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Citation details
Dittrich K, Boedeker K, Kluczniok D, Hindi Attar C, Winter SM, Roepke S, et al. Elevated inflammatory markers in women with remitted major depressive disorder and the role of early life maltreatment. Brain, Behavior, and Immunity. 2021;97: 219–225. DOI: 10.1016/j.bbi.2021.07.024

Running Head: INFLAMMATION IN REMITTED DEPRESSION

Elevated Inflammatory Markers in Women with Remitted Major Depressive Disorder and the Role of Early Life Maltreatment

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Word Count: 4709

Abstract

Major depressive disorder (MDD) has been linked to elevated inflammation markers. It remains unclear whether the elevation of C-reactive protein (CRP) and interleukin-6 (IL-6) levels are not only observable in acute MDD but also in patients after remission. MDD is a common sequela of early life maltreatment (ELM), which has also been associated with elevated inflammation markers. While the majority of studies investigated (acute) MDD and ELM as isolated predictors of inflammation, a few studies found inflammation levels to be more pronounced in patients with MDD that were exposed to ELM. This investigation included both ELM and MDD in one study and aimed at distinguishing between the effects of MDD in remission (rMDD) and ELM and investigating potential accumulative effects on the inflammatory markers CRP and IL-6 in a population of *N*=126 women (*n*=122 for CRP and *n*=66 for IL-6). We further investigated how disorder characteristics (course and severity) and specific types of ELM affect levels of CRP and IL-6. We found that rMDD predicted levels of CRP and IL-6 and physical abuse predicted levels of CRP when considering both predictors simultaneously, while other types of ELM did not. A later onset of MDD and a shorter time interval since the last episode were associated with higher levels of IL-6. Our findings contribute to the existing literature on the association between MDD and inflammation, suggesting that elevated levels of inflammation markers may persist even after remission of MDD. Our findings on physical abuse as a specific predictor of CRP in the presence of rMDD suggest that different types of ELM could result in distinct inflammation profiles.

Keywords: depression; maltreatment; early life stress; inflammation; CRP; IL-6

Highlights:

- rMDD and ELM were investigated together in one study.
- rMDD predicted higher levels CRP and IL-6 when controlling for ELM.
- Physical abuse predicted higher CRP (but not IL-6) when controlling for rMDD.
- Other types of ELM did not predict CRP or IL-6.
- Onset age of MDD and time elapsed since the last episode was associated with IL-6.

1. Introduction

Major depressive disorder (MDD) is a common disease affecting about 6% of the world population and the second leading cause of disability worldwide (Bromet et al., 2011; Ferrari et al., 2013; Lépine and Briley, 2011). Despite increasing research efforts, the exact mechanisms of the etiology and pathophysiology of MDD are not fully understood. A promising area of research focuses on the role of inflammation in MDD. A number of inflammatory markers that are significantly elevated in MDD have been identified, including the acute phase protein C-reactive protein (CRP) and the cytokine interleukin (IL)-6 (meta-analyses by Dowlati et al., 2010; Haapakoski et al., 2015; Howren et al., 2009). To date, not many studies have investigated whether inflammatory markers are also altered after remission of MDD. Only a few studies indicate that disturbances to the immune system might persist after remission, by showing altered levels in several inflammation markers. Previous findings include a reduction in serum immunoglobulin A (IgA) levels (Gold et al., 2012), and elevated levels of interleukin-8 (IL-8) (Vogelzangs et al., 2016), tumor necrosis factor-α (TNF-α) (Narita et al., 2006), and serum amyloid A (SAA) (Kling et al., 2007). Results on CRP and IL-6 are currently limited and somewhat conflicting: Kling et al. (2007) found higher levels of CRP in *n*=18 women with MDD in remission (rMDD) compared to healthy controls, but Frommberger et al. (1997) showed that IL-6 levels decreased after remission and were not significantly different from those of healthy controls in a sample of *n*=12 MDD patients. Further research is therefore needed to clarify whether the elevation of CRP and IL-6 levels is not only observable in patients with acute depression but also after remission of MDD. It is also not clear how specific disorder characteristics of MDD (like course and severity) might be linked with inflammation, as the research does not show a definite pattern. For example, while some studies found associations between MDD severity and immune marker levels (Dowlati

et al., 2010; Howren et al., 2009; Köhler-Forsberg et al., 2017), others did not (Haapakoski et al., 2015; Vogelzangs et al., 2012).

