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How childhood adversities shape minds and lives: An analysis across the affective-to-psychotic spectrum

Sophie-Kathrin Greiner [a,b,*], María Dech Pons [c], Ayimnisagul Ablimit [c], Elisa Brauße [c], Kristina Adorjan [b,d,e], Monika Budde [d], Maria Heilbronner [d], Urs Heilbronner [d], Janos L. Kalman [b,d], Alba Navarro-Flores [d,f], Mojtaba Oraki Kohshour [d,g], Daniela Reich-Erkelenz [b,d], Eva C. Schulte [b,d,i], Thomas Vogl [d], Till Andlauer [j], Ion-George Anghelescu [k], Volker Arolt [l], Bernhardt T. Baune [m,n,o], Udo Dannlowski [l], Franziska Degenhardt [p,q], Detlef E. Dietrich [r,s,t], Andreas J. Fallgatter [u,v], Christian Figge [w], Andreas Forstner [i,x], Markus Jäger [y,z], Georg Juckel [aa], Carsten Konrad [ab], Markus M. Nöthen [i], Fabian U. Lang [y], Jens Reimer [ac,ad], Eva Z. Reinighaus [ae], Marcella Rietschel [af], Max Schmauß [a], Andrea Schmitt [b,h,ag,ah], Simon Senner [ai], Carsten Spitzer [aj], Jens Wiltfang [ak,al,am], Stephanie H. Witt [af], Jörg Zimmermann [an], Alkomiet Hasan [a,ag], Peter Falkai [b,ag,ah], Thomas G. Schulze [d,ag,ao,ap], Sergi Papiol [b,d,ah], Fanny Senner [b,d,aq]

[a] *Department of Psychiatry, Psychotherapy, and Psychosomatics, Faculty of Medicine, University of Augsburg, Augsburg, Germany*
[b] *Department of Psychiatry and Psychotherapy, LMU University Hospital, LMU Munich, Munich, Germany*
[c] *Cognitive Systems Lab, Mathematics and Computer Science, University of Bremen, Bremen, Germany*
[d] *Institute of Psychiatric Phenomics and Genomics (IPPG), LMU University Hospital, LMU Munich, Munich, Germany*
[e] *University Hospital of Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland*
[f] *International Max Planck Research School for Translational Psychiatry (IMPRS-TP), Munich, Germany*
[g] *Department of Immunology, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
[h] *Laboratory of Neuroscience (LIM27), Institute of Psychiatry, University of Sao Paulo, São Paulo, SP, Brazil*
[i] *Institute of Human Genetics, University Hospital Bonn, Faculty of Medicine, University of Bonn, Bonn, Germany*
[j] *Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany*
[k] *Department of Psychiatry and Psychotherapy, Mental Health Institute Berlin, Berlin, Germany*
[l] *Institute for Translational Psychiatry, University of Münster, Münster, Germany*
[m] *Department of Psychiatry, University of Münster, Münster, Germany*
[n] *Department of Psychiatry, Melbourne Medical School, The University of Melbourne, Melbourne, Australia*
[o] *The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC, Australia*
[p] *Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany*
[q] *Department of Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy, University of Essen, University of Duisburg-Essen, Duisburg, Germany*
[r] *AMEOS Clinical Center Hildesheim, Hildesheim, Germany*
[s] *Center for Systems Neuroscience (ZSN), Hannover, Germany*
[t] *Department of Psychiatry, Social Psychiatry and Psychotherapy, Medical School of Hannover, Hannover, Germany*
[u] *Department of Psychiatry and Psychotherapy, Tübingen Center for Mental Health (TüCMH), University of Tübingen, Tübingen, Germany*
[v] *DZPG (German Center for Mental Health), partner site Tübingen, Tübingen, Germany*
[w] *Karl-Jaspers Clinic, European Medical School Oldenburg-Groningen, Oldenburg, Germany*
[x] *Institute of Neuroscience and Medicine (INM-1), Research Center Jülich, Jülich, Germany*
[y] *Department of Psychiatry II, Ulm University, Bezirkskrankenhaus Günzburg, Günzburg, Germany*
[z] *Bezirkskrankenhaus Kempten, Kempten, Germany*
[aa] *Department of Psychiatry, Ruhr University Bochum, LWL University Hospital, Bochum, Germany*
[ab] *Department of Psychiatry and Psychotherapy, Agaplesion Diakonieklinikum, Rotenburg, Germany*
[ac] *Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*
[ad] *Center for Psychosocial Medicine, Academic Hospital, Itzehoe, Germany*
[ae] *Division of Psychiatry and Psychotherapeutic Medicine, Research Unit for Bipolar Affective Disorder, Medical University of Graz, Graz, Austria*

* Corresponding author.
E-mail address: Sophie-Kathrin.Greiner@bkh-augsburg.de (S.-K. Greiner).

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[af] Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany
[ag] German Center for Mental Health (DZPG), partner site Munich/Augsburg, Germany
[ah] Max Planck Institute of Psychiatry, Munich, Germany
[ai] Center for Psychiatry Reichenau, Academic Hospital University of Konstanz, Konstanz, Germany
[aj] Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Rostock, Rostock, Germany
[ak] Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany
[al] German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany
[am] Neurosciences and Signaling Group, Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveiro, Aveiro, Portugal
[an] Psychiatrieverbund Oldenburger Land gGmbH, Karl-Jaspers-Klinik, Bad Zwischenahn, Germany
[ao] Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, NY, USA
[ap] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[aq] Centres for Psychiatry Suedwuerttemberg, Ravensburg, Germany

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ABSTRACT

Adverse childhood experiences (ACE) contribute significantly to mental disorders. While existing research has primarily focused on specific diagnostic categories, a comprehensive understanding of how childhood trauma interacts with biological factors, symptom severity and functioning requires a broader perspective. Therefore, this study adopted a cross-diagnostic approach to examine the impact of ACE on quality of life (QoL), psychosocial functioning, and symptom burden by analyzing data from the PsyCourse Study, a longitudinal, multicenter research project conducted in Germany and Austria. We used multivariate linear regression models and cluster analysis to evaluate data from 725 participants with affective and psychotic disorders and healthy controls who completed the self-assessed Childhood Trauma Screener (CTS) during the course of the study. The results showed that across diagnoses, QoL was significantly impacted by ACE, particularly emotional neglect. An ablation study revealed that 2.3 % to 6.2 % of the variability in QoL domains could be attributed to ACE. Across diagnoses, symptoms of depression were significantly associated with ACE, especially emotional abuse, but psychotic and manic symptoms were not. Polygenic risk scores (PRS) did not emerge as significant predictors for any examined outcomes. Cluster analysis revealed distinct symptom profiles: Averaged over time, patients with less trauma exposure were rather in the subclinical than in the clinically ill clusters. We conclude that the pervasive influence of ACE on disease severity should be considered when evaluating and treating patients with affective and psychotic disorders.

