Brain, Behavior, and Immunity 137 (2026) 106807

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Associations between CRP-related DNA methylation, stress exposure, and depression severity in a longitudinal clinical cohort☆

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A B S T R A C T

Background: Environmental adversity is linked to major depressive disorder (MDD), potentially via sustained low-grade inflammation. However, serum markers such as C-reactive protein (CRP) are transient and sensitive to acute states. In contrast, epigenetic signatures of inflammation may provide a more stable trace of how stress becomes biologically embedded and contributes to depression risk over time.
Methods: In a subsample of the Marburg-Münster Affective Disorders Cohort Study (MACS; $N = 579$; 320 healthy controls, 259 with MDD), we examined whether early life adversity (ELA; CTQ) and recent life stress (RLS; LEQ) are associated with CRP-related DNA methylation (CRPm) at baseline. We further tested whether CRPm predicts depressive symptom severity (HAMD) at baseline and at two-year follow-up ($n = 407$). DNA was extracted from whole blood, and CRPm scores were computed using publicly available genome-wide summary statistics.
Results: CRPm explained 21.3% of the variance in serum high-sensitivity CRP (hsCRP). Higher CRPm was significantly associated with both ELA ($b = 0.01$, $SE = 0.003$, $p = 0.017$) and RLS ($b = 0.01$, $SE = 0.004$, $p = 0.032$), after adjusting for age and sex. CRPm also predicted depressive symptom severity at baseline ($b = 0.68$, $SE = 0.27$, $p = 0.013$) and at follow-up ($b = 0.79$, $SE = 0.25$, $p = 0.002$). These associations remained after controlling for white blood cell-type composition but were attenuated after adjusting for BMI and smoking. In contrast, hsCRP was not associated with adversity or depressive symptoms.
Conclusion: Our study indicates that a methylation-based index of chronic inflammation is associated with stress exposure and depressive symptoms over time, in contrast to fluctuating serum hsCRP. The findings are more consistent with an indirect pathway in which environmental adversity is linked to inflammatory biology via stress-related health behaviors, rather than with a model of direct biological embedding.

1. Introduction

Stressful experiences across the lifespan are a major risk factor for mental disorders, such as major depressive disorder (MDD) (Teicher et al., 2022; Hughes et al., 2017; Liu et al., 2019). Among these, early life adversity (ELA) has been shown to exert particularly long-lasting effects

☆ This article is part of a special issue entitled: 'Inflammatory depression' published in Brain Behavior and Immunity.

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https://doi.org/10.1016/j.bbi.2026.106807
Received 21 August 2025; Received in revised form 4 March 2026; Accepted 10 May 2026
Available online 12 May 2026
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on mental health, possibly due to its impact during sensitive developmental periods (Agorastos et al., 2019) with Mendelian randomization studies providing additional support for a causal relationship (Warrier et al., 2021). In addition, recent life stress (RLS) has been associated with both the onset and progression of depressive symptoms (Rnic et al., 2023; Buckman et al., 2022). While the psychological consequences of stress are well recognized, the specific pathways through which stressful experiences become biologically embedded and confer long-term vulnerability remain only partially understood.

One prominent hypothesis posits chronic low-grade inflammation as a key biological mechanism linking stress exposure to depression, supported by extensive evidence of immune dysregulation following adversity. Both ELA and RLS have been associated with elevated levels of inflammatory markers such as C-reactive protein (CRP) (Agorastos et al., 2019; Berens et al., 2017; Hakamata et al., 2022; Agorastos and Chrousos, 2022; Bourassa et al., 2021; Hillmann et al., 2024). Elevated CRP, in turn, has been linked to depressive symptoms and MDD in both cross-sectional and longitudinal studies (Mac Giollabhui et al., 2021; Osimo et al., 2020; Osimo et al., 2019), and shares part of its genetic architecture with depression (Hindley et al., 2023; Kappelmann et al., 2021). However, commonly used acute-phase proteins like serum CRP have limitations as indicators of chronic inflammation, since their levels change in response to transient physiological states like infections, injuries, or metabolic and circadian fluctuations (Bogaty et al., 2013; Gough et al., 2024). Moreover, single-time-point measurements may not adequately capture the cumulative inflammatory burden associated with prolonged psychosocial stress.

Methodological advances in epigenetic research offer new tools to trace the long-term biological impact of environmental exposures. In the context of inflammation, large-scale epigenome-wide association studies (EWAS) have identified specific DNA methylation (DNAm) patterns associated with circulating CRP levels (Hillary et al., 2024; Wielscher et al., 2022; Ligthart et al., 2016). Based on these findings, DNAm-based predictors of CRP, referred to as CRP methylation scores (CRPm scores), have been developed. These scores aggregate DNAm levels across multiple CRP-associated CpG sites and may serve as a more stable molecular signature of chronic low-grade inflammation. In addition to their biological relevance, such composite scores may also improve statistical power compared to traditional single-site epigenetic analyses. While prior candidate gene studies and EWAS have linked DNAm variation in immune-related genes to stress exposure and depressive symptoms (Parade et al., 2021; Opsasnick et al., 2024; Robakis et al., 2022; Reuben et al., 2020; Palma-Gudiel et al., 2021; Pfeiffer et al., 2022; Li et al., 2022; Clark et al., 2020; Crawford et al., 2018; Gonzales et al., 2023; Ryan et al., 2017), findings in this area often lack reproducibility. This may reflect not only limited statistical power due to small effect sizes and the need for large samples, but also the stressor-specific nature of epigenetic signatures (Gladish et al., 2022; Zhang and Liu, 2022).

Initial studies have used CRPm scores to examine associations with environmental adversity and depression. Higher CRPm scores were prospectively linked to ELA, including neighborhood socioeconomic disadvantage (Reuben et al., 2020) and cumulative childhood maltreatment (Barker et al., 2018). While early studies reported no consistent associations with depressive symptoms (Edmondson-Stait et al., 2022; Green et al., 2021), more recent studies using improved methods have demonstrated significant links—often stronger than those observed for serum CRP (Verschoor et al., 2023). CRPm has also been associated with neurobiological alterations, including reduced cortical volume and disrupted white matter in brain regions implicated in MDD (Green et al., 2021). In one of the few studies explicitly addressing both stress and psychiatric outcomes, CRPm mediated the association between postnatal adversity and internalizing symptoms in later childhood (Barker et al., 2018).

Earlier CRPm scores typically explained only 6–10% of the variance in serum CRP (Ligthart et al., 2016; Stevenson et al., 2020). However, recent methodological advances, particularly the use of penalized regression models such as elastic net, have increased the explained variance to around 20% (Hillary et al., 2024), enabling more precise investigation of epigenetic pathways linking stress, inflammation, and depression.