Alterations in inflammatory systems, marked by significantly elevated levels of pro-inflammatory markers such as CRP and IL-6, have also been linked with a prior history of early life maltreatment (ELM) (meta-analysis by Baumeister et al., 2016). As individuals who experienced some form of severe early life stress show a more than twofold risk of developing MDD later in life (Heim and Binder, 2012), both a history of ELM and MDD often co-occur. Interestingly, while the overall effect sizes of ELM on CRP and IL-6 were rather small, the largest effects were found in clinical samples with a history of ELM (Baumeister et al., 2016). In accordance with these findings, other studies found inflammation levels to be more pronounced in patients with MDD that were exposed to ELM (Danese et al., 2008; De Punder et al., 2018; Grosse et al., 2016).

Not all studies came to the conclusion that ELM has a specific impact on immune system regulation. A recent study by Kuzminskaite (2020) conducted in a large sample (n>2500) found little evidence for effects of ELM on CRP and IL-6. They found only small effects in the comparison of patients with very severe ELM with a control group without maltreatment experiences, indicating that the severity of ELM might play a role in this context. They found no effects, however, when controlling for psychiatric disorders. These studies demonstrate the importance of observing these co-occurring risk factors together in one study to identify their individual and accumulative effects. Considering the diverging findings on inflammation in MDD in remission it might also answer the question whether elevated levels of inflammation would only be present in a certain subgroup of rMDD patients with ELM.

A possible explanation for these apparently contradictory findings between studies on the effects of ELM on inflammation could be related to the specific effects of the type of

maltreatment experienced. Baumeister et al. (2016) found that specific types of ELM might differentially impact on single inflammation markers. Specifically, they found that CRP levels correlated with experiences of parental absence, while levels of IL-6 correlated with a history of physical and sexual abuse. However, research on the specific effects of ELM type is still limited.

To address these open research questions, we examined serum levels of CRP and IL-6 in a group of women with rMDD and with a history of ELM. The primary aims of the present study were to investigate and distinguish the effects of rMDD and different types of ELM on the inflammatory markers CRP and IL-6. We were specifically interested in MDD after remission to clarify the role of inflammatory biomarkers as state or trait indicators of MDD. Considering previous research, we expected both rMDD and ELM to impact on CRP and IL-6. More precisely, we expected both rMDD and severity of ELM to predict higher levels of CRP and IL-6 and an interaction of both predictors in that the effect of severity of ELM would be even larger in women with rMDD.

Whether the effect of ELM would thereby depend on the type of maltreatment experienced was a specific further question that we wanted to address on an exploratory level as previous research on this topic has been contradictory. Our secondary aim was to further explore how disorder characteristics of MDD (course and severity) affect CRP and IL-6 levels in patients with rMDD. We expected severity of residual MDD symptoms to be positively and time since last episode and intake of antidepressants to be negatively correlated with CRP and IL-6.

