A history of childhood trauma and allostatic load in patients with psychotic disorders with respect to stress coping strategies

Patryk Piotrowski, Dorota Frydecka, Kamila Kotowicz, Bartłomiej Stańczykiewicz, Jerzy Samochowiec, Krzysztof Szczygiel, Błażej Misiak

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ABSTRACT

Elevated allostatic load (AL) index, which is a cumulative measure of biological dysregulations associated with stress exposure, has been demonstrated in patients with psychosis. However, it remains unknown whether a history of childhood trauma (CT) might contribute to elevated AL index in psychosis. Therefore, we aimed to investigate the association between AL index, a history of CT and coping styles in patients with psychotic disorders. Participants were 65 patients with schizophrenia-spectrum disorders and 56 healthy controls (HCs). The AL index was computed based on percentile distributions of 15 biomarkers in HCs. The AL index was significantly higher in patients with psychosis. A history of parental antipathy was associated with elevated AL index in both groups of participants. A history of any categories of CT and sexual abuse were associated with higher AL index only in patients with psychosis. Social diversion (seeking social interactions in case of stressful situations) mediated the association between sexual abuse and the AL index in the group of patients. There was a significant direct effect of sexual abuse on the AL index (this specific CT was associated with higher AL index). However, indirect effect of sexual trauma on AL through social diversion was opposite to direct effect. Childhood adversities, especially sexual abuse and parental antipathy, might contribute to elevated AL index in patients with psychosis. The effect of sexual abuse on the AL index might be specific to psychosis. Engagement in social interactions in case of stressful situations might alleviate biological dysregulations associated with CT.

1. Introduction

It has been reported that childhood traumatic events may play a role in the development of psychotic disorders (Misiak et al., 2017a). Childhood traumatic events are reported by around one third of patients with psychosis and are recognized as one of well-established risk factors for psychosis development (Bonoldi et al., 2013; Millan et al., 2017; Varese et al., 2012). Moreover, several studies have shown that patients with psychosis and a history of childhood trauma tend to present with a higher severity of positive symptoms (Bailey et al., 2018) and unfavourable functional outcomes (Palmer-Claus et al., 2016). However, it should be noted that early-life stress also contributes to the development of other mental disorders and there is a considerable number of patients with psychosis who do not report a history of childhood adversities. For instance, a recent meta-analysis revealed that although a history of any childhood trauma is significantly more prevalent among individuals at ultra-high risk (UHR) of psychosis, it is not associated with transition to psychosis, suggesting that trauma alone is not a sufficient risk factor for the development of psychosis (Peh et al., 2019). However, this meta-analysis revealed that sexual abuse might predict the development of psychosis (the effect driven by one large study).

One of potential explanations as to why patients with psychosis might be vulnerable to the effects of early-life stress is related to low capacity of coping with daily stressors (Nuechterlein et al., 1994). However, causality may also be reverse, i.e. early-life stress may lead to using ineffective coping styles. Nevertheless, there are studies showing that patients with psychosis are less likely to adopt active coping styles and prefer avoidant coping (Allott et al., 2015; Corrigan and Toomey, 1995; Horan and Blanchard, 2003; Lysaker et al., 2005; Piotrowski et al., 2019b; Ritsner et al., 2006; Takai et al., 1990; Ventura et al., 2004). This profile of coping styles preferences has been associated with
more severe psychotic and depressive symptomatology (Moritz et al., 2016; Piotrowski et al., 2019b), worse general functioning (Piotrowski et al., 2019b), and more robust cognitive deficits (Stramecki et al., 2019). There is also convincing evidence that maladaptive coping might occur already in the premorbid phase of psychosis (Mian et al., 2018). Finally, coping-oriented therapeutic interventions might be beneficial in terms of improving overall, depressive and anxiety symptoms in patients with schizophrenia (Schaub et al., 2016). However, it remains largely unknown as to whether there is any association between early-life stress and coping styles in patients with psychosis.