Building on these advances, we apply an updated and more robust CRPm score to examine inflammation-related epigenetic pathways linking ELA and RLS to depression. Using data from individuals with MDD and healthy controls (HC), we test the hypotheses that self-reported ELA and RLS at baseline (T1) are positively associated with CRPm scores, and that higher CRPm scores predict greater depressive symptom severity cross-sectionally (T1) and at two-year follow-up (T2). We further assess the impact of health risk variables (smoking, alcohol intake, body mass index) on these associations. To assess the potential advantage of CRPm as a temporally stable molecular marker of chronic, low-grade inflammatory processes relevant to mental health, we repeated analyses in which CRPm showed significant associations with adversity or depressive symptoms, replacing CRPm with log-transformed serum high-sensitivity CRP (hsCRP). By integrating data on environmental adversity, epigenetic inflammation markers, and longitudinal clinical outcomes, this study examines whether CRP-related DNA methylation indexes cumulative inflammatory burden shaped by stress exposure and related health risk behaviors, and whether this burden is linked to depressive symptom severity over time.

2. Materials and methods

2.1. Study sample

Data were drawn from the Marburg-Münster Affective Disorders Cohort Study (MACS), part of the FOR2107 consortium on the neurobiology of major psychiatric disorders (Kircher et al., 2019). Participants aged 18–65 were recruited in Germany from Marburg and Münster university hospitals, surrounding clinics, and through public advertisements. Trained raters conducted structured clinical interviews based on DSM-IV-TR criteria (Wittchen and Strukturiertes klinisches Interview für DSM-IV: SKID. Achse I, 1997) to confirm MDD diagnoses or to verify the absence of psychiatric history and psychotropic medication use in HC. All participants underwent detailed phenotyping, clinical assessment, and biomaterial collection. Written informed consent was obtained, and the study was approved by the ethics committees of Münster (2014–422-b-S) and Marburg (07/14), in accordance with the Declaration of Helsinki. Participants received monetary compensation. A subset of MACS participants with complete data on variables of interest was included. Cross-sectional analyses comprised individuals assessed at baseline (T1) with available data on ELA, RLS, depressive symptom severity, DNAm measures, and relevant covariates (sex, age, body mass index [BMI], alcohol intake, and genome-wide genotyping), yielding a total sample of $N = 579$ (HC $n = 320$; MDD $n = 259$). Longitudinal analyses were restricted to participants with available depressive symptom data at the two-year follow-up (T2; $M = 2.21$ years inter-measurement interval, $SD = 3.75$, Range = 1.88–4.25), resulting in HC $n = 222$ and MDD $n = 185$.

2.2. Exclusion criteria

Participants were excluded if they had a history of neurological disorders or severe medical conditions, current or lifetime alcohol dependence, current drug dependence or benzodiazepine use, or a verbal IQ < 80. Severe medical conditions comprised chronic inflammatory diseases (e.g., Crohn's disease, ulcerative colitis), systemic autoimmune disorders (e.g., lupus, rheumatoid arthritis), chronic infectious diseases (e.g., hepatitis C), as well as severe manifestations of conditions with variable inflammatory impact (e.g., psoriatic arthritis, hepatitis B). Additional exclusions applied if genotyping or DNA methylation data were unavailable, diagnostic information was missing, or consent was withdrawn.

3. Psychological and behavioral assessments

3.1. Early life adversity

ELA was assessed at T1 using the 28-item Childhood Trauma Questionnaire (CTQ) (Klinitzke et al., 2012), which retrospectively measures emotional, physical, and sexual abuse, as well as emotional and physical neglect during childhood and adolescence. Consistent with established research practice, we used the CTQ sum score as an index of cumulative maltreatment.

3.2. Recent life stress

RLS was assessed at T1 using the German version of the Life Events Questionnaire (LEQ) (Norbeck, 1984), covering 82 events across major life domains (health, work, school, home, love and marriage, family and close friends, parenting, personal and social, financial, crime and legal, and other). Participants indicated whether each event had occurred within the past 6 months, rated its valence (positive/negative), and evaluated its subjective impact on a scale from 0 to 3. For all current analyses, we used the total negative event impact score as an index of the cumulative burden of recent stressors.

3.3. Depressive symptoms

Depression severity was assessed at T1 and T2 using the 21-item Hamilton Depression Rating Scale (HAMD) (Williams and Terman, 2003) administered by trained raters. In line with common research practice, analyses were based on the sum score of the first 17 items, which index core depressive symptoms.

3.4. Demographic and health risk variables

Covariates were drawn from T1 data and included age, sex, BMI, alcohol intake (measured via the Alcohol Use Disorders Identification Test; AUDIT), and smoking status, indexed via AHRR (cg05575921) methylation, a validated epigenetic biomarker of tobacco exposure (Bojesen et al., 2017).

4. Biological assessments

4.1. Genotyping

Genomic DNA was extracted from peripheral blood samples using standard procedures. Genotyping was performed using the Illumina Infinium PsychArray-24 BeadChip (Illumina, San Diego, CA, USA) according to established protocols. Quality control and genotype imputation were conducted within the context of a larger cohort study (see Pelin et al., 2021) for details), of which the present study sample constitutes a subset.

4.2. DNA methylation profiling

Genome-wide DNAm was assessed using blood-derived DNA and the Illumina MethylationEPIC v1.0 BeadChip (Illumina, San Diego, CA, USA). Samples were randomized across arrays by sex and case–control status to minimize batch effects. Quality control was conducted in R (R Core Team, 2019) using the *minfi* and *ewastools* packages (Fortin et al., 2017; Heiss and Just, 2018). Samples were excluded if they had call rates <98%, failed Illumina control probes, exhibited sex mismatches, or showed SNP discordance with genotype data. Methylation intensities were normalized using stratified quantile normalization (Touleimat and Tost, 2012), and M-values were calculated for downstream analysis. Probes were excluded if they showed call rates <98%, targeted non-CpG or non-autosomal sites, overlapped with common SNPs (minor allele frequency >1%), or exhibited potential for cross-hybridization (McCartney et al., 2016). The final dataset was further restricted to individuals with high-quality genotype data and without genetically determined third degree or closer relatedness. Methylation profiling, quality control, and preprocessing were conducted in a larger sample, of which the sample included in this study represents a subset.

4.3. CRP-related DNA methylation score

CRPm scores were derived from DNAm data collected at T1. Following the approach by Hillary et al. (Hillary et al., 2024), scores were computed as a weighted sum of M-values across CpG sites, using weights derived from an elastic net regression model predicting circulating CRP levels. This method accounts for intercorrelations among CpG sites while optimizing predictive accuracy. The resulting composite score has demonstrated robust performance in independent cohorts, explaining up to 20% of the variance in serum CRP levels (Hillary et al., 2024). Of the 1,468 CpG sites included in the originally published predictor, 1,431 were available in our sample.

4.4. Serum high-sensitivity CRP

Serum hsCRP data measured at T1 were available for a subsample of participants (n = 322). Samples were quantified using an AU5822 clinical chemistry analyzer (Beckman Coulter) with a CRP Latex Highly Sensitive Calibrator (Cat# ODC0027, see Thomas-Odenthal et al., 2024). hsCRP values ranged from 0.08 to 47.04 mg/L (M = 2.30, SD = 4.26). Participants with hsCRP levels > 3 SD were excluded (n = 5).