2. Method

2.1 Participants and Procedure

This study was conducted within the framework of the Understanding and Breaking the Intergenerational Cycle of Abuse (UBICA) multicenter project that investigated the effects of a maternal history of abuse and depression on the next generation. Our investigation included *N*=126 women (for CRP *n*=122 and IL-6 *n*=66) with and without rMDD. A history of MDD was diagnosed using the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). MDD had to be in the remitted state, and only women with a Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) score of below or equal to seven were included. We intentionally recruited women with and without MDD and with and without ELM to ensure a (partial) co-occurrence of both risk factors in our sample in order to better distinguish between the effects of both on our outcomes of interest. A history of ELM was defined as having experienced at least one type of maltreatment or neglect according to the main scales (physical, sexual and/or emotional abuse, as well as neglect and/or parental antipathy) of the Childhood Experience of Care and Abuse Interview (CECA; Bifulco et al., 1994). In our sample 28 (22.2 %) experienced no maltreatment at all, 35 (27.8 %) mild, 35 (27.8 %) moderate, and 28 (22.2 %) severe forms of ELM. The frequencies of the types of ELM experienced with at least moderate severity and further sample characteristics are shown in Table 1. For our analyses we used a dimensional score of the CECA scales to account for the importance of ELM severity for immunological outcomes. Both rMDD and ELM were assessed using structured interviews instead of self-report measures to assure an objective and detailed assessment of both predictors.

We excluded women from the study who had neurological diseases, a lifetime history of schizophrenia or manic episodes, current or ongoing acute MDD, alcohol or drug abuse or

addiction, or chronic inflammatory diseases, and personality disorders as assessed by standardized interviews including the MINI (Sheehan et al., 1998) and the International Personality Disorder Examination (IPDE; Loranger et al., 1997; Mombour et al., 1996). Women with rMDD could have a comorbid DSM-IV axis I disorder, which was controlled for in our analyses if it did not interfere with study participation. However, current intake of anti-inflammatory medication and intake of benzodiazepines within the past 6 months was an exclusion criterion. Treatment with other psychotropic drugs was not an exclusion criterion if the dosages had been stable for at least 2 weeks prior to joining the study. As the UBICA project focuses on the intergenerational effects of ELM and MDD, only women with children at elementary school age (5-12 y.) were included. The study participants were recruited through advertisements in psychotherapeutic, psychiatric, gynecological and pediatric out-patient clinics, and educational counselling and youth welfare offices. All participants provided written informed consent. The study protocol was approved by the ethics committee of the Charité – Universitätsmedizin Berlin.

2.2 Measures

2.2.1 Inflammatory Measures

Serum high sensitivity CRP concentrations were analyzed using a commercially available Instant ELISA kit (eBioscience), according to the manufacturer's instructions. The limit of detection was 3 pg/ml. The intra- and inter-assay coefficients of variability for serum CRP measurements were 6% and 8%, respectively. Plasma IL-6 concentrations were analyzed using a commercially available high sensitivity ELISA kit (eBioscience), according to the manufacturer's instructions. The limit of detection was 0.03 pg/ml. The intra- and inter-assay coefficients of variability for plasma IL-6 measurements were 8% and 7%, respectively.

2.2.2 Major Depressive Disorder in remission (rMDD)

rMDD and other comorbid DSM-IV axis I disorders were assessed using the MINI (Lecrubier et al., 1997; Sheehan et al., 1998), a fully structured diagnostic interview reported to have good psychometric properties (Lecrubier et al., 1997; Sheehan et al., 1997). The interviews were conducted by trained clinical psychologists. For a further characterization of rMDD, we elaborated the interview data by also assessing the number of depressive episodes and suicide attempts, the onset age of depression, the time interval since the last episode, the level of intake of antidepressant medication and the severity of current symptoms using the Beck Depression Inventory II questionnaire (Beck et al., 1996; Kühner et al., 2007). Of note, Age of onset, number of episodes, time since last episode was unrelated to severity of early life maltreatment in our sample.

2.2.3 Early Life Maltreatment (ELM)

For the assessment of ELM, the German version (Kaess et al., 2011) of the CECA interview (Bifulco et al., 1994) was used. The CECA is a semi-structured clinical interview that collects retrospective accounts of adverse childhood (up to 17 y.) experiences including sexual, physical abuse, emotional abuse, neglect and parental antipathy. These are rated on a four-point scale of severity (‘severe’, ‘moderate’, ‘mild’ or ‘little/none’) according to predetermined criteria and manualized threshold examples. The interviews were conducted by psychologists that had been trained (3-day training) and approved by Prof. Antonia Bifulco who developed the interview guidelines. Originally, lower scores on the four-point scales indicated a higher level of maltreatment severity. These were recoded, with higher scores indicating higher levels of maltreatment severity, to ease interpretation.