1. Introduction

A comprehensive mental health survey by the World Health Organization (WHO) suggested that adverse childhood experiences (ACE) contribute significantly to the prevalence of mental disorders worldwide accounting for 29.8 % of cases. 38.8 % of the respondents reported experiences of ACE (Kessler et al., 2010). Similarly in Germany, 43.7 % of the respondents reported experiencing at least one type of ACE (Witt et al. 2019). An umbrella meta-analysis analyzing the impact of childhood trauma transdiagnostically found evidence of an association between childhood trauma and any mental disorder (Hogg et al. 2023).

The etiology of psychotic and affective disorders involves not only biological factors, particularly genetic ones (Visscher et al. 2021; Wray et al. 2014; Murray et al. 2021), but also environmental ones (Heim and Binder 2012). ACE are particularly important environmental factors because the childhood is a critical period of neurodevelopment when the brain and neuroendocrine and immune systems are highly susceptible to internal and external influences (Heim and Binder 2012; Jawahar and Baune 2018). This complex interaction between genes and the environment is central in shaping the risk of these disorders.

Studies evaluating the impact of ACE showed that patients with a history of ACE have a threefold higher risk for developing psychotic and bipolar disorders than those without a history of traumatic experiences (Varese et al. 2012; Palmier-Claus et al. 2016). Furthermore, individuals with ACE tend to experience more severe symptoms, including depressive episodes, lower remission rates, and reduced cognitive performance (M. Aas et al. 2023; Senner et al. 2023; Kessler et al. 2010). ACE can contribute to reduced QoL in patients with bipolar disorder (Rowe, Perich, and Meade 2023). In patients with schizophrenia, ACE are associated with a reduced QoL, more negative and depressive symptoms (Andrianarisoa et al. 2017; Inyang et al. 2022). Evidence for impact of ACE on global functioning across the affective-to-psychotic spectrum is emerging but mixed: A small study in patients with schizophrenia suggests effects on global functioning (De-Nardin et al. 2021), while another study in psychotic patients found only association on social functioning and interpersonal relations, but no impact on independent living or occupational functioning (Fares-Otero et al. 2023). In bipolar disorder, correlational data suggest a relationship between ACE and global functioning impairment, though causality remains to be established (Farias et al. 2019).

In order to fill this research gap, our study adopts a cross-diagnostic approach to examine ACE and polygenic traits in severe mental illness (SMI), which encompasses schizophrenia, bipolar disorder, and major depressive disorder - conditions that can be conceptualized along an affective-to-psychotic spectrum reflecting the continuum from predominantly mood symptoms to predominantly psychotic symptoms (Insel et al. 2010; Reininghaus et al. 2019). Schizophrenia and affective disorders exhibit substantial phenotypical and genetic overlap (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013; Segura et al. 2024; Schulte et al. 2022). While this cross-diagnostic approach acknowledges the potential limitations of strict diagnostic categories, we recognize that examining such a heterogeneous patient sample may yield results that require careful interpretation. Our study primarily investigates the impact of environmental factors (ACE) on cross-diagnostic outcomes (global functioning, quality of life) and symptom dimensions spanning these disorders, while controlling for clinical characteristics (treatment setting, number of medications), demographic factors (age, sex), genetic variables (polygenic risk scores) and diagnostic classifications. This approach allows us to explore shared patterns over time of how the interplay of ACE, clinical trajectories and polygenic traits impact mental health outcomes across diagnostic boundaries - an approach supported by genetic studies showing both disorder-specific and cross-diagnostic components in disease risk (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013; Service et al. 2020).

Given the study's exploratory design, our aim is to generate new insights and potential hypotheses rather than test predetermined hypotheses. We explore three main research questions: (1) What is the

impact of ACE on global functioning and QoL in patients from the affective-to-psychotic spectrum and healthy controls? (2) How do ACE affect psychotic, depressive, and manic symptoms in patients from the affective-to-psychotic spectrum? (3) Do clusters of symptoms exist and, if so, do ACE subtypes vary between the clusters? By answering these questions, we aimed to explore co-occurrences of ACE subtypes and their association with specific symptomatic constellations and thus to obtain a holistic understanding of the impact of ACE on psychiatric outcomes.

2. Materials and methods

2.1. Study participants

The data analyzed in this study were from the PsyCourse Study, a longitudinal, naturalistic, multicenter research project performed in Germany and Austria from 2012 to 2019 (Budde et al. 2019). The PsyCourse Study collected phenotypic and biological data from patients on the affective-to-psychotic continuum, i.e., across diagnostic categories, and from healthy controls. We used the PsyCourse data released on November 2022 (Heilbronner, Urs et al. 2021) and included 725 participants (mean[SD] age, 42.12[13.77] years; 48.5 % female) aged between 18 and 86 years who completed the self-assessed Childhood Trauma Screener (CTS), a short form of the Childhood Trauma Questionnaire (Grabe et al. 2012). Diagnoses were made with parts of the Structured Clinical Interview for DSM-IV (Wittchen, Zaudig, and Fydrich 1997). To rule out the presence of a mental disorder, healthy controls were assessed with the short form of the *Diagnostisches Interview bei psychischen Störungen* (Mini-DIPS) (Margraf 1994). Eligible participants were patients assigned to two broad diagnostic groups: The affective disorders group ($n = 299$) group comprised patients with bipolar disorder I ($n = 214$), bipolar disorder II ($n = 52$), and depression ($n = 33$). The psychotic disorders group ($n = 255$) comprised patients with schizophrenia ($n = 209$), schizoaffective disorder ($n = 41$), schizophreniform disorder ($n = 3$), and brief psychotic disorder ($n = 2$). The third group were healthy controls ($n = 171$). We used a complete case analysis approach, excluding participants ($n = 168$) with missing data. Given our large sample size ($n = 725$ after exclusion), this approach maintained sufficient statistical power.

The PsyCourse Study was approved by all local ethics committees of the different study sites and conformed with the Declaration of Helsinki; all participants gave written informed consent to participate. A detailed description of the study design is available in the publication by Budde et al. (Budde et al. 2019).

2.2. Clinical assessments

The study protocol included extensive phenotypic surveys, self-assessed questionnaires, a collection of biomaterial at four time points over an 18-month period (initial visit plus three follow-up visits after 6, 12, and 18 months). Questionnaires and psychiatric rating scales used in our analyses were assessed in patients and – if applicable – in healthy controls.

2.2.1. CTS

The CTS is a short version of the Childhood Trauma Questionnaire. It contains a self-rated, five-point scale that assesses five types of ACE (range: 5–25; Cronbach's α=0.757): emotional neglect, physical abuse, emotional abuse, sexual abuse, and physical neglect (Grabe et al. 2012). To rate ACE as present or not, we used the individual cut-off values (Glaesmer et al. 2013): emotional neglect (CTS1, threshold ≥4), physical abuse (CTS2, threshold≥3), emotional abuse (CTS3, threshold≥3), sexual abuse (CTS4, threshold≥2), and physical neglect (CTS5, threshold≥4). Participants completed the CTS at visit 3, i.e., the 12-month follow-up visit.