4.5. Covariates derived from genomic and methylation data

Ancestry components (ACs) were computed via multidimensional scaling of pruned genotype data prior to imputation, with the first three components retained to account for potential effects of population stratification. To adjust for technical variation in DNAm data, methylation components (MCs) were derived from control probe intensities of the Illumina MethylationEPIC array (excluding negative control probes) using R (v4.4.3) (R Core Team, 2019). The first five components were selected based on visual inspection of a scree plot (Supplementary Fig. 1). Estimated white blood cell-type composition was obtained from normalized methylation beta values using the Houseman approach (Houseman et al., 2016) as implemented in the *minfi* package, including B cells, $CD4^+$ and $CD8^+$ T cells, monocytes, and natural killer (NK) cells. Granulocytes were excluded from all models due to high collinearity with other cell-types.

4.6. Data handling and imputation

To address missing data, multiple imputation was applied to CTQ total scores, LEQ negative event scores, HAMD sum scores, AUDIT scores, and BMI. All genotyping- and DNAm-derived variables were complete, as their availability constituted an inclusion criterion. Missingness patterns were evaluated using Little's MCAR test (Little, 1988). For variables violating the MCAR assumption, missingness was assumed to be missing at random (MAR), consistent with common practice in observational research (Li et al., 2024; Stuart et al., 2009). Multiple Imputation by Chained Equations (MICE) was conducted in R (v4.5.0) (R Core Team, 2019) using the *mice* package (v3.18.0), chosen for its flexibility across variable types and robustness under diverse data conditions. Predictive mean matching was employed to preserve original variable distributions and accommodate potential non-normality (Li

et al., 2024; Stuart et al., 2009; Xu et al., 2020). Twenty imputed datasets were generated to ensure stable parameter estimates (Li et al., 2024; Xu et al., 2020). Variables with more than 15% missingness were excluded from imputation to limit imputation-related uncertainty (Stuart et al., 2009). Predefined sensitivity analyses were conducted for stress-related predictors (CTQ, LEQ) and health risk variables. When missingness exceeded minimal thresholds (5%) or differed across diagnostic groups, primary models were re-estimated in predictor complete-case samples (Supplementary; Sensitivity Analyses for Missing Data).

4.7. Statistical analyses

Group differences between patients with MDD and HC were assessed using Wilcoxon rank-sum tests to account for non-normal data distributions. A linear regression model with log-transformed serum hsCRP values as the dependent variable and CRPm as the predictor was used to assess the validity of the CRPm score. To examine associations between environmental stress and CRPm, multiple regression models were estimated using the *lavaan* package (v0.6–19) (Stuart et al., 2009) in R (R Core Team, 2019). Separate models were run with ELA and RLS as predictors and CRPm as the outcome variable. A base model included the respective stress exposure, ACs, MCs, and demographic covariates (age, sex). An extended model additionally controlled for health risk variables, specifically smoking, alcohol intake, and BMI. Both model versions were estimated with and without adjustment for estimated white blood cell-type composition, resulting in a total of 8 models per outcome. To assess whether CRPm assessed at T1 was associated with depressive symptom severity at T1 and T2, CRPm was included as the predictor in regression models with HAMD sum scores as the outcome. As with the life stress models, both base and extended versions were estimated, with and without adjustment for cell-type composition, resulting in a total of 8 models. In additional sensitivity analyses, all models were re-estimated in stratified subsamples (MDD vs. HC, acute vs. remitted MDD, and females vs. males). For more Information see Supplementary (Stratified Analyses). Post hoc exploratory mediation analyses were conducted using structural equation modeling (SEM) implemented in the *lavaan* package (v0.6–19) for R (R Core Team, 2019) to examine indirect pathways linking ELA and RLS to CRPm via health risk variables. BMI and AHRR (cg05575921) methylation were selected as parallel mediators, as these were the health risk variables that showed significant associations with CRPm in the main analyses For more Information see Supplementary (Mediation Analyses). All analyses were conducted with a significance threshold of $\alpha = 0.05$. Prior to conducting multiple regression analyses, assumptions (linearity, homoscedasticity, normality of residuals, and multicollinearity) were examined, and no violations were detected. A visual summary of the main analyses model specifications is provided in Fig. 1.

To explore whether findings observed for CRPm were specific to this methylation-based marker, we conducted follow-up analyses using serum hsCRP. Specifically, for associations in which CRPm showed significant effects with adversity or depressive symptoms, we reran the regression models, replacing CRPm with log-transformed hsCRP (n = 317). These analyses aimed to examine whether similar associations emerged for hsCRP, despite its known sensitivity to acute physiological fluctuations. All models were adjusted for age and sex. Participants with hsCRP values > 3 *SD* above the mean were excluded (n = 5).

5. Results

5.1. Sample characteristics

The analyzed sample comprised 579 participants (63.6% female; M = 35.29 years, SD = 13.19). Descriptive statistics and group comparisons between HC and individuals with major depressive disorder (MDD) are presented in Table 1. Participants with MDD reported significantly greater depressive symptom severity, more exposure to ELA, and higher

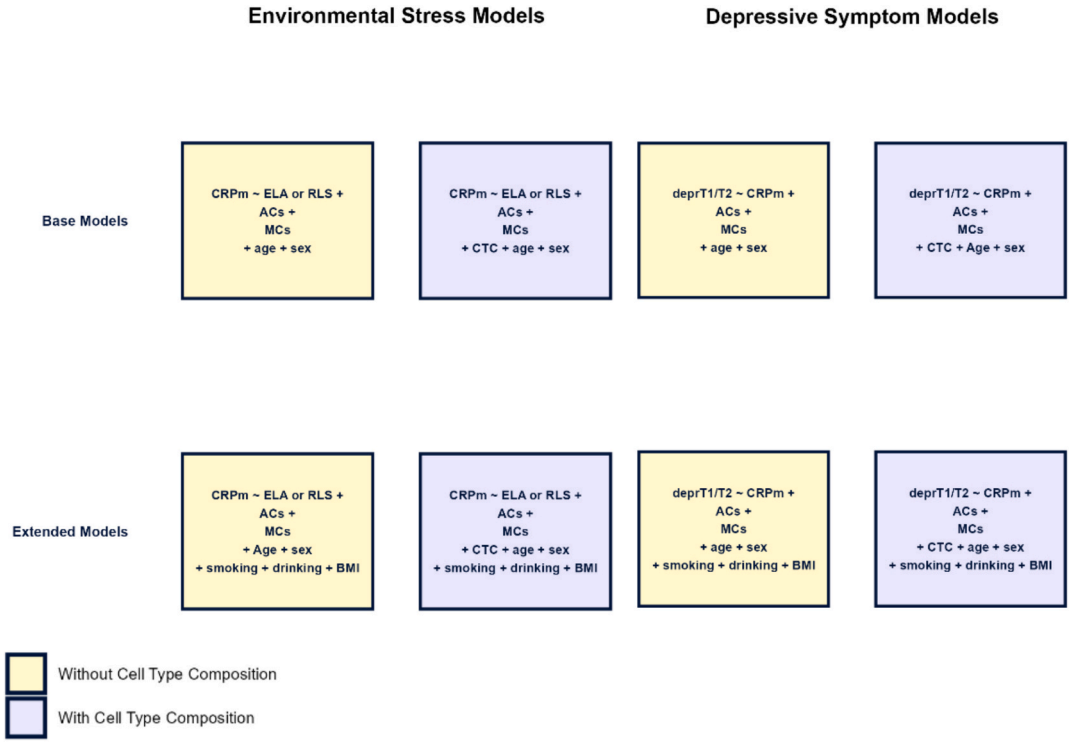

Fig. 1. Analysis overview.
Note. Overview of the analytical models tested, including different combinations of covariates and adjustment strategies. CRPm = CRP-related methylation score; ELA = early life adversity; RLS = recent life stress; ACs = ancestry components; MCs = methylation components; CTC = cell-type composition; deprT1/T2 = depression severity measured at baseline and follow-up; BMI = body mass index.

