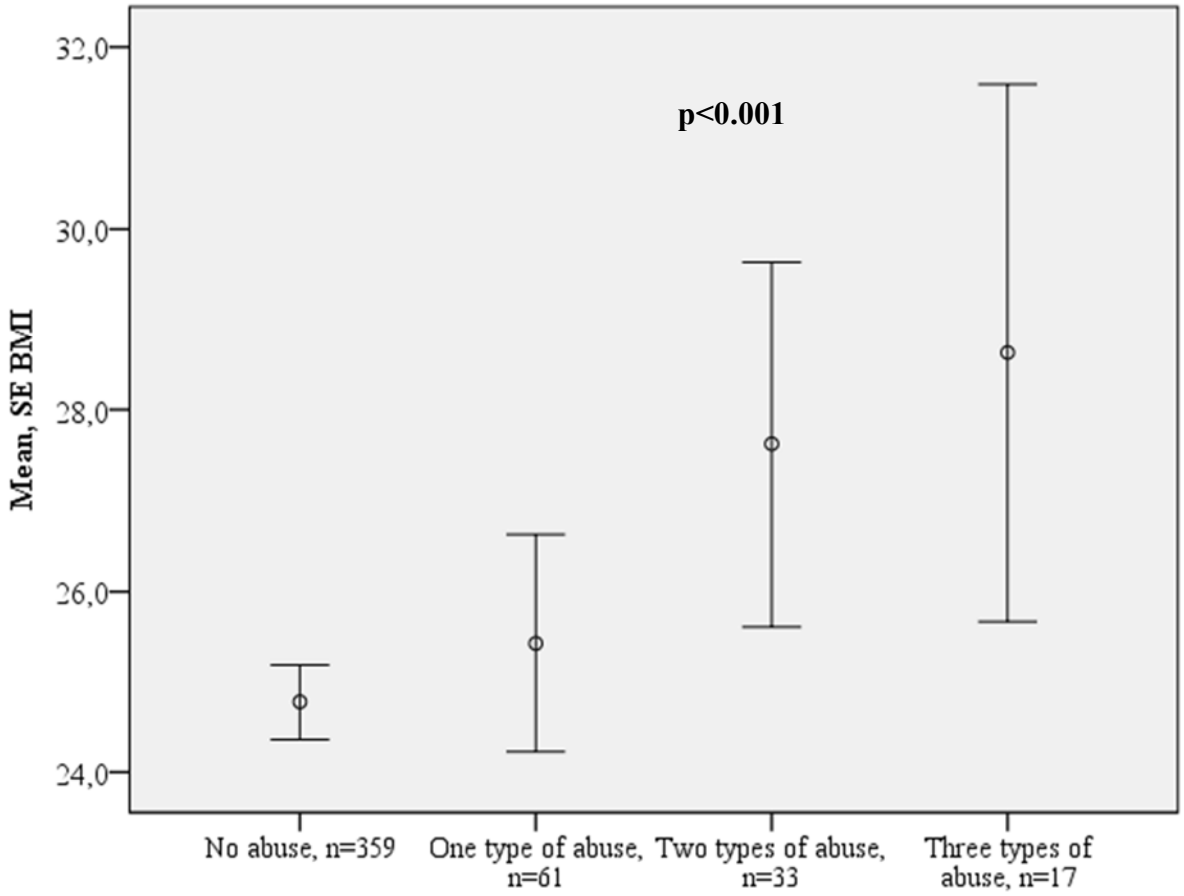
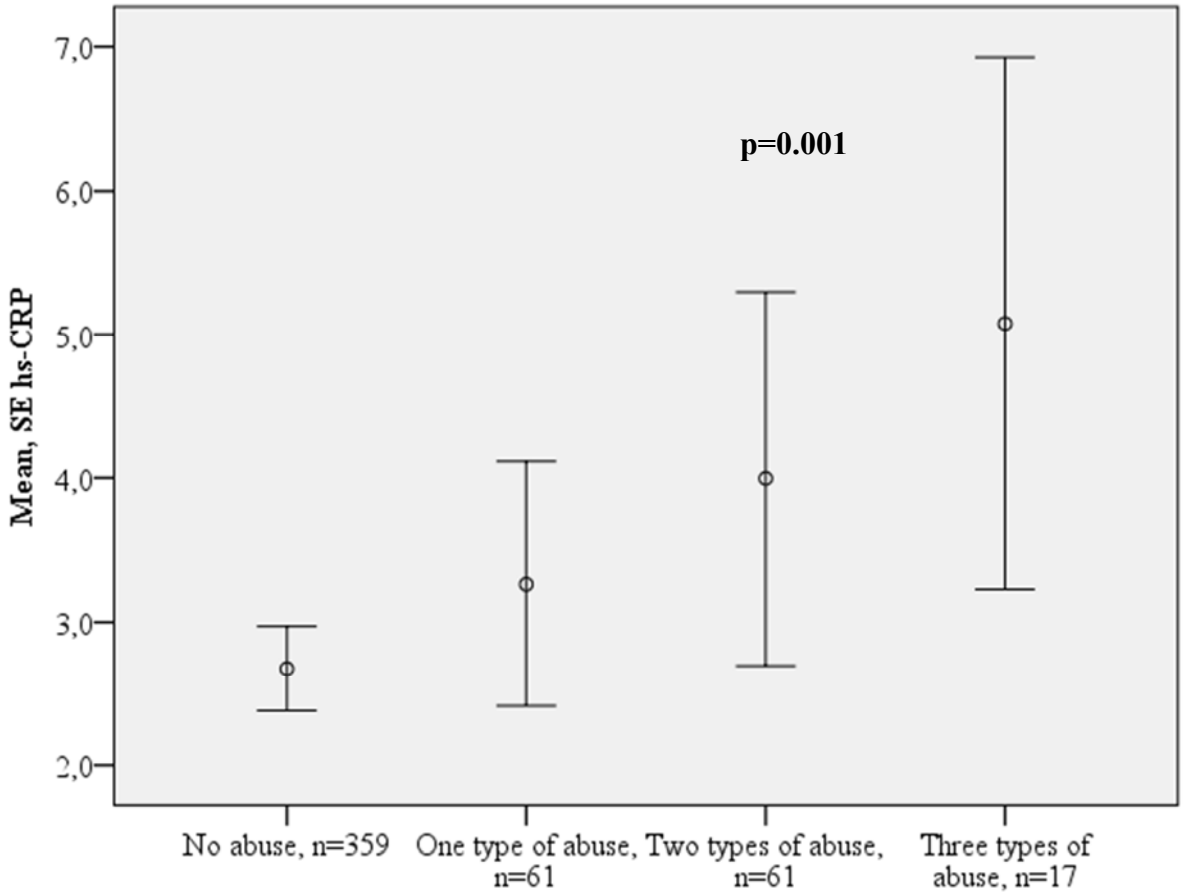
Figure 1: Participants with more types of childhood abuse had higher BMI levels