To date, several biological mechanisms have been proposed to understand the association between early-life stress and psychosis risk. It has been demonstrated that a history of childhood trauma is related to lower levels of brain-derived neurotrophic factor (BDNF) (Theileritis et al., 2014), a pro-inflammatory phenotype (Quide et al., 2018), dysregulation of hypothalamic-pituitary-adrenal (HPA) axis (Seitz et al., 2019) and global DNA hypomethylation (Misiak et al., 2015). However, some of these alterations, including low BDNF levels and increased levels of pro-inflammatory cytokines, have been associated with schizophrenia irrespective of a history of childhood trauma (Green et al., 2011; Miller et al., 2011). These findings suggest that early-life stress might lead to a number of biological dysregulations involved in the pathophysiology of psychosis.

It has been proposed that the allostatic load (AL) concept might be a useful framework capturing biological dysregulations associated with chronic stress (Misiak et al., 2014). The term ‘allostasis’ refers to various mechanisms that are activated in response to stressful stimuli in order to maintain homeostatic stability, and include activation of the HPA axis and the immune-inflammatory mechanisms, release of oxidative stress mediators as well as changes in insulin signalling. Prolonged exposure to mediators of allostasis might exert systemic and detrimental effects, leading to the state of AL (McEwen, 2006) and consequently various diseases related to chronic stress named as the allostatic overload (McEwen and Wingfield, 2003). The AL index has been developed to measure various biological dysregulations associated with chronic stress exposure, and includes cardiovascular, metabolic, endocrine and immune-inflammatory markers (Seeman et al., 2001). It is important to note that the AL index might better predict morbidity and mortality than traditional detection systems (Juster et al., 2010). Recent studies have demonstrated elevated AL index in patients with psychotic disorders at various stages of illness (Berger et al., 2018a; Chiappelli et al., 2017; Misiak et al., 2018a; Nugent et al., 2015; Piotrowski et al., 2019a; Savransky et al., 2017). Moreover, higher AL index has been associated with higher severity of positive and depressive symptoms, worse general functioning (Berger et al., 2018a; Nugent et al., 2015; Savransky et al., 2017), more robust cognitive impairments (Misiak et al., 2018b) and neurostructural alterations (Chiappelli et al., 2017; Savransky et al., 2017; Zhou et al., 2019) in patients with psychosis.

Our group also found that decreased use of active coping styles might contribute to higher AL index in patients with first-episode psychosis (FEP) (Misiak et al., 2018a). Coping can be defined as “the cognitive and behavioural efforts made to master, tolerate, or reduce external and internal demands and conflicts among them” (Folkman and Lazarus, 1980). There is evidence that patients with psychosis are more likely to use avoidance-focused coping and less likely to rely on active coping styles (Piotrowski et al., 2019b; Stramecki et al., 2019). Early-life stress is another important factor that may contribute to elevated AL index in patients with psychotic disorders. Indeed, a history of childhood trauma has been associated with a higher risk of psychosis, unfavourable clinical and functional outcomes of psychotic disorders and more pronounced biological dysregulations related to the pathophysiology of psychosis (for review see (Misiak et al., 2017a)). Therefore, in this study we tested the hypothesis whether childhood adversities might contribute to increased AL index in psychosis and whether this association is influenced by coping strategies.

2. Material and methods

2.1. Participants

Participants were 65 patients with psychotic disorders (39 FEP patients and 26 inpatients with schizophrenia) and 56 healthy controls. They mostly overlapped with the sample described in our previous studies addressing various aspects of the AL concept in psychosis (Misiak et al., 2018a; Piotrowski et al., 2019a). Patients were enrolled at two clinical sites in Poland (Department of Psychiatry at Wroclaw Medical University and Department of Psychiatry at Pomeranian Medical University in Szczecin). All participants were diagnosed using the Operational Criteria for Psychotic Illness (OPCRIT) checklist according to the DSM-IV criteria (McGuffin, 1991). The following diagnoses were established in patients with FEP: schizophrenia, schizoaffective disorder, brief psychotic disorder, schizoaffective disorder and delusional disorder.

Clinical manifestation and general functioning on the day of assessment were recorded using the Positive and Negative Syndrome Scale (PANSS), the Montgomery-Asberg Depression Rating Scale (MADRS) and the Social and Occupational Functioning Assessment Scale (SOFAS). The majority of patients were during antipsychotic treatment (there were 3 antipsychotic-naïve FEP) with the total chlorpromazine equivalent dosage (CPZeq) of 373.0 ± 216.5 mg/day. Healthy controls were enrolled through advertisements. They had a negative family history of psychotic and mood disorders. Patients and healthy controls were matched for age, sex and the level of parental education (a proxy measure of socio-demographic status).