Table 1
Sample characteristics.

Measure	Full Sample ($n = 579$)	HC ($n = 320$)	MDD ($n = 259$)	p	Cramér's V	r
Sex T1 (f/m)	368/211	204/116	164/95	0.984	0.00	
Current MDD (yes) T1	174 (30.1%)	0 (0%)	174 (67.2%)	**<0.001**	0.73	
Current MDD (yes) T2 ($n = 407$)	62 (15.2%)	0 (0%)	62 (33.5%)	**<0.001**	0.46	
Comorbidity (yes) T1	69 (11.9%)	0 (0%)	69 (26.6%)	**<0.001**	0.38	
Age T1 (mean/SD)	35.29 (13.19)	35.21 (13.03)	35.39 (13.41)	0.975		0.00
CTQ Sum T1 (mean/SD)	38.29 (13.50)	33.55 (9.67)	44.14 (15.19)	**<0.001**		−0.42
LEQ Sum T1 (mean/SD)	8.96 (12.08)	5.31 (9.36)	13.46 (13.47)	**<0.001**		−0.43
HAMD T1 (mean/SD)	4.61 (6.19)	1.44 (2.49)	8.53 (7.09)	**<0.001**		−0.57
HAMD T2 (mean/SD) ($n = 407$)	3.06 (4.75)	1.15 (1.89)	5.34 (5.98)	**<0.001**		−0.59
CRPm score T1 (mean/SD)	−0.18 (0.01)	−0.19 (0.01)	−0.18 (0.01)	**0.049**		−0.08
AHRR methylation T1 (mean/SD)	2.77 (0.51)	2.84 (0.42)	2.68 (0.59)	**0.001**		0.14
BMI T1 (mean/SD)	24.74 (4.89)	24.24 (4.25)	25.37 (5.53)	0.086		−0.07
AUDIT Sum T1 (mean/SD)	4.16 (3.52)	4.27 (2.98)	4.02 (4.09)	**0.004**		0.12
hsCRP T1 (mean/SD)	1.52 (2.12)	1.34 (1.66)	1.77 (2.62)	0.301		−0.06
CD8T T1 (mean/SD)	0.07 (0.04)	0.07 (0.04)	0.06 (0.04)	0.060		0.08
CD4T T1 (mean/SD)	0.17 (0.05)	0.17 (0.05)	0.17 (0.05)	0.397		−0.04
NK cells T1 (mean/SD)	0.05 (0.04)	0.06 (0.04)	0.05 (0.04)	0.154		0.06
B cells T1 (mean/SD)	0.05 (0.02)	0.05 (0.02)	0.05 (0.02)	0.982		0.00
Monocytes T1 (mean/SD)	0.07 (0.02)	0.07 (0.02)	0.07 (0.02)	0.351		−0.04
Granulocytes T1 (mean/SD)	0.60 (0.08)	0.60 (0.08)	0.60 (0.08)	0.290		−0.04

Note. Descriptive characteristics of the total sample and stratified by diagnostic group HC vs. MDD. Group comparisons were conducted using Wilcoxon rank-sum tests. HAMD at T2 and Current MDD at T2 were assessed in a subsample of n = 407, hsCRP in a subsample of n = 317; all other variables were available for the full sample after imputation (n = 579). Cell-type composition (CD8T, CD4T, natural killer cells, B cells, monocytes, granulocytes) was estimated using the Houseman method (values range from 0 to 1; sum ~ 1). Comorbidities refer to lifetime diagnoses.

RLS than HC. AHRR (cg05575921) methylation was significantly lower in the MDD group, indicating greater tobacco exposure. BMI did not differ significantly between groups.

5.2. Validation of the CRP-related DNA methylation score

To validate the CRPm score and replicate previous findings (Hillary et al., 2024), we regressed hsCRP on CRPm. CRPm significantly predicted hsCRP ($b = 0.601$, $SE = 0.065$, $p < 0.001$), accounting for 21.3% of the variance (adjusted $R^2 = 0.213$). These findings support the validity of CRPm as an epigenetic proxy for systemic inflammation.

5.3. Associations between adversity and CRP-related DNA methylation

We next examined associations between life stress and CRPm using base models (adjusted for demographics and technical covariates) and extended models (additionally adjusting for health risk variables). Where CRPm showed significant associations with life stress, we conducted supplementary analyses using serum hsCRP to assess whether CRPm outperformed this conventional, but more transient, inflammatory marker.

5.4. Early life adversity

Higher CTQ scores were significantly associated with elevated CRPm scores in the base model ($b = 0.01$, $p = 0.017$, $R^2 = 0.015$, Fig. 2a and Table 2), explaining a modest amount of variance. This association remained robust after adjusting for estimated cell-type composition. Notably, no significant association was found between CTQ and acute hsCRP levels ($b = 0.00$, $p = 0.874$; Supplementary Table 1). In the extended model, the association between CTQ and CRPm was attenuated and no longer significant ($b = 0.00$, $p = 0.783$). In contrast, AHRR (cg05575921) methylation ($b = -0.25$, $p = 0.002$) and BMI ($b = 0.10$, $p < 0.001$) emerged as strong predictors, increasing explained variance (adjusted $R^2 = 0.257$; Supplementary Table 2). Exploratory mediation analyses indicated that the association between CTQ and CRPm was indirectly accounted for by BMI and AHRR (cg05575921) methylation (Supplementary Fig. 2; Supplementary Mediation Analyses). This highlights the role of health risk variables in shaping the association between early adversity and CRPm.

5.5. Recent life stress

Exposure to greater levels of RLS within the past six months was significantly associated with elevated CRPm in the base model ($b = 0.01$, $p = 0.032$; Fig. 2b and Table 2), accounting for a modest amount of variance (adjusted $R^2 = 0.013$). Results were consistent across models with and without correction for cell-type composition. Again, no corresponding association was observed for acute hsCRP levels ($b = 0.00$, $p = 0.591$; Supplementary Table 1). The association between RLS and CRPm was no longer significant in the extended model that accounted for health risk variables ($b = 0.00$, $p = 0.499$). Similar to the findings for early adversity, AHRR (cg05575921) methylation ($b = -0.24$, $p = 0.003$) and BMI ($b = 0.10$, $p < 0.001$) emerged as strong predictors of CRPm, increasing the explained variance (adjusted $R^2 = 0.258$; Supplementary Table 2). Again, exploratory mediation analyses suggested indirect pathways linking recent life stress to CRPm via BMI and AHRR (cg05575921) methylation (Supplementary Fig. 3; Supplementary Mediation Analyses). Results underscore the central role of health risk variables in the biological embedding of RLS.