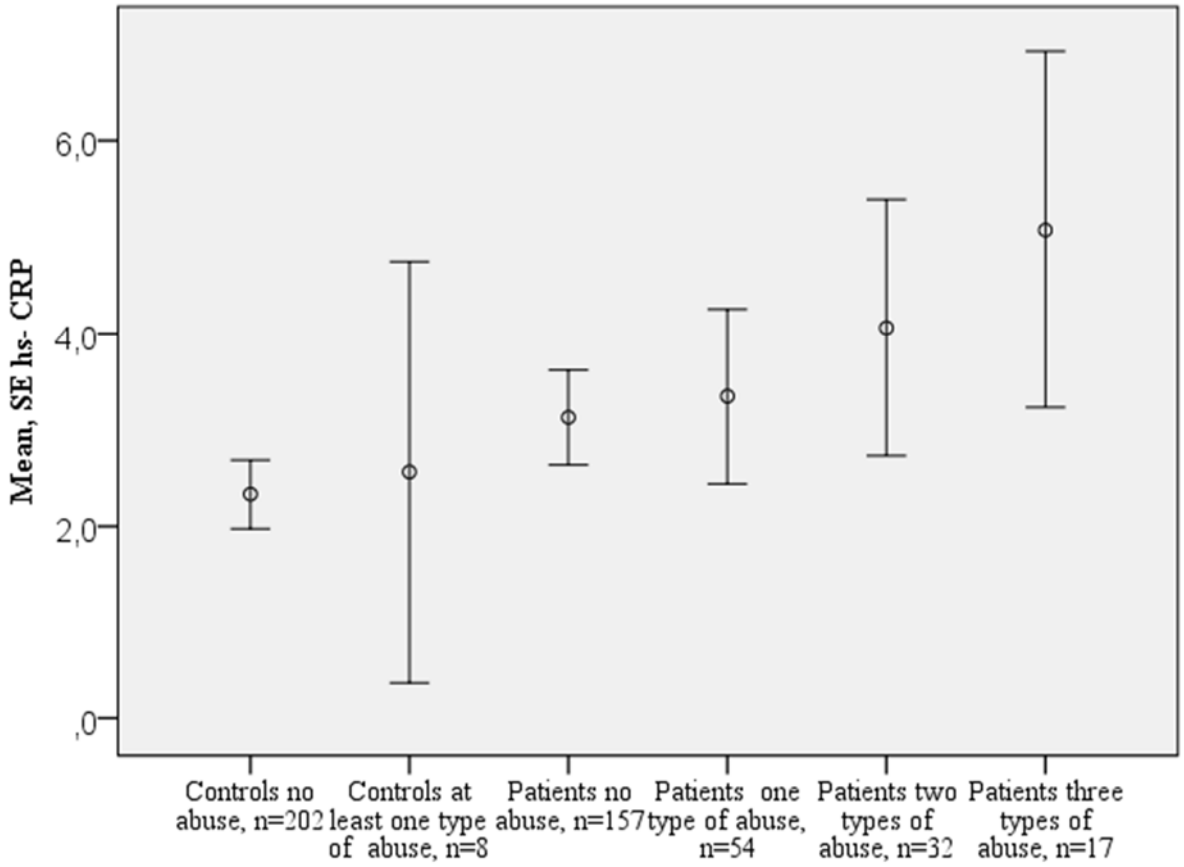
Mean, SE. f=8.46, *P*<0.001. No abuse, N=359; one type of abuse, N=61; two types of abuse, N=33; three types of abuse subtypes, N=17.