2.2. Assessment of childhood trauma

Childhood traumatic events were assessed using the Childhood Experience of Care and Abuse Questionnaire (CECA.Q) (Bifulco et al., 2005). It is a retrospective self-report that records a history of childhood trauma before the age of 17 years. The CECA.Q records various childhood adversities, including parental loss (any death of mother or father or any continuous separation of at least one year), parental anti- affect and neglect, physical as well as sexual abuse. It has good psychometric properties and has been validated in the population of patients with psychosis (Fisher et al., 2011). Internal consistency for the CECA.Q in our sample was acceptable or good (Cronbach’s alpha was as follows: 0.854 for maternal anti-affect, 0.783 for maternal neglect, 0.846 for paternal anti-affect and 0.840 for paternal neglect).

2.3. Assessment of coping styles

Coping strategies were evaluated using the Coping Inventory for Stressful Situations (CISI) (Endler and Parker, 1990). The CISI consists of 48 items that are based on a 5-point Likert scale, and recognizes three specific strategies: task-focused coping (refers to taking direct actions to reduce the level of stress), emotion-focused coping (limiting responses to stress by focusing on emotional arousal) and avoidance-focused coping (engagement in activities that do not lead to deal with the stressor). The latter one includes two subscales (distraction and social diversion). Social diversion is defined as seeking social interactions in case of stressful experiences). Distraction refers to engagement in other activities to avoid dealing with stress. Higher scores indicate a higher frequency of using specific coping strategies. The Cronbach’s alpha for the CISI in our sample was 0.871.

2.4. Allostatic load

The AL index was computed based on percentile distribution of 15 biomarkers in healthy controls according to a widely accepted approach (Berger et al., 2018a; Chen et al., 2012). These biomarkers represented the following parameters: 1) anthropometric measures: body-mass...
index (BMI) and waist-to-hip ratio (WHR); 2) cardiovascular markers: systolic and diastolic blood pressure; 3) lipids: total cholesterol, low- and high-density lipoproteins (LDL and HDL) and triglycerides; 4) glucose homeostasis parameters: glucose and insulin; 5) neuroendocrine markers: cortisol and dehydroepiandrosterone sulfate (DHEA-S) and 6) immune-inflammatory markers: high-sensitivity C-reactive protein (hsCRP), fibrinogen and albumin. A detailed description of laboratory procedures and the method of calculating the AL index was provided in our previous study (Misiak et al., 2018a).

Briefly, the 75th percentile for HDL and albumin was determined according to the distribution in healthy controls. In case of significant sex differences, percentile cut-offs specific for males and females were calculated. The sum of all markers with the level above 75th percentile (below 25th percentile for DHEA-S, HDL and albumin) in each category (cardiovascular markers, anthropometric measures, inflammatory markers, glucose homeostasis, lipids and steroids) was divided by a total number of markers in each category. Scores from these calculations (mean numbers of dysregulations in specific categories) were summarized to compute the AL index.

2.5. Statistics

Normal distribution of continuous variables was tested using the Kolmogorov-Smirnov test. Group differences in continuous variables were assessed using the Mann-Whitney U test (non-normal distribution) or the t-test (normal distribution). The analysis of co-variance (ANCOVA) was performed to test the effect of diagnostic group (psychosis vs. healthy controls) and a history of specific childhood adversities on the AL index. The number of education years and CPZeq were added as co-variates. The CPZeq was added due to previously reported effects of antipsychotic treatment on the AL index (Berger et al., 2018a). The ANCOVA was also used to test differences in the AL index between patients and healthy controls to control for the effects of age, CPZeq and cigarette smoking status. In turn, the number of education years was included due to significant between-group differences in educational attainment. Bivariate correlations were tested using the Spearman’s rank correlation coefficients. Mediation analysis was performed using the PROCESS macro and was based on model 4 (Hayes, 2017). The scores of the PANSS subscales (positive and negative symptoms) and MADRS were added as covariates. The bootstrap estimation with 5000 samples was used to assess indirect effects. The Monte Carlo method was used to perform a post-hoc power analysis (Selig and Preacher, 2008). Mediation was considered significant if the 95% CI of indirect effect did not include zero (Preacher and Hayes, 2008). In other analyses, p < 0.05 was considered significant. Data analysis was performed using the Statistical Package for Social Sciences, version 20 (SPSS Inc., Chicago, Illinois, USA).