2.2.2. Global assessment of functioning

The Global Assessment of Functioning (GAF) is a clinician-rated instrument that measures psychological, social, and occupational functioning on a continuous scale ranging from one to 100. (I. M. Aas 2011). It represents the last seven days up to and including the day of the interview. Intraclass correlation of 0.79 was obtained for the GAF (Sonesson, Tjus, and Arvidsson 2010). The GAF was assessed in all study participants at all visits.

2.2.3. World health organization quality of life questionnaire, brief version

The self-rated World Health Organization Quality of Life Questionnaire, brief version (WHOQOL-BREF) was used to assess QoL in the previous two weeks in the domains global, physical health, psychological health, social relationships, and environment (α between 0.68 - 0.85) (Oliveira, Carvalho, and Esteves 2016). The score for all domains ranges from a minimum of 4 to a maximum of 20 (The WHOQoL Group 1998). The WHOQOL-BREF was completed at all study visits.

2.2.4. Treatment setting and medication

Treatment setting was rated at all study visits on a scale from 1 to 4: 1, no treatment; 2, outpatient treatment; 3, day patient treatment; and 4, inpatient. Thus, higher values represented higher treatment intensity. During each study visit, the total number of medications was recorded, including antidepressants, antipsychotics, mood stabilizers, and other psychopharmacological drugs.

2.2.5. Symptom severity

To assess the severity of symptoms, the PsyCourse Study used the clinician-rated Positive and Negative Symptom Scale (PANSS) (Kay, Fiszbein, and Opler 1987) with α between 0.70 to 0.85 (Van Den Oord et al. 2006), Young Mania Rating Scale (YMRS) (Young et al. 1978) with α=0.74 (Mühlbacher et al. 2011), and Inventory of Depressive Symptomatology ($IDS\text{-}C_{30}$) (Rush et al. 1996) with α between 0.81 to 0.94 (Trivedi et al. 2004). The instruments were presented to all study participants at all visits.

2.3. Genetic analyses

A total of $n = 1783$ participants of the PsyCourse study were genotyped on Illumina's Global Screening Array version 1 and 3 (Illumina, San Diego, USA). Quality control (QC) was performed using PLINK v1.9/v2 (Chang et al. 2015). Single-nucleotide polymorphisms (SNPs) were excluded if they had a missing call rate greater than 2 %, had a Minor Allele Frequency (MAF) <0.5 %, or deviated from Hardy-Weinberg equilibrium with $p < 0.0001$. Individuals were excluded if they had a missing call rate greater than 2 % ($n = 1738$ individuals remaining), if the phenotypic sex of the individual did not match the genotypic sex ($n = 1731$ individuals remaining), if they were duplicated samples according to the pairwise identity by descent method ($n = 32$ duplicate samples/identical twins, $n = 34$ first-degree relatives and 3 pairs of third-degree relatives) or had a large deviation in their heterozygosity value ($n = 6$). Additionally, we excluded $n = 56$ individuals that had non-European ancestry according to a Multidimensional Scaling (MDS) analysis ($n = 1600$ individuals post-QC). MDS analysis was carried out with PLINK v1.9 to obtain a representation of genetic ancestry in our study, extracting the first 10 ancestry components. The first two components PC1 and PC2 were included in our analysis as covariates. Likewise, palindromic SNPs and SNPs with a large MAF deviation (>10 %) with respect to European reference populations were also removed. Imputation was performed using the Haplotype Reference Consortium panel (McCarthy et al. 2016) in the Michigan Imputation Server (Das et al. 2016). A post-imputation QC was carried out to exclude SNPs that had an imputation quality score of R2 <<0.3; or had a MAF <1 %. After genotype imputation, genotype dosage data were used to calculate polygenic risk for schizophrenia, depression, and bipolar disorder based on the results of corresponding genome-wide association studies (Wray

et al. 2018). Posterior single nucleotide polymorphism effect sizes were inferred under continuous shrinkage priors using PRS-CS (Ge et al. 2019). The *auto* settings were selected and global shrinkage parameter (φ) was estimated using a fully Bayesian approach. Of the remaining participants after quality control, $n = 725$ had complete data on the phenotypic and genetic variables required for our analyses and were included in the present study.

2.4. Statistical analyses

In order to statistically test for significant differences between (not normally distributed) groups or in pairwise comparisons, we used the non-parametric Kruskal-Wallis-Test for equal means. Post-hoc analyses were performed with the Dunn's test. Significance levels were always corrected for multiple testing errors with the Bonferroni method. Statistical analyses were performed with Python version 3.8.5 (scipy.stats and scikit-posthocs packages).

2.4.1. Averaging scores

Since ACE were expected to have consistent effects, we calculated mean scores across all four visits for our analyses, averaging the domain scores of GAF, WHOQOL-BREF, PANSS (including subscales), YMRS, and IDS-C_{30}. The independent variables that fluctuated over time, such as the number of medications and treatment setting, were also averaged across the four visits.

2.4.2. Multivariate linear regression models

To answer research questions (1) and (2), we used regression analyses to determine the association between ACE and functional outcome (assessed with the GAF and WHOQOL-BREF) and clinical outcome (assessed with the PANSS, YMRS, and IDS-C_{30}).

We used Spearman's Rank correlation to calculate the correlation between the independent and dependent outcome variables and to measure potential multicollinearity within the independent variables. When we used a correlation coefficient (r) > 0.5 as the threshold for a strong effect, as proposed by Cohen in his guide for interpreting effect sizes (Cohen 1992), we found a strong positive correlation between the mean of the total number of medications and treatment setting ($r = 0.63$, $p < 0.0001$) (**Supplementary Material 1**). When we measured multicollinearity with the variation inflation factor (VIF), we found a maximum VIF (VIFmax) of 24.12 for treatment setting. To further reduce multicollinearity and obtain more easily interpretable results, we standardized all input variables to a mean (μ) of 0 and standard deviation (σ) to 1. Then, we calculated the VIF again for all input variables and obtained a VIFmax value of 5.30 for the variable *psychotic disorders*. Because we standardized the respective scales, the resulting regression coefficient (β) was interpreted such that if we change the independent variable by one standard deviation (σ), then the predicted variable changes by β units. The standard deviations of each independent variable are shown in Table 1.

We tested the residuals for homoscedasticity with the Breusch-Pagan-test, and wherever the residuals did not comply with the assumption of equal variances, we used the heteroscedasticity consistent standard error estimator 3 (HC3) method to correct towards robust standard errors, as implemented in the package we used for the regressions (statsmodel package for python) (Seabold and Perktold 2010). Given the large sample size, we did not need to apply the normality assumption for residuals, and transformations to correct this may even have introduced bias into the model estimates (Schmidt and Finan 2018). Because the score ranges of all respective scales limited the values, all samples were included and none were defined as outliers.