Figure 2: Participants with higher number of different types of childhood trauma have higher hs-CRP levels



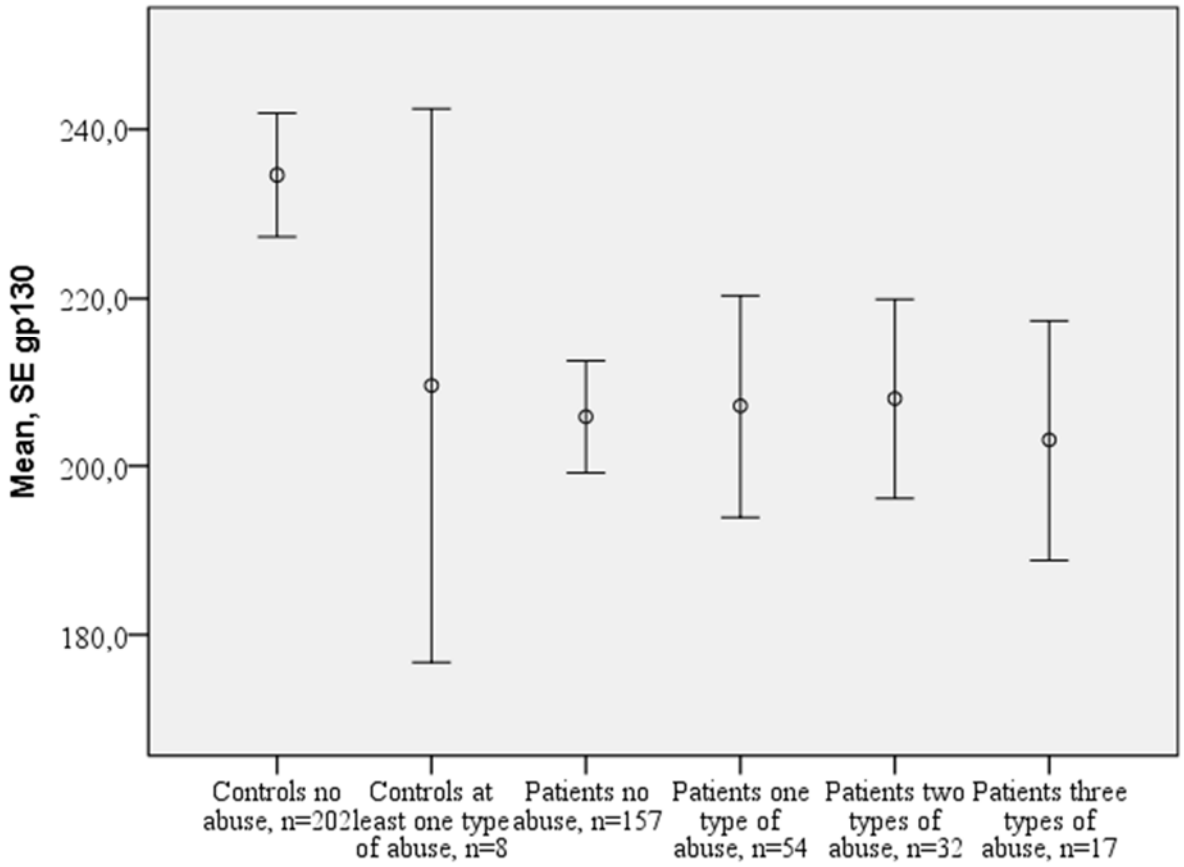
Mean, S.E. f=5.47, *P*<0.001. No abuse, N=359; one type of abuse, N=61; two types of abuse, N=33; three types of abuse subtypes, N=17.

Figure 3: Combined effects of patient status and childhood abuse severity on elevated hs-CRP



Controls no abuse, n=202, controls at least one type of abuse, n=8, patients no abuse, n=157, patients one type of abuse, n=54, patients two types of abuse, n=32, patients three types of abuse, n=17.