3. Results

General characteristics of our sample were presented in Table 1. As expected, patients with psychosis presented with significantly lower number of education years, higher rates of cigarette smoking and lower levels of general functioning. A history of any childhood traumatic events, physical and sexual abuse was significantly more frequent in patients with psychosis. Patients with psychosis had significantly higher scores of distraction and lower scores of task-focused coping. Finally, the AL index was significantly higher in the group of patients compared to healthy controls. Further stratification of the sample revealed that the AL index was significantly higher in multiple-episode schizophrenia patients compared to FEP patients (2.65 ± 1.02 vs. 1.83 ± 0.99, p = 0.003) and healthy controls (2.65 ± 1.02 vs. 1.16 ± 0.96, p < 0.001). Similarly, patients with FEP had significantly higher AL index than healthy controls (1.83 ± 0.99 vs. 1.16 ± 0.96, p = 0.002) (Fig. 1). These differences remained significant (F = 6.88, p = 0.002) after covarying for age (F = 5.56, p = 0.020), CPZeq (F = 1.34, p = 0.249) and cigarette smoking status (F = 2.07, p = 0.153).

The ANCOVA models testing for differences in the AL index with respect to a history of childhood trauma were shown in Table 2. There was a significant main effect of parental antipathy on the AL index that appeared to be higher in participants who experienced this category of childhood adversities in comparison with those who did not. A significant effect of diagnostic group on the AL index was present in the models including a history of physical and sexual abuse (the AL index was higher in patients with psychosis compared to healthy controls). There was a significant effect of interaction between childhood adversities and diagnostic group on the AL index in the models with a history of sexual abuse and any traumatic events. Higher AL index in individuals who experienced these categories of childhood adversities compared to those who did not was found in the group of patients with psychosis but not in healthy controls.

A history of sexual abuse was associated with significantly higher scores of social diversion in patients with psychosis, while a history of parental neglect was related to significantly higher scores of task-focused coping in healthy controls (Table 3). There was a significant negative correlation between the scores of social diversion and the AL index in patients with psychosis. Due to significant associations between childhood sexual, social diversion and the AL index in patients with psychosis, we tested the hypothesis whether social diversion mediates the association between a history of sexual abuse and the AL index. Results of mediation analysis were shown in Fig. 2. There was a significant and positive direct effect of sexual abuse on the AL index. Social diversion mediated the effect of sexual abuse on the AL index. However, indirect effect (through social diversion) was opposite to direct effect. The effects of co-variates (scores of the PANSS subscales and the MADRS) were non-significant. Our sample had a power of 0.68 to detect significant mediation in this model.

4. Discussion

This study confirmed elevated AL index and a higher frequency of various childhood adversities in patients with psychosis (Berger et al., 2018a; Chiappelli et al., 2017; Misiak et al., 2018a; Nugent et al., 2015; Piotrowski et al., 2019a; Savransky et al., 2018). The AL index appeared to be elevated in both subgroups of patients – multiple-episode schizophrenia patients and FEP patients. Moreover, the AL index was significantly higher in multiple-episode schizophrenia patients compared to FEP patients. This difference can be explained by several factors, including comorbid physical health impairments that tend to be more prevalent in chronic patients, medication effects or accumulating stressors (for more detailed discussion see (Piotrowski et al., 2019a)). At this point, it is important to note that the AL index in patients with psychosis was relatively lower compared to previous studies. This difference can be attributed to medication effects or lower severity of psychopathological symptoms in our sample.