5.6. Associations between CRP-related DNA methylation and depression

We then assessed associations between CRPm at baseline (T1) and depressive symptom severity at baseline (T1) and follow-up (T2), using base and extended models. Again, to evaluate whether CRPm outperforms the conventional inflammation marker, we ran corresponding analyses using serum hsCRP as the predictor where CRPm showed significant effects on depressive symptoms.

5.7. Cross-sectional associations

CRPm was significantly associated with depressive symptoms at T1 ($b = 0.68$, $p = 0.013$; Fig. 2c and Table 3). The effect remained significant after adjusting for cell-type composition, though explained variance was modest ($R^2 = 0.011$). Notably, no significant association was found between hsCRP and depressive symptoms at T1 ($b = 0.39$, $p = 0.145$; Supplementary Table 3). In the extended model, the association

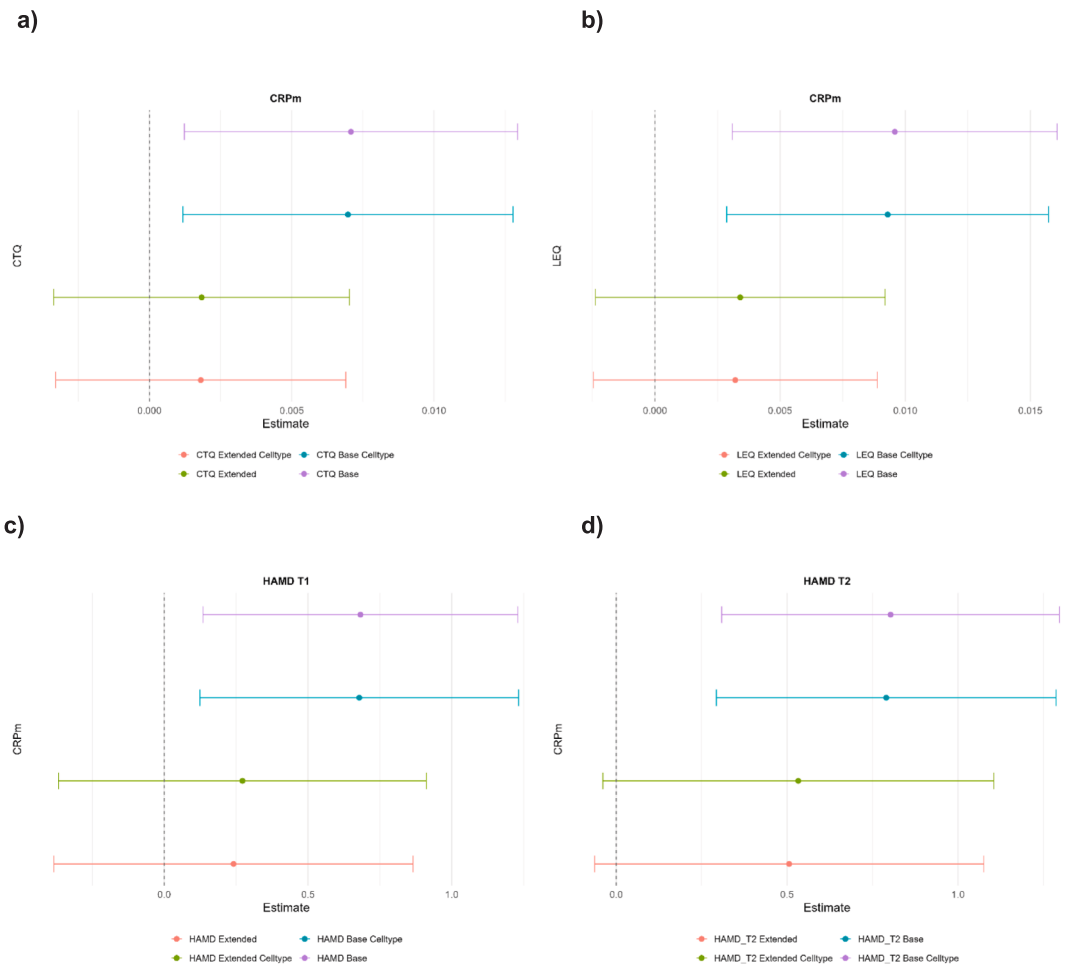

Fig. 2. Regression estimates across model specifications for associations between ELA, RLS, CRPm, and depression severity.
Note. Unstandardized regression estimates (points) with 95% confidence intervals (±2 SE) for CTQ and LEQ predicting CRPm, and CRPm predicting depressive symptoms at T1 and T2, across different model specifications. Models include base and extended versions, with and without adjustment for estimated cell-type composition. Colors indicate model specifications as shown in the legend. The dashed horizontal line at 0 denotes no effect. CRPm = CRP-related methylation score; ELA = early life adversity; RLS = recent life stress; CTQ = Childhood Trauma Questionnaire; LEQ = Life Events Questionnaire; HAMD T1/T2 = Hamilton Depression Rating Scale at baseline and 2 year follow-up.

between CRPm and depressive symptoms was attenuated and no longer significant (b = 0.24, p = 0.441). In contrast, AHRR (cg05575921) methylation emerged as a significant predictor of symptom severity (b = -1.84, $p < 0.001$), contributing to a modest increase in explained variance (adjusted R^2 = 0.034; Supplementary Table 4). These findings suggest that while CRPm may capture low-grade inflammatory processes linked to depressive symptoms, its predictive utility is substantially influenced by health risk variables.

5.8. Longitudinal associations

Baseline CRPm predicted depressive symptoms at T2 (b = 0.79, p = 0.002; Fig. 2d and Table 3), with effects remaining after adjusting for cell-type composition (R^2 = 0.024). No significant association was found between hsCRP and depressive symptoms at T2 (b = 0.29, p = 0.196; Supplementary Table 3). This association was non-significant in the extended model (b = 0.51, p = 0.076). In contrast, AHRR (cg05575921) methylation (b = -1.29, p = 0.004) and alcohol intake (b = 0.15, p = 0.037) at baseline emerged as significant predictors of depressive symptoms at T2 (Supplementary Table 4). After adjusting for cell-type composition, the effect of age also reached significance (b = 0.04, p = 0.040). The extended model explained a slightly larger proportion of variance (adjusted R^2 = 0.055). These results suggest that while CRPm may carry predictive information for future depressive symptoms, its effect is partly accounted for by health risk variables.