2.3 Data Analysis

CRP and IL-6 measures were first log transformed to normalize distributions. In a first step, we conducted correlation analyses to identify associations of rMDD and ELM (specific types and sum severity score) with levels of CRP and IL-6. Because specific types of ELM were part of the sum severity score of ELM we applied a Holm-Bonferroni correction for multiple testing on the *p*-values of these correlations. In favor of transparency for the reader and because these types of analyses have been exploratory, we presented raw *p*-values in Table 2, but noted which correlations would be significant after correction.

We then wanted to distinguish between the effects of rMDD and the severity of ELM on the inflammatory markers CRP and IL-6. Therefore, we conducted linear regression analyses with CRP and IL-6 as the outcomes and the severity of ELM and presence of rMDD (yes/no) as parallel predictors. Subsequently, we added the interaction term of rMDD and ELM to investigate a potential moderating effect of ELM on rMDD. We repeated these analyses for ELM types that showed significant correlations with CRP and IL-6 in the previous analyses. ELM was entered as a sum severity score of the five CECA main scales or a severity level of each specific type of ELM. ELM scores were mean-centered to counteract the problem of multicollinearity in moderation analyses. Within the group of women with rMDD (*n*(CRP) = 76; *n*(IL-6) = 33) we conducted correlation analyses to identify potential associations of disorders characteristics (like course and severity of MDD) with levels of CRP and IL-6. In all analyses, we controlled for other current DSM-IV axis I disorders, BMI and age, and intake of contraceptive medication. The BMI data was not available in two cases and was replaced by simple mean imputation. Due to limited funding IL-6 was only assessed in a smaller part of the sample. There was a large overlap of the CRP and IL-6 samples. 62 women provided both CRP and IL-6 samples. In only four cases IL-6 was available but no CRP (due to extraction issues). 122 women provided CRP but no IL-6 samples. Sample characteristics separately for the CRP

and IL-6 samples, respectively, can be found in the supplement. All analyses were performed with IBM SPSS Statistics 24 for Windows (IBM, Armonk, NY, USA).

3. Results

3.1 Effects of rMDD and ELM on Inflammatory Markers

The presence of rMDD was positively correlated with both CRP and IL-6 and the sum severity of ELM was correlated with CRP but not IL-6. When looking at specific types of ELM, we found that both higher neglect and physical abuse scores were associated with higher CRP, while higher neglect scores were also associated with higher IL-6. Of note, when applying a Holm-Bonferroni correction to these correlation analyses of sub-type, neglect would no longer be significantly related to CRP (p_{corr}=.072) and IL-6 (p_{corr}=.070), but physical abuse would yield a significant correlation (p_{corr}=.025) with CRP. All significant correlations showed medium effect sizes (see Table 2).

Regression analyses showed that women with rMDD had higher levels of CRP and IL-6 than did women without rMDD, also when controlling for ELM (Table 3). The sum severity of ELM did not have an impact on CRP or IL-6 levels when simultaneously considering rMDD as a predictor. No significant interaction effect was observed, meaning the effect of rMDD on CRP and IL-6 was not moderated by the severity of ELM. The results of the regression analyses are summarized in Table 3. When repeating these analyses for different subtypes of ELM, rMDD remained significant in all cases. The only type of ELM that was still significant when controlling for rMDD was Physical Abuse (b = .104, β = .187, p = .021), and no significant interaction effects were identified. Detailed analysis results on the types of ELM can be found in the Supplementary Material.

3.2 Disorder Characteristics in patients with rMDD

We found the onset age and time interval since the last episode of MDD to be associated with IL-6: a later onset age and a shorter time interval since the last episode correlated with higher levels of IL-6. As shown in Table 4, no significant association of CRP or IL-6 levels with the number of depressive episodes or suicide attempts, the severity of current symptoms, or the intake of antidepressant medication was found.