For the first time, we report a significant relationship between a history of childhood trauma and the AL index in patients with psychotic disorders. More specifically, we found that parental antipathy might contribute to higher AL index in patients with psychosis and healthy controls. However, the effect of any childhood adversities and sexual abuse on the AL index appeared to be significant in patients with psychosis but not in healthy controls. These findings are in agreement with previous studies showing the association between a history of childhood adversities and the AL index in clinical and non-clinical populations (for review see (Danese and McEwen, 2012)). Although all categories of childhood trauma have been associated with psychosis risk, there are studies showing differential effects of childhood adversities on biological alterations related to stress exposure (Shrivastava et al., 2017). For instance, a recent meta-analysis revealed that sexual and physical abuse is related to significantly higher levels of interleukin(IL)-6 and tumour necrosis factor-α (TNF-α) but not CRP (Baumeister et al., 2016). Moreover, it has been demonstrated that the relationship
Significant differences (p < 0.05) were marked with bold characters.

Table 1
General characteristics of the sample.

|                      | Psychosis, n = 65 | HCs, n = 56 | p     |
|----------------------|-------------------|-------------|-------|
| Age, years           | 34.0 ± 12.9       | 34.0 ± 29.6 | 0.097 |
| Sex, M/F (%)         | 30 (46.2)/35 (53.8) | 17 (30.4)/39 (69.6) | 0.075 |
| Education, years     | 13.4 ± 2.7        | 16.0 ± 2.4  | < 0.001 |
| Maternal education, higher/other than higher (%) | 16 (24.6)/49 (75.4) | 17 (30.4)/39 (69.6) | 0.500 |
| Paternal education, higher/other than higher (%) | 14 (21.5)/51 (78.5) | 15 (26.8)/41 (73.2) | 0.479 |
| Smoking, yes/no (%)  | 28 (43.1)/37 (56.9) | 5 (9.0)/51 (81.0) | < 0.001 |
| PANSS-P              | 13.7 ± 5.1        | –           | –     |
| PANSS-N              | 20.0 ± 9.1        | –           | –     |
| MADRS                | 8.1 ± 7.5         | –           | –     |
| SOFAS                | 48.1 ± 14.2       | 96.2 ± 5.6  | < 0.001 |
| GAF                  | 47.9 ± 16.8       | –           | –     |
| Parental loss, yes/no (%) | 18 (27.7)/47 (72.3) | 12 (21.4)/44 (78.6) | 0.426 |
| Parental antipathy, yes/no (%) | 14 (21.5)/51 (78.5) | 10 (17.9)/46 (82.1) | 0.613 |
| Parental neglect, yes/no (%) | 9 (16.1)/56 (83.9) | 10 (17.9)/46 (82.1) | 0.545 |
| Physical abuse, yes/no (%) | 26 (40.0)/39 (60.0) | 13 (23.2)/43 (76.8) | 0.049 |
| Sexual abuse, yes/no (%) | 11 (16.9)/54 (83.1) | 3 (5.4)/53 (94.6) | 0.047 |
| Any childhood trauma, yes/no (%) | 44 (67.7)/21 (32.3) | 28 (50.0)/28 (50.0) | 0.048 |
| Task-focused coping   | 54.3 ± 12.3       | 60.4 ± 8.7  | 0.003 |
| Emotion-focused coping| 43.85 ± 13.3      | 41.2 ± 12.1 | 0.355 |
| Distraction          | 21.3 ± 5.9        | 16.5 ± 5.6  | < 0.001 |
| Social diversion     | 16.5 ± 4.9        | 16.7 ± 3.5  | 0.829 |
| AL index             | 2.1 ± 1.1         | 1.2 ± 1.0   | < 0.001 |

Abbreviations: AL – allostatic load, GAF – the General Assessment of Functioning, MADRS – the Montgomery-Asberg Depression Rating Scale, PANSS-N – the Positive and Negative Syndrome Scale – negative symptoms, PANSS-P – the Positive and Negative Syndrome Scale – positive symptoms, SOFAS – the Social and Occupational Functioning Assessment Scale.

Fig. 1. Differences in the AL index between first-episode psychosis (FEP) patients, multiple-episode schizophrenia patients (SCZ) and healthy controls. Error bars represent 95 %CI.

between a history of childhood trauma and higher BMI together with CRP in patients with FEP is specific to sexual abuse (Heppul et al., 2012). Similarly, the study by Theleritis et al. (2014) revealed that physical and sexual abuse, separation from either parent, but not death of either parent and being taken into local authority care, are associated with lower BDNF levels in patients with psychosis and healthy controls.