5.9. Sensitivity analyses

Sensitivity analyses indicated that the main findings were robust across missing-data patterns, alternative model specifications, and subgroup stratification. Missingness was generally low (Supplementary Table 5). Although CTQ missingness differed across diagnostic groups, complete CTQ case re-estimation of all CTQ–CRPm models yielded results fully consistent with the main analyses (Supplementary Table 6). Stratified analyses indicated that adversity–CRPm and CRPm–depression associations were more consistent in males and, to a lesser extent, in individuals with MDD. For more information see Supplementary Analyses.

6. Discussion

Low-grade inflammation is increasingly recognized as a potential driver of depressive symptom development and persistence (Mac Giollabhui et al., 2021; Osimo et al., 2020; Milaneschi et al., 2021; Barbu et al., 2022; Moriarity et al., 2020). Building on this evidence, the present study examined CRPm, a DNA methylation–derived proxy of CRP as a potential molecular mechanism linking environmental adversity to depressive symptoms. This approach addresses a key gap in

Table 2
Regression statistics for ELA and RLS models predicting CRPm at baseline.

Model	CTQ Base		CTQ Base + Cell-Types		LEQ Base		LEQ Base + Cell-Types	
Predictors	Estimate	p	Estimate	p	Estimate	p	Estimate	p
Intercept	−0.06 (−1.69 – 1.58)	0.945	0.26 (−1.50 – 2.01)	0.774	0.17 (−1.45 – 1.78)	0.840	0.45 (−1.28 – 2.18)	0.611
CTQ Sum T1	0.01 (0.00 – 0.02)	**0.017**	0.01 (0.00 – 0.02)	**0.024**				
LEQ Sum T1					0.01 (0.00 – 0.02)	**0.032**	0.01 (0.00 – 0.02)	**0.039**
Age T1	0.00 (−0.00 – 0.01)	0.377	0.00 (−0.00 – 0.01)	0.385	0.00 (−0.00 – 0.01)	0.259	0.00 (−0.00 – 0.01)	0.319
Sex T1	−0.31 (−1.29 – 0.66)	0.526	−0.29 (−1.27 – 0.69)	0.563	−0.31 (−1.29 – 0.67)	0.531	−0.28 (−1.26 – 0.71)	0.582
Technical Covariates								
AC 1 T1	2.01 (−5.64 – 9.66)	0.605	3.11 (−4.63 – 10.84)	0.430	2.34 (−5.30 – 9.98)	0.548	3.46 (−4.27 – 11.18)	0.379
AC 2 T1	−6.30 (−14.24 – 1.64)	0.120	−6.75 (−14.68 – 1.18)	0.095	−6.79 (−14.74 – 1.17)	0.094	−7.24 (−15.19 – 0.70)	0.074
AC3 T1	2.30 (−5.59 – 10.19)	0.567	2.31 (−5.61 – 10.22)	0.567	2.15 (−5.75 – 10.05)	0.593	2.07 (−5.85 – 9.99)	0.607
MC1 T1	0.00 (−0.00 – 0.00)	0.344	0.00 (−0.00 – 0.00)	0.382	0.00 (−0.00 – 0.00)	0.402	0.00 (−0.00 – 0.00)	0.438
MC2 T1	0.00 (−0.00 – 0.00)	0.669	0.00 (−0.00 – 0.00)	0.672	0.00 (−0.00 – 0.00)	0.723	0.00 (−0.00 – 0.00)	0.730
MC3 T1	0.00 (−0.00 – 0.00)	0.804	0.00 (−0.00 – 0.00)	0.746	0.00 (−0.00 – 0.00)	0.740	0.00 (−0.00 – 0.00)	0.684
MC4 T1	0.00 (−0.00 – 0.00)	0.275	0.00 (−0.00 – 0.00)	0.252	0.00 (−0.00 – 0.00)	0.281	0.00 (−0.00 – 0.00)	0.258
MC5 T1	0.00 (−0.00 – 0.00)	0.434	0.00 (−0.00 – 0.00)	0.455	0.00 (−0.00 – 0.00)	0.432	0.00 (−0.00 – 0.00)	0.454
Cell-Types								
CD8T T1			−0.16 (−3.21 – 2.89)	0.917			−0.45 (−3.50 – 2.60)	0.772
CD4T T1			−2.52 (−4.51 – -0.53)	**0.013**			−2.51 (−4.50 – -0.51)	**0.014**
NK cells T1			0.69 (−1.78 – 3.17)	0.582			0.73 (−1.75 – 3.21)	0.561
B cells T1			1.31 (−4.09 – 6.70)	0.634			1.74 (−3.66 – 7.13)	0.527
Monocytes T1			−0.27 (−5.23 – 4.69)	0.915			−0.19 (−5.16 – 4.78)	0.941
R^2 adjusted	0.015		0.021		0.013		0.018	

Note. Unstandardized regression coefficients (b) with 95%-CI, p-values, and adjusted R^2 values from linear regression models predicting CRPm based on CTQ or LEQ. Base models, with and without adjustment for estimated cell-type composition, are displayed. Empty cells indicate that the predictor was not included in the respective model. CRPm = CRP-related methylation score; CTQ = Childhood Trauma Questionnaire; LEQ = Life Events Questionnaire; ACs = ancestry components; MCs = methylation components.

Table 3
Regression statistics for baseline CRPm predicting depression severity at T1 and T2.

Model	HAMD T1 Base		HAMD T1 Base + Cell-Types		HAMD T2 Base		HAMD T2 Base + Cell-Types	
Predictors	Estimate	p	Estimate	p	Estimate	p	Estimate	p
Intercept	5.70 (−2.73 – 14.14)	0.185	4.87 (−4.29 – 14.03)	0.297	4.93 (−3.08 – 12.93)	0.227	3.23 (−5.25 – 11.72)	0.454
CRPm T1	0.68 (0.14 – 1.22)	**0.013**	0.68 (0.13 – 1.22)	**0.015**	0.79 (0.30 – 1.28)	**0.002**	0.80 (0.32 – 1.29)	**0.001**
Age T1	0.01 (−0.03 – 0.05)	0.684	−0.00 (−0.04 – 0.04)	0.918	0.04 (0.00 – 0.07)	**0.046**	0.05 (0.01 – 0.09)	**0.013**
Sex T1	−0.83 (−5.97 – 4.30)	0.750	−0.32 (−5.47 – 4.83)	0.903	−1.92 (−6.78 – 2.94)	0.438	−1.67 (−6.49 – 3.14)	0.494
Technical Covariates								
AC 1 T1	−5.33 (−51.98 – 41.33)	0.823	−7.37 (−54.30 – 39.55)	0.758	24.65 (−13.28 – 62.59)	0.202	20.25 (−17.64 – 58.14)	0.294
AC 2 T1	25.49 (−24.66 – 75.64)	0.318	25.64 (−24.54 – 75.82)	0.316	34.48 (−5.13 – 74.09)	0.088	32.82 (−6.27 – 71.91)	0.100
AC 3 T1	30.53 (−19.52 – 80.58)	0.231	29.98 (−20.34 – 80.30)	0.242	−3.12 (−42.37 – 36.13)	0.876	1.98 (−36.88 – 40.85)	0.920
MC 1 T1	−0.00 (−0.00 – 0.00)	0.905	0.00 (−0.00 – 0.00)	0.991	−0.00 (−0.00 – 0.00)	0.495	−0.00 (−0.00 – 0.00)	0.499
MC 2 T1	−0.00 (−0.00 – 0.00)	0.998	0.00 (−0.00 – 0.00)	0.913	−0.00 (−0.00 – 0.00)	0.197	−0.00 (−0.00 – 0.00)	0.310
MC 3 T1	0.00 (−0.00 – 0.00)	0.413	0.00 (−0.00 – 0.00)	0.555	0.00 (−0.00 – 0.00)	0.471	0.00 (−0.00 – 0.00)	0.663
MC 4 T1	0.00 (−0.00 – 0.00)	0.782	0.00 (−0.00 – 0.00)	0.846	0.00 (−0.00 – 0.00)	0.419	0.00 (−0.00 – 0.00)	0.511
MC 5 T1	−0.00 (−0.00 – 0.00)	0.168	−0.00 (−0.00 – 0.00)	0.167	0.00 (−0.00 – 0.00)	0.791	0.00 (−0.00 – 0.00)	0.963
Cell-Types								
CD8T T1			−14.64 (−30.04 – 0.77)	0.063			4.82 (−10.15 – 19.79)	0.527
CD4T T1			5.05 (−6.22 – 16.32)	0.379			2.86 (−6.99 – 12.71)	0.568
NK cells T1			−13.20 (−26.84 – 0.44)	0.058			−18.02 (−30.16 – -5.88)	**0.004**
B cells T1			−1.66 (−29.55 – 26.23)	0.907			−19.98 (−46.45 – 6.48)	0.138
Monocytes T1			18.13 (−8.75 – 45.01)	0.186			28.83 (4.46 – 53.21)	**0.021**
R^2 adjusted	0.011		0.019		0.024		0.054	