4. Discussion

The primary aim of the present study was to investigate and disentangle the effects of rMDD and different types of ELM on the inflammatory markers CRP and IL-6. When considering both rMDD and ELM in one analysis, the diagnosis of rMDD predicted higher levels of CRP and IL-6 in comparison to healthy controls, and a higher severity of physical abuse predicted higher levels of CRP. However, neither severity of other types of ELM nor the sum severity of ELM predicted these inflammatory markers when simultaneously considering rMDD. The second aim was to investigate whether certain disorder characteristics (course and severity) might affect CRP and IL-6 levels in patients with rMDD. In the group of women with rMDD, we found a later onset of depression and a shorter time interval since the last episode to be linked with higher levels of IL-6, but no significant association to the number of depressive episodes or suicide attempts, the severity of current symptoms, or the intake of antidepressant medication with levels of CRP and IL-6.

4.1 Inflammation in rMDD

While there are a large number of studies and meta-analyses that reported elevated levels of CRP and IL-6 in patients with acute MDD (meta-analyses by Dowlati et al., 2010; Haapakoski et al., 2015; Howren et al., 2009), only a few studies have been conducted on rMDD patients. Our results showing elevated levels of CRP and IL-6 in women with rMDD

may contribute to closing this gap. Our results correspond to those of Kling et al. (2007), who found higher levels of CRP in *n*=18 women with rMDD in comparison to healthy controls, but not to those of Frommberger et al. (1997), who showed that IL-6 levels decreased after remission and were not significantly different from healthy controls in a sample of *n*=12 MDD patients. We provided a larger and thoroughly diagnosed sample to confirm that, even after remission of depressive symptoms, the levels of inflammatory markers are elevated. Additionally, we could show that these effects remained significant also when controlling for a history of ELM. Our present findings on CRP and IL-6 are in accordance with findings on other inflammatory markers such as IgA, IL-8, TNF-α, and SAA, which have also shown alterations in rMDD (Gold et al., 2012; Kling et al., 2007; Narita et al., 2006; Vogelzangs et al., 2016).

These findings from patients with rMDD, in combination with results on the development of MDD, could help to facilitate a better understanding of the role of inflammation for the high recurrence rates in patients with MDD. As previously mentioned, up to 80% of rMDD patients experience at least one other episode in their life (Vos et al., 2004), and the elevated inflammatory markers in patients with rMDD might reflect this recurrence risk. Longitudinal studies have shown that elevated levels of CRP and IL-6 may also precede the development of MDD (Valkanova et al., 2013). For example, elevated IL-6 levels already evident in childhood may predict the later development of MDD in adulthood (Khandaker et al., 2014). Additionally, patients with severe infections and autoimmune diseases or who receive cytokines as part of their treatment show a higher risk of subsequent diagnosis of MDD (Benros et al., 2013; Myint et al., 2009).

Elevated inflammation markers might also pose an additional physical health risk and negatively affect treatment response in these patients. When becoming chronic, these alterations of the immune system in combination with HPA-axis and autonomic nerve system

alterations may lead to a higher risk for cardiovascular and metabolic diseases and have a pathological effect on the central nervous system (Otte et al., 2016). They also reflect a reduced ability to positively respond to conventional antidepressant therapy (Chamberlain et al., 2019). Patients with (r)MDD and elevated inflammation markers may therefore benefit from specific anti-inflammatory medical treatments (Köhler et al., 2014), but also from targeting inflammatory pathways through mindfulness-, exercise- and nutrition-based interventions (Creswell et al., 2012; Galland, 2010; Gleeson et al., 2011; Villalba et al., 2019).