Figure 4: Controls without abuse had the highest gp130



Controls no abuse, n=202, controls with at least one type of abuse, n=8, patients no abuse, n=157, patients with one type of abuse, n=54, patients two types of abuse, n=32, patients three types of abuse, n=17.

Table 1: Demographics divided into schizophrenia, bipolar disorders and healthy controls

	Schizophrenia, SZ (n=148)	Bipolar disorders BD (n=123)	Healthy individuals HCs (n=212)	Statistics	Post-Hoc Analysis
Age (mean±SD)[1]	28.6±9.3	32.2±11.7	30.9±7.5	F=5.46, df=2, p=0.004	SZ< BD and HCs
sex, M (%)/F (%) [2]	88 (59.0)/55(41.0)	50 (41)/73 (59)	122 (59)/86 (41.0)	X^2=12.68, df =2, p=0.002	BD>F than SZ and HCs
Physical abuse, median (min-max) mean±SD[3-4]	5 (5-25) 7.0±3.5	5 (5-25) 6.5±3.4	5 (5-11) 5.1±0.6	X^2 =84.08, df=2, p<0.001	HCs< SZ and BD
Sexual abuse, Median (min-max) mean±SD[3-4]	5 (5-21) 6.8±3.4	5 (5-25) 6.8±3.9	5 (5-11) 5.1±0.6	X^2 =54.40, df=2, p<0.001	HCs< SZ and BD
Emotional abuse, median (min-max) mean±SD[3-4]	10 (5-25)11.4±5.2	9 (5-24) 10.1±4.7	5 (5-19) 6.3±2.1	X^2 =144.31, df=2, p<0.001	HCs< SZ and BD
Hs-CRP, median (min-max) mean±SD [1]	2.4(0.2-12.9)3.4±3.2	1.7 (0.2- 13.7)3.3±3.4	1.2 (0.2-13.5)2.3.±2.5	F =7.6, df=2, p=0.001	HCs< SZ and BD
BMI, median (min-max) mean±SD [1]	25.9 (15.8-45.1)26.3±5.5	25.6 (18.4-42.5) 25.8±4.3	23.5 (16.9-38.6) 24.0±3.4	F =12.3, df=2, p<0.001	HCs< SZ and BD
sTNFR1, median (min-max) mean±SD [1]	1.7 (0.17-4.45)1.8±0.6	1.6(0.14-4.59)1.8±0.7	1.8 (0.89-6.23)1.95±0.75	F=2.1, df=2, p=0.13	N.S
GP130, median (min-max) mean±SD [1]	200.9 (128.33-358.10) 206.9±42.4	201.5 (141.1-419.3) 206.4±43.7	230.6 (43.1-400.9) 234.0±51.7	F =20.0, df=2, p<0.001	HCs>SZ and BD
DDD[5]	1.0.±1.3	0.9±0.7		*t*=0.68, p=0.50	N.S

*1= ANOVA; 2=Chi square test; 3=Kruskal-Wallis Test; 4=Mann-whitney-U test. 5=**Defined Daily Dosage (DDD) antipsychotic medication.***

Table 2: Hs-CRP is higher in participants with childhood trauma and in patients compared to controls

Source	df	Mean Square	F	Sig.	Cohens *d*
Corrected Model	4	51.87	5.91	<0.001	0.5
Intercept	1	1552.75	176.80	<0.001	0.3
Severity of abuse	3	24.32	2.77	0.041	0.2
Group(patient/control)	1	61.61	7.02	0.008	0.2

ANOVA, Dependent variable: hs-CRP; Independent variables: group status (patients/controls) and severity of abuse.

Supplementary Material

Table S1: CTQ moderate to severe cutoff score for abuse

CTQ, Childhood abuse subtypes	Moderate to severe cutoff
Physical abuse	≥10
Sexual abuse	≥8
Emotional abuse	≥13

For estimates of frequencies of childhood abuse we used the moderate to severe predefined cutoff suggested by Bernstein (Bernstein and Fink, 1998).

Table S2: Number of CTQ abuse subtypes

CTQ subtypes	
Zero	359
One	61
Two	33
Three	17

"Zero"=no childhood abuse, n=359; "one"=one type of childhood abuse subtype, n=61; "two"=two types of childhood abuse subtypes, n=33; and "three"=three types of childhood abuse subtypes, n=17

Table S3: Gp130 is significantly different in patients compared to controls

Source	df	Mean Square	F	Sig.
Corrected Model	4	22049.68	10.22	<0.001
Intercept	1	6094155.20	2825.02	<0.001
Severity of abuse	3	238.22	0.11	0.95
Group (patient/control)	1	68414.78	31.72	<0.001