Importantly, previous studies have shown that recent and lifetime stressors are not related to elevated AL index in patients with psychotic disorders (Misiak et al., 2018a; Nugent et al., 2015; Piotrowski et al., 2019a). Therefore, it might be concluded that only early-life stress might lead to robust and lasting biological dysregulations. According to the neural-diathesis stress model, psychosocial stressors act upon a pre-existing vulnerability to psychosis (Walker and Diforio, 1997). It has been proposed that childhood adversities, ineffective coping and subsequent stressors may further affect critical periods of brain development (Davis et al., 2016). In this regard, it is not surprising that stressors appearing in the preceding month, assessed by means of the Perceived Stress Scale (Cohen et al., 1983), were not associated with the AL index. At this point, it is important to note that a lack of association between any childhood traumatic events and time of transition from the UHR state to psychosis, does not preclude the effect of early-life stress on psychosis risk in this population (Peh et al., 2019). Moreover, the effect of sexual abuse on time to transition, although driven by a single large study (Thompson et al., 2014), was observed in this meta-analysis. It is important to note that several limitations of studies in this field need to be taken into account. These include a heterogeneity of measures used to assess childhood trauma, possible role of timing and severity of exposure, differences in duration of longitudinal studies and potential additive effects of early-life stressors and other vulnerabilities. These factors should also be considered in future studies investigating the association between a history of childhood trauma and the AL index in psychosis.

Our findings suggest that patients with psychosis might be particularly vulnerable to the effects of childhood trauma on the AL index either due to increased exposure to early-life stress or specific intrinsic mechanisms. Indeed, our group has recently demonstrated elevated AL index in patients with FEP and individuals at familial high risk of psychosis (Piotrowski et al., 2019a). The AL index was similar in these two groups of participants. There is also evidence that relatives of patients with schizophrenia show increased emotional reactivity to daily stressors, increased adrenocorticotropic hormone response to stress, increased pituitary volume and reduced hippocampal volume (Aiello et al., 2012). Moreover, combined effects of childhood maltreatment together with a diagnosis of schizophrenia and bipolar disorder on CRP levels have also been reported (Aas et al., 2017). Finally, it should be
to our own termed as the AL index in patients with psychosis. This phenomenon has been case of stressful events) might suppress the impact of sexual abuse on stress through social diversion (engagement in social interactions in coping (Allott et al., 2015; Corrigan and Toomey, 1995; Horan and avoidance-focused coping styles and are less likely to use task-focused coping (Allott et al., 2015; Corrigan and Toomey, 1995; Horan and Blanchard, 2003; Lysaker et al., 2005; Piotrowski et al., 2019b; Ritsner et al., 2006; Takai et al., 1990; Ventura et al., 2004). Moreover, in our previous analysis of data from the sample overlapping with the one reported in this study, we found that higher AL index is related to worse social functioning measured by the SOFAS. Interestingly, the study by Berger et al. (2018b), which also used the SOFAS, revealed that higher baseline AL index predicted worse general functioning in individuals at ultra-high risk of psychosis after 6 months.

| Table 3 |

Importantly, our mediation analysis demonstrated that coping with stress through social diversion (engagement in social interactions in case of stressful events) might suppress the impact of sexual abuse on the AL index in patients with psychosis. This phenomenon has been termed as ‘inconsistent mediation’ (MacKinnon et al., 2007). As similar previous analysis of data from the sample overlapping with the one reported in this study, we found that higher AL index is related to worse social functioning measured by the SOFAS. Interestingly, the study by Berger et al. (2018b), which also used the SOFAS, revealed that higher baseline AL index predicted worse general functioning in individuals at ultra-high risk of psychosis after 6 months.

However, little is known about the association between coping styles and the AL index. In the population-based study by Fernandez

Abbreviations: AL – allostatic load, CPZeq – chlorpromazine equivalent dosage, HCs – healthy controls. Significant effects (p < 0.05) were marked with bold characters.

| Table 2 |

Allostatic load index with respect to a history of childhood adversities.