Subsequently, we performed multivariate linear regressions to assess the impact of ACE on the dependent variables of interest while controlling for the covariates (age, sex, center, medication, treatment setting, diagnostic group, and PRS for schizophrenia, depression, and bipolar disorder, as well as ancestry components). In all regressions, we divided the data into training and test sets and performed a 10-fold cross-validation to test the validity of the results. When fitting the regression, the R^2a values referred to the adjusted R^2 values on the training data. To adjust for multiple testing, we applied the Bonferroni method ($p < 0.05/17 = 0.003$).

In addition, we performed ablation studies for the ACE subtype variables, i.e., we excluded these variables from the independent ones and repeated the multiple linear regression to evaluate whether the prediction performance changed. We measured the resulting difference in the R^2 values on the test data. This approach allowed us to identify the information encoded in the ACE variables that influenced the respective dependent variable (i.e., the ACE variables that explained some of the variability in the respective dependent variable). Small effect size is typically associated with <1–5 % of variance explained, a medium effect size with 5–20 % of variance explained, and a large effect size with >20 % of variance explained (Field 2013).

Table 1
Descriptive data.

	Mean	SD	Minimum	Maximum
Age (years)	42.12	13.77	18.00	86.00
Total number of medications	1.62	1.34	0.00	7.00
Treatment setting	1.92	0.64	1.00	4.00
PRS bipolar	−2.00	0.07	−2.24	−1.78
PRS depression	−2.44	0.07	−2.67	−2.21
PRS schizophrenia	−6.53	0.28	−7.49	−5.66
PC1	0.00	0.01	−0.01	0.02
PC2	0.00	0.01	−0.02	0.03
Emotional neglect score	2.27	1.14	1.00	5.00
Physical abuse score	1.53	0.99	1.00	5.00
Emotional abuse score	1.75	1.18	1.00	5.00
Sexual abuse score	1.29	0.77	1.00	5.00
Physical neglect score	1.94	1.17	1.00	5.00
GAF score	66.92	15.33	30.50	95.75
WHOQOL global score	14.28	3.20	4.00	20.00
WHOQOL physical health score	15.14	2.71	6.57	20.00
WHOQOL psychological health score	14.28	2.89	5.33	20.00
WHOQOL social relationships score	14.14	2.91	4.00	20.00
WHOQOL environment score	15.88	2.24	7.12	20.00
PANSS total score	42.17	12.08	30.00	101.25
PANSS positive score	9.17	3.13	7.00	26.25
PANSS negative score	10.70	4.27	7.00	29.75
PANSS general score	22.31	6.04	16.00	49.33
YMRS total score	2.13	2.86	0.00	26.00
IDS-C30 total score	10.54	8.81	0.00	48.00

Treatment setting was rated at all study visits on a scale from 1 to 4: 1, no treatment; 2, outpatient treatment; 3, day patient treatment; and 4, inpatient.
Abbreviations: GAF = Global Assessment of Functioning, IDS-C_{30} = Clinician-rated Inventory of Depressive Symptomatology;; PANSS = Positive and Negative Syndrome Scale; PC = principle component; PRS = polygenic risk score; SD = standard deviation; WHOQOL = World Health Organization Quality of Life Questionnaire, brief version; YMRS = Young Mania Rating Scale.

2.4.3. Cluster analysis

To address research question (3), we performed a cluster analysis with the k-nearest-neighbor (kNN) cluster method with a k value of 4. Silhouette coefficients were optimal (0.40–0.45) for $k = 2$ and $k = 4$. We selected $k = 4$ as it better aligned with established clinical severity grades (symptom-free, mild, and moderate depressive/psychotic symptoms). The analysis included all PANSS subscale scores and the YMRS and IDS-C_{30} total scores as variables. After forming the clusters, we analyzed the distribution of ACE subtype (ordinal trauma load) by performing Kruskal-Wallis tests and a pairwise Dunn's post hoc analysis.

3. Results

3.1. Descriptive analyses and occurrence of ACE

Descriptive data are shown in Table 1 and **Supplementary Material**

2. The psychotic disorders group had the highest ACE exposure (53.1 %), followed by the affective disorders group (46.6 %); among the healthy controls, 24.2 % reported having experienced at least one type of ACE.

Regarding the severity of ACE, healthy controls showed significantly less ACE than both clinical groups in all ACE subtypes with one exception: emotional abuse. Here, we found no significant difference between the healthy controls and the affective group. The load of emotional abuse was significantly lower in the affective disorders group ($p < 0.05$) and the healthy controls ($p < 0.001$) than in the psychotic disorders group. The psychotic disorders group had a higher load of physical neglect than the affective disorders group ($p < 0.05$) (**Supplementary Material 3**).

3.2. Multivariate linear regression models

3.2.1. Research question 1: impact of ACE on global functioning (assessed with the GAF) and QoL (assessed with the WHOQOL-BREF)

The multiple regression model with global functioning as the dependent variable showed a statistically significant effect ($F(17)=107.89$, $p < 0.001$, $R^2a=0.626$); the effect was significantly driven by the diagnostic groups, total number of medications, and treatment setting (Table 2, **Supplementary Material 4**). In the ablation study, in which the model was performed without the ACE variables, the R^2a of the training data was reduced by 1.8 %. Hence, 1.8 % of the variability in the global functioning can be attributed to ACE.

All five multiple regression models with the WHOQOL-BREF domains as the dependent variables showed significant effects: *global* ($F(19.39)$, $p < 0.001$, $R^2a=0.324$), *physical health* ($F(32.09)$, $p < 0.001$, $R^2a=0.447$), *psychological health* ($F(20.15)$, $p < 0.001$, $R^2a=0.333$), *social relationships* ($F(18.37)$, $p < 0.001$, $R^2a=0.275$), and *environment* ($F(16.51)$, $p < 0.001$, $R^2a=0.288$). The effect in the domain *global* was significantly driven by the diagnostic groups, total number of medications, and emotional neglect; in the domain *physical health*, by the diagnostic groups, total number of medications, and treatment setting; in the domain *psychological health*, by the diagnostic groups, emotional neglect, and total number of medications; in the domain *social relationship*, by the diagnostic groups, emotional neglect, and female sex; in the domain *environment*, by the psychotic disorders diagnostic group (Table 2, **Supplementary Material 4**). The ablation study showed that 6.2 % of the variability in the psychological health score, 4.9 % of that in social relationships score, 4.0 % of that in the environment score, 3.1 % of that in the global score, and about 2.3 % of that in the physical health score could be attributed to ACE.

Table 2
Multivariate linear regression models of Global Assessment of Functioning and World Health Organization Quality of Life Questionnaire (brief version) domains as dependent variables.