Note. Unstandardized regression coefficients (b) with 95%-CI, p-values, and adjusted R^2 values for CRPm predicting depressive symptom severity (HAMD scores) at baseline (T1) and follow-up (T2). Base models with and without adjustment for estimated cell-type composition are shown. Empty cells indicate that the predictor was not included in the respective model. CRPm = CRP-related methylation score; ACs = ancestry components; MCs = methylation components.

understanding how stress may become biologically embedded via epigenetic regulation of inflammatory pathways. Consistent with prior work (Hillary et al., 2024), we showed that CRPm explained 21.3% of the variance in hsCRP levels, more than twice the variance reported in previous studies. Importantly, both ELA and RLS were significantly associated with increased CRPm. Furthermore, CRPm predicted depressive symptoms both cross-sectionally and prospectively over two years. These associations could not be replicated when hsCRP was used instead of CRPm. Together, our results underscore CRPm as a comparatively stable epigenetic proxy of chronic, low-grade inflammation with relevance for depressive symptomatology.

Our findings are consistent with those of previous EWAS, which suggest that exposure to environmental adversity is associated with DNAm alterations at CpG sites relevant to genes involved in immune regulation (Parade et al., 2021; Opsasnick et al., 2024; Robakis et al., 2022; Reuben et al., 2020; Palma-Gudiel et al., 2021; Pfeiffer et al., 2022; Liu et al., 2023). However, the results of many of these studies are limited by smaller sample sizes and are inconsistent at the single-CpG-site level. While epigenetic scores offer promising tools to investigate how adversity may contribute to chronic low-grade inflammation, their application has remained relatively limited. Supporting our results, one study found that cumulative postnatal adversity across the first seven years of life prospectively predicted elevated CRPm at age 7 (Barker et al., 2018). Similarly, data from the E-Risk Longitudinal Twin Study demonstrated higher CRPm at age 18 among individuals raised in socioeconomically disadvantaged neighborhoods (Reuben et al., 2020). Extending these findings, our results suggest that adversity-related changes in CRPm may endure from childhood into mid-adulthood, potentially explaining the persistence of low-grade inflammation well beyond the period of stress exposure.

In terms of clinical relevance, our results differ from earlier studies that failed to identify associations between previous versions of the CRPm score and MDD. For example, initial analyses from the Avon Longitudinal Study of Parents and Children (ALSPAC) linked CRPm at birth, but not at age 7, to psychotic experiences between ages 10 and 28, while no association with depressive episodes was observed (Edmondson-Stait et al., 2022). Similarly, in the Stratifying Resilience and Depression Longitudinally study, CRPm was unrelated to any measure of MDD but associated with reductions in grey matter volume and white matter integrity (Green et al., 2021). However, a more recent study reported an association with depression when employing an updated, more robust CRPm score, stronger even than those observed for serum CRP (Verschoor et al., 2023), although this score still explained only half the variance in CRP levels compared to the one used in our study. Together, these findings tentatively suggest that advances in CRPm score development, such as the use of elastic net regression

(Hillary et al., 2024), may improve the detection of associations with mental health outcomes, where effect sizes are usually small. Notably, we also observed stronger predictive effects of CRPm on depressive symptoms over time than at baseline, suggesting that low-grade inflammation may exert a more cumulative or delayed influence on mental health. These findings are consistent with what is, to our knowledge, the only existing study to have linked CRPm to both stress exposure and psychopathology. Using data from the ALSPAC cohort, that study showed that postnatal adversity was associated with elevated CRPm at age 7, which in turn predicted internalizing symptoms later in childhood and adolescence (Barker et al., 2018).

Sensitivity and stratified analyses further informed the interpretation of our findings. While CRPm did not robustly differentiate diagnostic groups, associations between adversity, CRPm, and depressive symptom severity were primarily observed in individuals with MDD. This pattern suggests that CRPm is not a simple diagnostic marker per se but rather reflects stress-related inflammatory burden that becomes most relevant in clinically affected individuals. Exploratory sex-stratified analyses further indicated that men showed higher CRPm scores, consistent with earlier studies (Barker et al., 2018; Verschoor et al., 2023), and that associations between adversity, CRPm, and depressive symptom severity were more pronounced in men. Although meta-analytic evidence indicates higher average levels of acute inflammatory markers in women with depression (Jarkas et al., 2024), mean level differences do not necessarily translate into stronger associations with depressive symptom severity. Consistent with this pattern, some epidemiological studies have reported stronger associations between serum CRP and depressive symptoms in men, even after adjustment for lifestyle factors (Elovainio et al., 2009; Ford and Erlinger, 2004). These patterns should be interpreted cautiously and may reflect sex-related differences in cardiometabolic risk profiles, health-related behaviors, differences in biological susceptibility, or a combination of these factors.