| Parental loss | Group | Trauma | Group × trauma | CPZeq | Education years |
|---------------|-------|--------|----------------|-------|----------------|
| yes | F = 3.73 | F = 0.17 | F = 3.26 | F = 1.31 |
| no | F = 0.04 | p = 0.07 | p = 0.25 |
| Parental antipathy | F = 0.02 | p = 0.01 | p = 0.04 |
| yes | F = 5.22 | F = 1.68 | F = 2.27 | F = 1.50 |
| no | F = 0.61 | p = 0.04 | p = 0.02 |
| Parental neglect | F = 0.00 | p = 0.01 | p = 0.01 |
| yes | F = 0.33 | F = 1.50 | F = 3.26 | F = 1.50 |
| no | F = 0.33 | p = 0.01 | p = 0.01 |
| Physical abuse | F = 5.12 | F = 1.50 | F = 2.46 | F = 1.50 |
| yes | F = 0.65 | p = 0.04 | p = 0.02 |
| no | F = 0.65 | p = 0.04 | p = 0.02 |
| Sexual abuse | F = 0.96 | F = 0.02 | F = 0.02 |
| yes | F = 0.96 | p = 0.02 | p = 0.02 |
| no | F = 0.96 | p = 0.02 | p = 0.02 |
| Any childhood adversities | F = 0.96 | F = 0.02 | F = 0.02 |
| yes | F = 0.96 | p = 0.02 | p = 0.02 |
| no | F = 0.96 | p = 0.02 | p = 0.02 |

Significant differences and correlations (p < 0.05) were marked with bold characters.

Abbreviations: AL – allostatic load, HCs – healthy controls. Significant effects (p < 0.05) were marked with bold characters.

| Table 4 |

Coping styles, a history of childhood trauma and the AL index.

| Psychosis | HCs |
|-----------|-----|
| Task-focused coping | Emotion-focused coping | Distraction | Social diversion | Task-focused coping | Emotion-focused coping | Distraction | Social diversion |
| Parental loss | 56.1 ± 8.4 | 46.3 ± 14.3 | 22.4 ± 5.4 | 17.2 ± 4.2 | 61.3 ± 7.5 | 43.3 ± 12.5 | 15.8 ± 4.9 | 16.6 ± 3.1 |
| yes | F = 0.11 | p = 0.80 | p = 0.80 | p = 0.80 | p = 0.80 | p = 0.80 | p = 0.80 | p = 0.80 |
| no | 53.5 ± 13.6 | 43.0 ± 12.9 | 21.0 ± 6.1 | 19.2 ± 5.3 | 60.1 ± 9.0 | 41.2 ± 12.1 | 16.7 ± 5.8 | 16.7 ± 3.7 |
| Parental antipathy | 58.6 ± 13.6 | 49.1 ± 11.1 | 23.0 ± 4.7 | 15.4 ± 3.5 | 58.4 ± 9.4 | 49.9 ± 9.0 | 17.7 ± 4.3 | 16.9 ± 3.9 |
| yes | F = 0.02 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 |
| no | 53.0 ± 11.7 | 42.3 ± 13.6 | 20.8 ± 6.2 | 16.9 ± 5.3 | 60.8 ± 8.6 | 40.7 ± 12.6 | 16.2 ± 5.9 | 16.9 ± 3.5 |
| Parental neglect | 55.1 ± 12.9 | 47.1 ± 15.1 | 20.6 ± 6.2 | 15.4 ± 4.9 | 65.4 ± 8.6 | 41.4 ± 11.8 | 14.6 ± 4.8 | 18.1 ± 4.4 |
| yes | F = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 |
| no | 54.1 ± 12.3 | 43.3 ± 13.1 | 21.4 ± 5.9 | 16.7 ± 5.0 | 59.3 ± 8.4 | 41.7 ± 12.3 | 16.9 ± 6.0 | 16.4 ± 3.3 |
| Physical abuse | 55.7 ± 11.6 | 47.2 ± 13.5 | 21.2 ± 6.2 | 17.2 ± 4.3 | 60.0 ± 11.2 | 44.5 ± 13.4 | 18.9 ± 5.5 | 16.3 ± 3.6 |
| yes | F = 0.02 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 |
| no | 53.3 ± 12.7 | 41.5 ± 12.9 | 21.4 ± 5.7 | 16.1 ± 5.4 | 60.5 ± 7.9 | 40.9 ± 11.8 | 15.8 ± 5.5 | 16.8 ± 3.5 |
| Sexual abuse | 55.3 ± 12.4 | 45.2 ± 18.2 | 22.5 ± 4.4 | 20.5 ± 4.2 | 53.3 ± 1.5 | 49.7 ± 8.1 | 36.7 ± 4.5 | 17.3 ± 2.9 |
| yes | F = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 |
| no | 54.1 ± 12.4 | 43.6 ± 12.4 | 21.1 ± 6.1 | 18.8 ± 4.7 | 60.8 ± 8.7 | 41.2 ± 12.2 | 40.9 ± 8.7 | 16.5 ± 3.6 |
| AL index | r = 0.210 | r = 0.034 | r = 0.033 | r = 0.027 | r = 0.125 | r = 0.120 | r = 0.120 | r = 0.120 |
| yes | F = 0.02 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 | p = 0.01 |
| no | 54.4 ± 11.0 | 44.7 ± 13.8 | 21.4 ± 5.5 | 16.4 ± 4.8 | 60.1 ± 8.7 | 43.6 ± 12.4 | 17.1 ± 5.3 | 16.5 ± 3.4 |
| r = 0.013 | p = 0.080 | p = 0.082 | p = 0.035 | p = 0.373 | p = 0.393 | p = 0.754 | p = 0.186 |
et al. (2015), disengagement coping was related to significantly higher AL index in females. Previous studies have also shown that positive social experiences might be associated with lower AL index (Seeman et al., 2002). Social support may moderate genetic and environmental vulnerabilities as well as confer resilience to stress (Ozbay et al., 2008; Taylor, 2010). In both animal and human studies, social support and social contact are reliable and significant predictors of health outcomes, with effect sizes in humans on par with smoking status and the levels of lipids (Taylor, 2010). Social support has been shown to be protective factor that may be able not only to buffer against but even reverse negative stress influences (Holz et al., 2019). In animal studies “social buffering” has been linked to lower increase in cortisol and prolactin, lower immune reactivity and smaller brain neural activity in brain structures associated with stress response (for review see (Kikusui et al. 2006)). In humans, low social support has been linked to stress-related elevated heart rate (Stansfeld et al., 1997) and increased blood pressure (Lepore et al., 1993; Stansfeld et al., 1997), increased noradrenergic and HPA axis reactivity (Steptoe et al., 2004; Taylor et al., 2008), as well as heightened pro-inflammatory cytokine activity (Chiang et al., 2012). Recent studies show that social support influence psychological and physiological responses by modulating neural reactivity to stress (for review on regulatory neural brain circuits linked to stress resilience due to social support see (Holz et al., 2019)). Finally, social support has been shown to mediate negative consequences of perceived stress in individuals exposed to sexual violence (Catabay et al., 2019; Hébert et al., 2014). However, it remains unknown as to why mediation effect reported in our study appeared only in the group of patients with psychosis.