GAF score	**R^2**	**R^2_a**	**F statistic**	**p-value (F)**	**robust SE**		
	0.635	0.626	107.89	< 0.001	True		
		beta	**SE**	**t-value**	**p-value**	**p-value $_a$**	**significant**
Psychotic disorders		−7.86	0.93	−8.43	< 0.001	< 0.001	****
Affective disorders		−5.49	0.88	−6.24	< 0.001	< 0.001	****
Total number of medications		−3.37	0.55	−6.16	< 0.001	< 0.001	****
Treatment setting		−2.72	0.68	−3.97	0.001	0.001	**
WHO-QoL global score	**R^2**	**R^2_a**	**F statistic**	**p-value (F)**	**robust SE**		
	0.341	0.324	19.39	< 0.001	False		
		beta	**SE**	**t-value**	**p-value**	**p-value $_a$**	**significant**
Psychotic disorders		−0.95	0.24	−3.91	< 0.001	0.002	**
Affective disorders		−0.90	0.23	−3.86	< 0.001	0.002	**
Total number of medications		−0.52	0.14	−3.61	< 0.001	0.006	**
Emotional neglect score		−0.43	0.14	−3.09	0.002	0.034	**
Domain Physical Health	**R^2**	**R^2_a**	**F statistic**	**p-value (F)**	**robust SE**		
	0.462	0.447	32.09	< 0.001	False		
		beta	**SE**	**t-value**	**p-value**	**p-value $_a$**	**significant**
Psychotic disorders		−0.84	0.18	−4.56	< 0.001	< 0.001	***
Affective disorders		−0.71	0.18	−3.97	< 0.001	0.001	**
Treatment setting		−0.58	0.14	−4.15	< 0.001	0.001	***
Total number of medications		−0.52	0.11	−4.75	< 0.001	< 0.001	****
Domain Psychological Health	**R^2**	**R^2_a**	**F statistic**	**p-value (F)**	**robust SE**		
	0.35	0.333	20.15	< 0.001	False		
		beta	**SE**	**t-value**	**p-value**	**p-value $_a$**	**significant**
Affective disorders		−1.09	0.21	−5.18	< 0.001	< 0.001	****
Psychotic disorders		−0.94	0.22	−4.32	< 0.001	< 0.001	***
Emotional neglect score		−0.46	0.12	−3.70	< 0.001	0.004	**
Total number of medications		−0.39	0.13	−3.08	0.002	0.039	*
Domain Social Relationships	**R^2**	**R^2_a**	**F statistic**	**p-value (F)**	**robust SE**		
	0.294	0.275	18.37	< 0.001	True		
		beta	**SE**	**t-value**	**p-value**	**p-value $_a$**	**significant**
Affective disorders		−1.14	0.23	−4.98	< 0.001	< 0.001	****
Psychotic disorders		−1.11	0.24	−4.53	< 0.001	< 0.001	****
Emotional neglect score		−0.49	0.14	−3.59	< 0.001	0.006	**
Female sex		0.41	0.10	3.96	< 0.001	0.001	**
Domain Environment	**R^2**	**R^2_a**	**F statistic**	**p-value (F)**	**robust SE**		
	0.306	0.288	16.51	< 0.001	False		
		beta	**SE**	**t-value**	**p-value**	**p-value $_a$**	**significant**
Psychotic disorders		−0.73	0.17	−4.19	< 0.001	0.001	***

Robust standard errors were calculated using the HC3 estimator to account for potential heteroscedasticity. The table shows significant variables only, ordered by beta weights (high negative to high positive). P-value $_a$ represents the p-values after Bonferroni adjustment for multiple testing (alpha 0.05/17) with $*p <$ adjusted α, $**p <$ adjusted α/5, $***p <$ adjusted α/50, and $****p <$ adjusted α/500.
Abbreviations: *a* = adjusted; GAF = Global Assessment of Functioning; HC3 = heteroscedasticity consistent standard error 3; PC = principle component; PRS = polygenic risk score; SE = standard error; WHOQOL = World Health Organization Quality of Life Questionnaire, brief version.

3.2.2. Research question 2: impact of ACE on symptomatic burden (assessed with the PANSS, YMRS, and IDS-C_{30})

All multiple regression models with the PANSS subscales as the dependent variables showed significant effects: *total score* ($F(61.79)$, $p < 0.001$, $R^2a=0.485$), *positive score* ($F(23.59)$, $p < 0.001$, $R^2a=0.348$), *negative score* ($F(45.17)$, $p < 0.001$, $R^2a=0.419$), and *general score* ($F(47.94)$, $p < 0.001$, $R^2a=0.438$). The effects in the PANSS total score and PANSS positive score were significantly driven by the treatment setting, psychotic disorders diagnostic group, and female sex; in the PANSS negative score, by the psychotic disorders diagnostic group and treatment setting; in the PANSS general score, by the treatment setting, study site, and psychotic disorders diagnostic group (Table 3, **Supplementary Material 5**). The ablation study showed that 2.0 % of the variability in the PANSS general score, 0.9 % in the PANSS total score, 0.1 % in the PANSS positive score, and 0.04 % in the PANSS negative score could be attributed to ACE.

The multivariate regression analysis with the independent variables and the YMRS total score as the dependent variable was significant ($F(17)=8.97$, $p < 0.001$, $R^2a=0.126$); yet none of the independent variables had a significant effect on YMRS (Table 3, **Supplementary Material 5**). The ablation study showed that only 0.1 % of the variability in the YMRS total score could be attributed to ACE.

The multivariate regression analysis with the independent variables and the IDS-C_{30} total score as dependent variable was significant ($F(17)=25.79$, $p < 0.001$, $R^2a=0.352$) and significantly driven by emotional abuse, study site, total number of medications and treatment setting (Table 3, **Supplementary Material 5**). The ablation study showed that 5.7 % of the variability in the IDS-C_{30} total score could be attributed to ACE.

3.3. Cluster analysis

3.3.1. Research question 3: symptom clusters and differences in ACE subtypes between clusters

We used the kNN algorithm to calculate clusters on the symptom level (PANSS positive, negative, and general subscale; YMRS; and IDS-C_{30}) and found the following clusters: cluster A, which included participants whose mean symptom scores were below any cut-off values; cluster B, which included participants with predominantly psychotic symptoms; cluster C, which included participants with predominantly depressive symptoms; and cluster D, which included participants with values in all scales that were slightly elevated but below any cutoff values. Thus, cluster D included participants with subclinical symptoms. The diagnoses aligned with the symptom clusters but overlapped somewhat (Table 4, **Supplementary Material 6**, and Fig. 1).

When comparing the clusters regarding exposure to ACE subtypes, we found no significant differences between cluster A (no symptoms) and cluster D (subclinical symptoms). However, cluster A differed significantly from cluster B (predominantly psychotic symptoms) regarding emotional neglect and emotional abuse and from cluster C (predominantly depressive symptoms) regarding emotional neglect, emotional abuse, physical neglect, and physical abuse (Fig. 2).