4.2 Distinguishing between the Effects of MDD and ELM

Previous studies found higher inflammation levels in individuals with a history of ELM and more pronounced levels of CRP and IL-6 in MDD patients that were exposed to ELM than in MDD patients without a history of ELM (Baumeister et al., 2016; Danese et al., 2008; De Punder et al., 2018; Grosse et al., 2016). However, in a large-scale study, Kuzminskaite et al. (2020) found no evidence for effects of ELM on CRP and IL-6 when controlling for psychiatric disorders. Our results could help to clarify the apparent discrepancy. We found significant correlations of sum severity of ELM with CRP when rMDD was not included as a covariate. However, when rMDD was simultaneously considered as a predictor, the sum severity of ELM was no longer significant, which underlines the findings by Kuzminskaite. But, when investigating specific subtypes of ELM, we found the severity of physical abuse to predict higher levels of CRP even when controlling for rMDD. Therefore, in accordance with Baumeister et al. (2016), we conclude that specific types of ELM may be associated with distinct inflammation profiles, which could explain discrepant results between studies. An explanation might be that individuals react differently to deprivation (absence of environmental inputs) and threat (e.g. threat of an individual's physical integrity). These might be different dimension of ELM that affect outcomes distinctively or also even interact as they often co-occur (Reid and Danese, 2020). As the few existing results on types of ELM are heterogeneous

– Baumeister et al. (2016) in their meta-analysis found physical abuse related to IL-6 but not CRP – and most studies did not differentiate between different types of maltreatment (Fagundes and Way, 2014), further research is needed to draw definite conclusions. However, approaches based on single subtypes of ELM could also neglect the complexity and clustering of different types of ELM: Several studies found association of sexual abuse with inflammation, which is often co-occurring with other types of ELM and could therefore represent a higher severity of ELM exposure overall (Kerr et al., 2021).

There are further explanations for the discrepant findings between studies which complicate the comparability of studies (review by Reid and Danese, 2020): First of all, there are high levels of heterogeneity in the measurement of ELM and inflammation and the methods of analyses. While the majority of studies administered retrospective self-report measures, only few studies have used prospective measures of ELM, which resulted in more consistent findings of significant associations of ELM and inflammation (review by Kerr et al., 2021). Baldwin et al. (2019) assessed retrospective and prospective data of childhood maltreatment and found poor agreement within the same individuals. To date it is not clear how this might affect associations with inflammatory outcomes and further studies are needed to gain clarification whether inflammatory outcomes depend on types of measurement of ELM (subjective vs. objective, prospectively vs. retrospectively) (Reid and Danese, 2020).

Other methodological challenges are that there is little correlation between different markers of inflammation (salivary, blood and cerebral spinal fluid) and it is unclear whether this is simply due to a lack of connection or whether there are moderating factors that impact these correlations that would be needed to be considered (Reid and Danese, 2020). Studies using different markers might result in discrepant outcomes. Also the selection of biomarkers is an important issue, as the commonly measured markers, IL-6 and CRP, may not be sufficient

to establish the existence of an inflammatory state and might be elevated even in the absence of inflammation (Del Giudice and Gangestad, 2018).

.4.3 Disorder Characteristics in rMDD associated with Inflammation

Previous findings by other researchers on the effects of MDD characteristics on inflammation markers have been mixed. While some studies report associations of MDD severity with immune marker levels (Dowlati et al., 2010; Howren et al., 2009; Köhler-Forsberg et al., 2017), Haapakoski et al. (2015) found no significant associations between immune markers and symptom severity in their meta-analysis. Vogelzangs et al. (2012) found higher inflammation levels in men with current MDD and a later age of depression onset, but no effects due to duration and severity. These studies in patients with acute MDD are in line with our results in rMDD. We found an association between higher levels of IL-6 and a later MDD onset, but no links with markers for severity or duration. Increased inflammation could be a particular characteristic in patients with late-onset depression, which appears to corroborate findings of higher rates of familial history of vascular disease in patients with late-onset MDD (Kendler et al., 2009). We also found higher IL-6 levels in patients with more recent episodes of MDD, indicating that IL-6 levels possibly normalize when remission stabilizes over time. This could explain why Frommberger et al. (1997) found significant decreases in IL-6 levels after remission and no difference to healthy controls, while in our sample IL-6 levels were significantly elevated in rMDD patients.