Certain limitations of our study need to be acknowledged. Firstly, our sample was not large and thus type I error cannot be excluded. At is point, low statistical power of detecting significant mediation in our sample should be taken into consideration. Therefore, we were not able address our findings separately in multiple-episode schizophrenia patients and FEP patients. Secondly, comparability of our results to those from other studies is limited due to a lack of general consensus, which specific biomarkers should be included in the AL index. However, Berger et al. (2018a,b) have shown that the use of the 10-biomarker AL index pioneered by Seeman et al. (2001) and the 24-biomarker AL index used in their study can provide similar results. Thirdly, although we controlled for the total CPZeq, medication effects cannot be excluded as observational studies revealed that the AL index decreases with antipsychotic treatment (Berger et al., 2018a). Another important point is that assessment of childhood adversities was limited to self-reports that might be characterized by a recall bias; however, they are widely used by similar studies. Finally, a cross-sectional study design does not allow to conclude regarding direction of causality.

In summary, results of this study indicate that childhood adversities, especially sexual abuse and parental antipathy, might contribute to systemic biological dysregulations captured by the AL index in patients with psychotic disorders. It is of great importance that patients with psychosis might be more vulnerable to the effects of early-life stress. However, this hypothesis needs further confirmation in large, longitudinal cohort studies. Furthermore, our findings imply that engagement in social interactions in case of stressful situations might alleviate biological dysregulations associated with traumatic stress. This observation holds a great promise for personalizing therapeutic interventions in patients with psychosis.

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**Declaration of Competing Interest**

None.

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