4. Discussion

Our study examined the relationship between ACE and symptom severity, functioning, and QoL across diagnostic groups and sheds light on the nuanced interplay of these variables along the affective-to-psychotic spectrum.

Table 3
Multivariate linear regression models with the burden of symptoms as measured by assessment scales as the dependent variables.

PANSS total score	**R^2**	**R^2_a**	**F statistic**	**p-value (F)**	**robust SE**		
	0.497	0.485	61.79	< 0.001	True		
		beta	**SE**	**t-value**	**p-value**	**p-value $_a$**	**significant**
Female sex		−1.16	0.36	−3.23	0.001	0.022	*
Psychotic disorders		3.69	0.90	4.10	< 0.001	0.001	***
Treatment setting		4.29	0.84	5.09	< 0.001	< 0.001	****
PANSS positive score	**R^2**	**R^2_a**	**F statistic**	**p-value (F)**	**robust SE**		
	0.365	0.348	23.59	< 0.001	True		
		beta	**SE**	**t-value**	**p-value**	**p-value $_a$**	**significant**
Female sex		−0.46	0.10	−4.53	< 0.001	< 0.001	***
Psychotic disorders		0.81	0.26	3.12	0.002	0.033	*
Treatment setting		1.11	0.24	4.56	< 0.001	< 0.001	****
PANSS negative score	**R^2**	**R^2_a**	**F statistic**	**p-value (F)**	**robust SE**		
	0.432	0.419	45.17	< 0.001	True		
		beta	**SE**	**t-value**	**p-value**	**p-value $_a$**	**significant**
Treatment setting		0.98	0.30	3.24	0.001	0.022	*
Psychotic disorders		1.51	0.33	4.62	< 0.001	< 0.001	****
PANSS general score	**R^2**	**R^2_a**	**F statistic**	**p-value (F)**	**robust SE**		
	0.453	0.438	47.94	< 0.001	True		
		beta	**SE**	**t-value**	**p-value**	**p-value $_a$**	**significant**
Study site		0.66	0.19	3.42	0.001	0.011	*
Psychotic disorders		1.38	0.43	3.20	0.001	0.025	*
Treatment setting		2.18	0.41	5.37	< 0.001	< 0.001	****
YMRS total score	**R^2**	**R^2_a**	**F statistic**	**p-value (F)**	**robust SE**		
	0.149	0.126	8.97	< 0.001	True		
IDS-C_{30} total score	**R^2**	**R^2_a**	**F statistic**	**p-value (F)**	**robust SE**		
	0.368	0.352	25.79	< 0.001	True		
		beta	**SE**	**t-value**	**p-value**	**p-value $_a$**	**significant**
Study site		1.00	0.31	3.20	0.001	0.025	*
Emotional abuse score		1.51	0.41	3.68	< 0.001	0.004	**
Total number of medications		1.89	0.45	4.18	< 0.001	0.001	***
Treatment setting		2.23	0.72	3.08	0.002	0.037	*

Robust standard errors were calculated using the heteroscedasticity-consistent standard error estimator to account for potential heteroscedasticity. The table shows significant variables only, ordered by beta weights (high negative to high positive). P-value $_a$ represents the p-values after Bonferroni adjustment for multiple testing (alpha 0.05/17) with *$p <$ adjusted α, **$p <$ adjusted α/5, ***$p <$ adjusted α/50, and ****$p <$ adjusted α/500.
Abbreviations: a = adjusted; IDS-C_{30} = Clinician-rated Inventory of Depressive Symptomatology, PANSS = Positive and Negative Syndrome Scale; PC = principle component; PRS = polygenic risk score; SE = standard error; YMRS = Young Mania Rating Scale.

Table 4
Descriptive data of the four identified clusters.

	Cluster			
	A	**B**	**C**	**D**
Cluster description	**Symptom free**	**Predominantly psychotic symptoms**	**Predominantly depressive symptoms**	**Subclinical symptoms**
n	472	51	121	160
Control group	43 %	–	1 %	–
Psychotic group	17 %	86 %	31 %	74 %
Affective group	40 %	14 %	68 %	26 %
PANSS total, mean (SD)	33.96 (3.72)	71.82 (11.26)	50.27 (7.48)	51.44 (6.61)
YMRS, mean (SD)	1.20 (1.72)	6.60 (5.16)	2.60 (2.51)	3.11 (3.08)
IDS-C_{30}, mean (SD)	5.87 (4.28)	19.46 (10.42)	25.25 (7.00)	10.70 (4.64)
Emotional neglect, mean (SD)	2.01 (1.03)	2.90 (1.19)	2.69 (1.28)	2.42 (1.13)
Physical abuse, mean (SD)	1.37 (0.75)	1.65 (1.04)	1.88 (1.34)	1.67 (1.15)
Emotional abuse, mean (SD)	1.49 (0.92)	2.49 (1.47)	2.31 (1.41)	1.88 (1.32)
Sexual abuse, mean (SD)	1.20 (0.61)	1.57 (1.01)	1.54 (1.13)	1.31 (0.75)
Physical neglect, mean (SD)	1.72 (1.01)	2.59 (1.31)	2.28 (1.31)	2.14 (1.27)

For post hoc significance levels see **Supplementary Material 6**.
Abbreviations: IDS-C_{30} = Clinician-rated Inventory of Depressive Symptomatology; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation; YMRS = Young Mania Rating Scale.

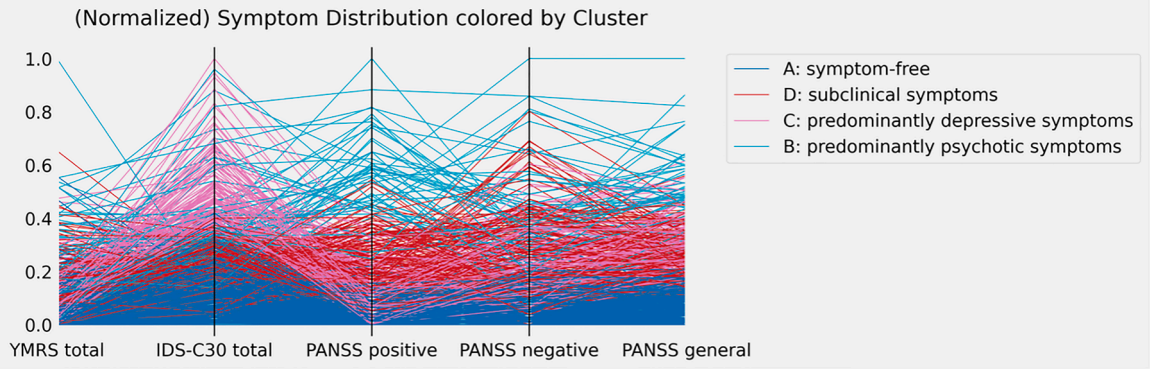

Fig. 1. Cluster Analysis.
The parallel coordinates plot visualizes normalized symptom scale values of the symptom scales IDS-C_{30}, PANSS and YMRS for different patient clusters (A to D). Each line represents an individual case, with colors indicating cluster membership.
Abbreviations: IDS-C_{30} = Clinician-rated Inventory of Depressive Symptomatology; PANSS = Positive and Negative Syndrome Scale; YMRS = Young Mania Rating Scale.