4.4 Strengths and Limitations

The key strengths of the present study include the thorough assessment of mental health and ELM using structured clinical interviews and the detailed assessment of ELM types and MDD characteristics combined with the investigation of both rMDD and ELM in one study, that allowed for the assessment of both predictors. Also while most studies administered a

dichotomous approach in the assessment of maltreatment (Kerr et al., 2021), we provided dimensional data on the severity of ELM.

Other investigators argue that more pronounced inflammatory markers in individuals with both MDD and ELM may speak for a causal pathway from ELM to MDD (Danese et al., 2008; De Punder et al., 2018). However, the present cross-sectional analyses using retrospective measures of ELM do not allow conclusions on causal relationships. Studies investigating the mediational pathway from ELM to MDD via inflammatory markers would be desirable. The present data did not allow such analyses, as recruitment explicitly aimed at a group of individuals with concurrent ELM and MDD.As described above, retrospective and prospective measures of maltreatment might also result in different outcomes and would ideally be incorporated both in one study.

Another important issue is a potential lack of power to detect certain effects. Previous studies report small effect sizes for the effect of ELM on adult inflammation (Baumeister et al., 2016; Kerr et al., 2021). Therefore, larger sample sizes might be needed to detect effects of ELM. Especially our sample size of women with IL-6 (n=66) might have been too small to detect effects on ELM. This also concerns the investigation of specific subtypes of ELM, which might have been under-represented (see Table S3 in the supplement for detailed description of sample). Another issue worth mentioning is that for some parameter estimates (e.g. effect of rMDD on IL-6) CIs are quite large and the lower boundary close to zero, which represents great uncertainty about the true size of the effect and raises concerns about its meaningfulness. Therefore, especially these results should be interpreted with caution. The large CIs could also be a result of the low sample size in our investigation of IL-6, as mentioned above, which increases the width of the CI. Future studies in larger samples investigating several markers of inflammation should ideally assess ELM prospectively and retrospectively. Thus, immune

markers could also potentially be assessed prior to the development of a first episode, as well as during, between, and after MDD episodes.

Additionally, while some studies on inflammatory markers control for smoking as a lifestyle marker, these data were not assessed in our study. Also, acute psychosocial stress might activate peripheral inflammation (Kerr et al., 2021), which we could not control for. And even though we used a sum score of severity as a cumulative measure of ELM, timing and duration of exposure, which was not assessed, might also be of great interest in order to draw conclusions about sensitive periods in the development of the immune system (Kerr et al., 2021). Other potential variables of interest that were not considered in our study, but could be included in models on inflammation markers are socioeconomic status, childhood economic status, migratory background, and urban vs. rural living during childhood/period of study assessment. However, we controlled for BMI and other possible confounders as mentioned in the current literature (age, contraceptive usage and other current disorders). The sample restriction to female participants might also have been a limitation, as sex may affect the levels of inflammatory marker in rMDD.

4.5 Conclusion

Our findings contribute to the existing literature on inflammation in MDD and ELM by distinguishing between the effects of rMDD and different types of ELM on levels of CRP and IL-6. Our results suggest that the elevation of inflammation markers may persist after MDD remission. This could shed light on mental and physical health risks for patients with rMDD, as elevated inflammation markers pose a risk for a range of somatic diseases (Minihane et al., 2015) and may predict subsequent MDD episodes (Valkanova et al., 2013). Our findings on physical abuse as a specific predictor of CRP levels (when controlled for rMDD) suggest that different types of ELM could result in distinct inflammation profiles. Further research is needed

to clarify how certain types of ELM might contribute to elevated inflammatory markers, in order to better respond to the mental and physical health risks associated with inflammation.

Acknowledgements:

We thank all women who participated in our study.