Importantly, the observed associations between CRPm and both stress exposure and depressive symptoms were attenuated in extended models including BMI, smoking behavior (AHRR [cg05575921] methylation), and alcohol intake, with BMI and smoking behavior health-related emerging as independent predictors of CRPm and, to a lesser extent, depressive symptoms. In line with this pattern, exploratory mediation analyses suggested that associations of both ELA and RLS with CRPm were largely accounted for by BMI and AHRR methylation. Rather than acting as mere confounders, health-related behaviors may therefore constitute key pathways through which environmental adversity becomes biologically embedded (Opsasnick et al., 2024). From this perspective, CRPm may be conceptualized as an integrative index of inflammatory burden shaped by stress-related health behaviors, with relevance for mental health. Consequently, interventions aimed at improving health behavior, such as smoking cessation and weight reduction, may influence DNAm patterns and thereby modulate inflammatory risk profiles (Lu et al., 2022). Such approaches could be particularly effective when integrated into personalized treatment plans for individuals with inflammation-linked depression and stress-related mental health problems.

Interestingly, unlike for CRPm, we did not observe associations between adversity and serum hsCRP, nor between serum hsCRP and depressive symptoms. Although limited to a smaller subsample (n = 317), these results align with prior findings showing that CRPm is more strongly associated with MDD and with structural brain alterations, such as reductions in cortical volume and white matter integrity, compared to serum CRP (Green et al., 2021; Verschoor et al., 2023; Stevenson et al., 2020). These findings support the notion that CRPm may better reflect chronic, low-grade inflammatory processes relevant to mental health. In particular, CRPm has been shown to exhibit higher temporal stability and is less sensitive to transient influences such as infections or acute stressors (DeGoma et al., 2012; Bower et al., 2012), making it a more robust proxy of cumulative inflammation exposure than single-time-point serum CRP. From a methodological perspective, this distinction is particularly relevant for mental health research, where inflammatory processes of interest are often subtle, chronic, and embedded in long-term exposure patterns rather than acute immune responses. Accordingly, CRPm may offer a complementary approach for research designs aiming to link cumulative inflammatory burden to long-term biological signatures, without requiring repeated serum measurements.

Despite several strengths, including the use of a robust, state-of-the-art CRPm score, rigorous control for genetic and cellular confounds, interview-based clinical phenotyping, and a partially longitudinal design, certain limitations warrant consideration. First, stress exposure was assessed retrospectively via self-report, which may be susceptible to recall bias (Goltermann et al., 2023; Colombo et al., 2020). Second, while the HAMD provides a rater-based assessment of depressive symptom severity, it may be less sensitive to symptom profiles often associated with inflammation-related depression, such as fatigue or hypersomnia. Incorporating scales that are specifically designed to detect immune-related symptom profiles could strengthen future research. Third, CRPm was measured at a single time-point, limiting the ability to track intra-individual temporal dynamics. Lastly, the observational design of our study precludes any definitive conclusions about causality. Future studies should further broaden the scope to include diverse psychiatric populations, given the growing recognition of inflammation as a transdiagnostic vulnerability factor (Milaneschi et al., 2021; Costello et al., 2019; Misiak et al., 2021; Park and Miller, 2020; Yuan et al., 2019).

In summary, this study provides novel evidence that a methylation-based index of chronic inflammation is shaped by psychosocial stress through health-related risk behaviors and predicts depressive symptoms over time. Together, these findings support inflammation as a key biological pathway linking stress exposure to depression, while underscoring the importance of health-related behaviors in shaping this pathway. By integrating the biological imprint of stress-related behavioral factors, CRPm emerges as a promising and temporally stable marker for studying inflammation in depression. With increasing sample sizes, methylation-based inflammatory indices such as CRPm may further enable dimensional or exploratory stratified analyses of inflammation-related symptom profiles, for example, by distinguishing individuals with relatively higher versus lower chronic inflammatory burden. However, the clinical utility and relevance of such stratification approaches remain important targets for future research.

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

During the preparation of this work, some authors used ChatGPT (GPT-5, OpenAI) for language editing (grammar and spelling). The authors subsequently reviewed and revised the content as necessary and take full responsibility for the final version of the manuscript.

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Funding

This work is part of the German multicenter consortium "Neurobiology of Affective Disorders. A translational perspective on brain structure and function", funded by the German Research Foundation (Deutsche Forschungsgemeinschaft DFG; Forschungsgruppe/Research Unit FOR2107). The principal investigators are Tilo Kircher (speaker FOR2107; DFG grant numbers KI 588/14-1, KI 588/14-2, KI 588/15-1, KI 588/17-1), Udo Dannlowski (co-speaker FOR2107; DA 1151/5-1, DA 1151/5-2, DA 1151/6-1), Igor Nenadić (NE 2254/1-2, NE2254/2-1, NE2254/3-1, NE2254/4-1), Markus M. Nöthen (NO 246/10-1, NO 246/10-2), Tim Hahn (HA 7070/2-2), Andreas Jansen (JA 1890/7-1, JA 1890/7-2), Benjamin Straube (STR 1146/18-1). Nina Alexander, Tilo Kircher, Benjamin Straube, and Igor Nenadić were further supported by the Hessian Ministry of Higher Education, Science, Research and Art (LOEWE project "DYNAMIC" Grant Number: LOEWE1/12/519/03/09.001(0009)/98). This work was supported in part by the SFB/TRR 393 consortium from the German Research Foundation (DFG). The principal investigators are Tilo Kircher (speaker SFB/TRR 393), Nina Alexander, Udo Dannlowski, Andreas Forstner, Tim Hahn, Hamidreza Jamalabadi, Andreas Jansen, Elisabeth J. Leehr, Igor Nenadić, Susanne Meinert, Frederike Stein, Benjamin Straube. Nico Melzer was supported by the German Federal Ministry of Education and Research (Comprehensive, Orchestrated, National Network to Explain, Categorize and Treat autoimmune encephalitis and allied diseases within the German Network for Research on Autoimmune Encephalitis – CONNECT GENERATE 2.0; Grant Number: 01GM2208A). Jonathan Repple was supported by the LOEWE program of the Hessian Ministry of Science and Arts (Grant Number: LOEWE1/16/519/03/09.001(0009)/98).

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Tilo Kircher** received unrestricted educational grants from Servier, Janssen, Recordati, Aristo, Otsuka, Neuraxpharm. **Markus Nöthen** reported personal fees from HMG Systems Engineering GmbH, Deutsches Ärzteblatt, and EVERIS Belgique outside the submitted work; employment by Life & Brain GmbH; and holding shares in Life & Brain GmbH. **Jonathan Repple** received speaker's honoraria from Janssen, Hexal, Neuraxpharm and Novartis. **Nico Melzer** received honoraria for lecturing and travel expenses for attending meetings from Biogen Idec, GlaxoSmith Kline, Teva, Novartis Pharma, Bayer Healthcare, Genzyme, Alexion Pharmaceuticals, Fresenius Medical Care, Diamed, UCB Pharma, AngeliniPharma, BIAL and Sanofi-Aventis. He further received royalties for consulting from UCB Pharma, Alexion Pharmaceuticals and Sanofi and received financial research support from Euroimmun, Fresenius Medical Care, Diamed, Alexion Pharmaceuticals, Novartis Pharma, and Sanofi. The remaining authors have no conflicts of interest.

Acknowledgments

We are deeply indebted to all study participants and staff. A list of acknowledgments can be found at: for2107.de/acknowledgements.

Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.bbi.2026.106807.

Data availability

Data will be made available on request.

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