In order to focus on stable effects, we averaged outcome variables (QoL, functioning, and symptom severity) across four time points despite losing detailed time-specific information. And we deliberately assessed ACE at visit 3 when patients were typically in a less acute phase of their illness, supported by evidence on temporal stability of retrospective trauma reports (Simpson et al. 2019; Vila-Badia et al. 2022) and high test-retest reliability (Cay et al. 2022).

QoL was affected by diagnostic group, especially psychotic disorders, and also by ACE, in particular emotional neglect. This aligns with known ACE-related QoL reduction in schizophrenia (Andrianarisoa et al. 2017). QoL, a patient-reported outcome, capturing individuals' overall well-being and satisfaction across various life domains seems to be particularly vulnerable to early adverse experiences (Erten et al. 2014; Inyang et al. 2022). ACE showed a clear negative impact on psychological health and social relationship domains across diagnostic boundaries. ACE accounted for 2.3 % to 6.2 % of QoL variance. This result adds important information to a previous study by Rowe et al. (2023) that found that ACE together with related factors collectively explain 62 % of QoL variance in patients with bipolar disorder; however, the specific contribution of ACE in this study was difficult to discern due to intercorrelated variables and an unusually high trauma burden (78 %) (Rowe, Perich, and Meade 2023). The effect sizes observed in our ablation studies were relatively small. One reason might be that the diagnosis mediated the relationship between ACE and clinical symptoms and QoL. Yet, it is important to recognize that even modest effects can have significant clinical implications, particularly when considering the complex and multifactorial nature of the outcomes we are examining.

Regarding variability in functioning (measured by GAF), covariates (diagnostic group, number of medications, treatment setting) had stronger effects than ACE and might have masked ACE effects. These associations likely reflect that patients with more severe symptoms require more intensive treatment, rather than suggesting negative treatment effects. In comparison, ACE had a stronger effect on QoL than on functioning. The differential impact may reflect that QoL, being self-assessed, captures emotional and interpersonal domains, while functioning, being observer-rated, focuses on more objective domains like independent living and occupational functioning, which may be more amenable to compensation (Fares-Otero et al. 2023).

Our examination showed that emotional abuse was associated with elevated depressive symptoms across the affective-to-psychotic spectrum. This effect even exceeded the impact of the variable affective disorders diagnostic group underscoring the value of examining trauma impact beyond traditional diagnostic boundaries. This is consistent with the known three-fold higher depression risk in emotionally abused individuals (Norman et al. 2012) and a recent publication showing that ACE affect mood episodes in patients with schizophrenia and bipolar disorder (M. Aas et al. 2023). We found no significant impact of ACE on psychotic symptoms (PANSS). This contrasts with existing research and may be explained by two factors: First, treatment setting and number of medications had a particularly strong impact in our sample, potentially

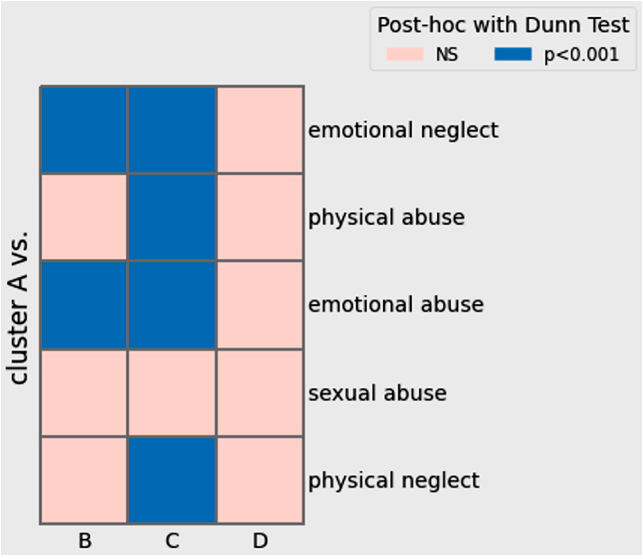

Fig. 2. Subtypes of ACE subtypes.
The significance plot displays the results of Dunn's Post hoc Test, which was conducted to assess pairwise statistical differences between Clusters A to D and subtypes of ACE. P-Values are adjusted after Bonferroni for multiple testing: $\alpha = 0.05/6 = 0.008$.
Abbreviation: NS, not significant.

masking the more subtle impact of ACE. Second, our sample represents the broader affective-to-psychotic spectrum rather than being trauma-selected, with a predominance of emotional abuse and neglect rather than sexual or physical abuse that had been previously linked to psychotic symptoms (Grindey and Bradshaw 2022). Regarding manic symptoms, the interpretability of our results is limited because these symptoms showed little variability.

Genetic factors (in the form of PRS) did not emerge as predictors for any examined outcomes. ACE and other variables such as treatment setting, number of medications, sex, and diagnostic classifications had a strong impact and might have masked the very subtle impact of genetic predisposition.

The study site had a significant influence on the variability in the PANSS general and IDS-C_{30} scores. This finding might be explained by regional differences between study sites, including varying diagnostic distributions and unmeasured factors like socioeconomic status.

To improve the interpretability, we performed a cluster analysis examining four distinct clusters of patients and healthy controls, where differentiation between clusters could not be solely explained by diagnostic group. Each cluster differed significantly regarding their ACE history. Especially the cluster C (predominantly depressive symptoms) showed substantial burden of emotional abuse and neglect, and physical abuse and neglect. 43 % of the symptom-free individuals (cluster A), belonged to the healthy control group. This cluster had significantly less ACE than clusters B (predominantly psychotic symptoms) and C (predominantly depressive symptoms). Most notably, patients with subclinical symptoms (cluster D) provided compelling evidence for the role of ACE in symptom severity across diagnoses: Their ACE load was comparable to symptom-free individuals (cluster A), while patients with predominant psychotic (cluster B) or depressive symptoms (cluster C) showed significantly higher ACE loads. A previous cluster analysis by Schulte et al. (2022) in the PsyCourse study identified clusters that differed significantly in global functioning and illness course. Our symptom-severe clusters B and C showed similarities to their clusters characterized by severe psychopathology, although direct comparison is limited as their analysis included different symptom variables and considered only patients with schizophrenia and bipolar disorder but no healthy controls (Schulte et al. 2022). Our findings support previous research suggesting that ACE play a crucial role in the symptom severity of mental disorders and possibly in disease onset and prognosis, although these outcomes were not evaluated in the current analyses (Kessler et al. 2010).

Our study also has some limitations that we would like to address: 1) We maintained diagnostic group as a predictor in our analyses, which consistently showed significant associations with outcomes. This approach may have led to an underestimation of cross-diagnostic effects of other variables - highlighting the tension between traditional diagnostic categories and transdiagnostic mechanisms. 2) We found high multicollinearity in the data. We addressed this by applying VIFmax. Nevertheless, in the ablation study the effect of explained variance may have been larger because our approach did not include the impact of synergistic effects of correlated variables. 3) The self-rating nature of the CTS and QoL makes it susceptible to self-report and mood-related biases, as current emotional states can influence the recollection and evaluation of past experiences and current condition, potentially leading to over- or under-reporting of ACE. 4) There is a higher variance in the variables of emotional abuse and emotional neglect, different ACE subtypes are highly intercorrelated, and each subtype is assessed with only a single question. This can lead to biased results, suggesting that these two subtypes might have a stronger impact. 5) Relevant further diagnoses (such as PTSD) were not assessed in a structured manner, so important information is missing. 6) Our genetic analyses were carried out only on European samples as we had to exclude non-European subjects during the quality control of genetic data. And, 7) one limitation is that extensive research has already been performed on the influence of ACE on mental disorders (Hogg et al. 2023). Yet, our study supports these previous findings and it also adds value because it consolidates previous results in a comprehensive and comparable approach. Additionally, it suggests that despite the recognition that ACE have a significant impact on modulating the course of mental illnesses, there are areas, such as psychotic and manic symptoms and overall global functioning, that are not or only marginally influenced by ACE. Evidently, other variables play a larger role in these aspects.

We obtained answers to our research questions, as follows: (1) ACE, specifically emotional neglect, affect QoL; (2) ACE, specifically emotional abuse, have a significant impact on depressive symptoms across diagnostic boundaries; and (3) clusters of symptoms exist and participants with subclinical rather than pronounced clinical symptoms had less ACE.

In conclusion, our study underscores the need for clinicians to routinely assess the history of ACE in patients within the affective-to-psychotic spectrum, especially when they suffer from depressive symptoms, because ACE have a significant influence on symptom severity and QoL across diagnostic categories. Incorporating ACE-informed care approaches into treatment protocols may enhance recovery by addressing underlying ACE-related factors. Future research should explore the mechanistic pathways through which ACE impact mental disorders and should further evaluate the efficacy of ACE-focused interventions in the affective-to-psychotic spectrum. Our research highlights the importance of research on ACE in mental disorders that are not direct sequelae of trauma.

CRediT authorship contribution statement

Sophie-Kathrin Greiner: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **María Dech Pons:** Writing – original draft, Visualization, Methodology, Formal analysis. **Ayimnisagul Ablimit:** Methodology. **Elisa Brauße:** Methodology. **Kristina Adorjan:** Writing – review & editing. **Monika Budde:** Writing – review & editing, Data curation. **Maria Heilbronner:** Writing – review & editing. **Urs Heilbronner:** Writing – review & editing, Supervision, Data curation. **Janos L. Kalman:** Writing – review & editing. **Alba Navarro-Flores:** Writing – review & editing. **Mojtaba Oraki Kohshour:** Writing – review & editing. **Daniela Reich-Erkelenz:** Writing – review

& editing, Project administration. **Eva C. Schulte:** Writing – review & editing. **Thomas Vogl:** Writing – review & editing. **Till Andlauer:** Writing – review & editing, Methodology. **Ion-George Anghelescu:** Writing – review & editing, Resources. **Volker Arolt:** Writing – review & editing, Resources. **Bernhardt T. Baune:** Writing – review & editing, Resources. **Udo Dannlowski:** Writing – review & editing, Resources. **Franziska Degenhardt:** Writing – review & editing, Methodology. **Detlef E. Dietrich:** Writing – review & editing, Resources. **Andreas J. Fallgatter:** Writing – review & editing, Resources. **Christian Figge:** Writing – review & editing, Resources. **Andreas Forstner:** Writing – review & editing, Methodology. **Markus Jäger:** Writing – review & editing, Resources. **Georg Juckel:** Writing – review & editing, Resources. **Carsten Konrad:** Writing – review & editing, Resources. **Markus M. Nöthen:** Writing – review & editing, Methodology. **Fabian U. Lang:** Writing – review & editing, Resources. **Jens Reimer:** Writing – review & editing, Resources. **Eva Z. Reinighaus:** Writing – review & editing, Resources. **Marcella Rietschel:** Writing – review & editing, Methodology. **Max Schmauß:** Writing – review & editing, Resources. **Andrea Schmitt:** Writing – review & editing, Resources. **Simon Senner:** Writing – review & editing, Supervision. **Carsten Spitzer:** Writing – review & editing, Resources. **Jens Wiltfang:** Writing – review & editing, Resources. **Stephanie H. Witt:** Writing – review & editing, Methodology. **Jörg Zimmermann:** Writing – review & editing, Resources. **Alkomiet Hasan:** Writing – review & editing, Supervision. **Peter Falkai:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition. **Thomas G. Schulze:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition. **Sergi Papiol:** Writing – review & editing, Methodology, Data curation. **Fanny Senner:** Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

I.G. Anghelescu has been a consultant and/or has received honoraria from Aristo, Janssen, Merck, Recordati, and Schwabe. V. Arolt received a grant from the EU Horizon 2020 Program (Project MOODSTRATIFICATION) and is advisor for Sanofi-Aventis Germany. P. Falkai has been an honorary speaker for AstraZeneca, Bristol Myers Squibb, Lilly, Essex, GE Healthcare, GlaxoSmithKline, Janssen Cilag, Lundbeck, Otsuka, Pfizer, Servier, and Takeda and a member of the advisory boards of Janssen-Cilag, AstraZeneca, Lilly, Lundbeck, Richter, Recordati, and Boehringer Ingelheim. S.-K. Greiner is an advisor to the GOLDKIND Foundation. A. Hasan has been a member of the advisory boards of Boehringer-Ingelheim, Lundbeck, Janssen, Otsuka, Rovi, and Recordati and received paid speakerships from these companies and rom AbbVie and Advanz; he is also an editor of the German schizophrenia guideline. C. Konrad has received fees for an educational program from Aristo Pharma, Janssen-Cilag, Lilly, MagVenture, Servier, and Trommsdorff and travel support and speakers honoraria from Aristo Pharma, Janssen-Cilag, Lundbeck, Neuraxpharm, and Servier. S. Senner is a member of the advisory board of wellster healthtech and nilo.health and the founder of brains work. J. Zimmermann was a member of Biogen Advisory Idorsia Advisory Boards. All other authors report no conflicts of interest.

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Declaration of generative AI and AI-assisted technologies in the writing process

During preparation of this work, the authors used ChatGPT 3.5 by Open AI and Claude 3.5 Sonnet by Anthropic in order to improve language and readability. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2025.116536.

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