Funding:

This work was supported by the German Federal Ministry of Education and Research (BMBF) [Grant numbers: 01KR1207C and 01KR1803C] and the German Research Foundation (DFG) [Grant numbers: BE2611/2-1; LE560/5-1; RO3935/1-1; HE2426/5-1].

Conflicts of interest:

The authors have no conflicts of interests to declare.

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Table 1

Demographic and Clinical Characteristics of Study Participants.

	M (*SD*)/ %
Age in years	39.22 (5.78)
Years of education	17.37 (3.60)
Partnership status	
married/in a relationship,	81 (64.3 %)
single, separated from partner/husband, divorced, or widowed	45 (35.7%)
Nationality (German)	113 (89.7 %)
Moderate/severe ELM	53 (42.1 %)
Sexual abuse	28 (22.2 %)
Physical abuse	41 (32.5 %)
Emotional abuse	16 (12.7 %)
Neglect	18 (14.3 %)
Parental antipathy	42 (33.3 %)
Diagnosis of rMDD	78 (61.9 %)
Age at onset (years)[a]	27.15 (8.86)
Number of episodes [a]	2.37 (1.49)
Depression Score (BDI) [a]	15.12 (11.32)
Time since last episode (months) [a]	53.57 (66.22)
Number of suicidal attempts [a]	0.45 (1.36)
Intake of SSRI/SSNRI [a]	10 (12.8 %)
Intake of other antidepressants [a]	7 (9.0 %)
Moderate/severe ELM [a]	40 (51.3 %)
Other current diagnoses (additional to rMDD) [a]	15 (19.2 %)
Dysthymia	2 (2.6 %)
Panic Disorder	2 (2.6 %)
Agoraphobia without panic	4 (5.1 %)
Social Phobia	2 (2.6 %)
Post-Traumatic Stress Disorder	2 (2.6 %)
Generalized Anxiety Disorder	4 (5.1 %)
CRP (µg/ml)	0.48 (0.54)
IL-6 (pg/ml)	0.87 (0.90)

Notes. *N*=126 (*n* = 122 for CRP and *n* = 66 for IL-6). [a]*n*=76-78 (sub-sample of rMDD; in 2 cases missing information on antidepressive medication). *M*=Mean; *SD*=standard deviation; ELM=early life maltreatment; rMDD=major depressive disorder in remission; BDI=Beck Depression Inventory II. CRP=C-reactive protein; IL-6=Interleukin-6.

Table 2

Correlations of CRP and IL-6 with rMDD and ELM.

			Specific Types of ELM				
r (*p*)	rMDD	Sum severity of ELM	Neglect	Physical abuse	Sexual abuse	Emotional maltreatment	Parental antipathy
CRP	.293 (.001)	.156 (.046)	.193 (.018[a])	.237 (.005[a])	-.016 (.430)	.065 (.242)	.113 (.111)
IL-6	.299 (.009)	.186 (.073)	.279 (.014[a])	.125 (.167)	.011 (.468)	.118 (.180)	.200 (.060)

Note. *N*(CRP) = 122. *N*(IL-6) = 66. Pearson *r* correlation coefficients (one-tailed tests). Analyses controlled for other current DSM-IV axis I disorder, BMI, age, and intake of contraceptive medication. [a] Correlations with neglect would no longer be significant when controlling for multiple testing with the Holm-Bonferroni method applied to the five sub-scales of ELM. The Bonferroni-Holm corrected p-value for the correlation of CRP with physical abuse is $p = .025$.

Table 3

Linear regression model of CRP and IL-6 levels predicted by rMDD and ELM.

	CRP				IL-6			
	R^2	*b (CI)*	*β*	*p*	R^2	*b (CI)*	*β*	*p*
Step 1 - Covariates only	.250				.122			
Age		.014 (.001, .029)	.155	.060		.008 (-.004, .021)	.127	.311
Current DSM-IV axis I disorder		.074 (-.187, .344)	.046	.572		.122 (-.116, .399)	.104	.407
BMI		.049 (.032, .065)	.403	<.001		.028 (.004., .053)	.301	.021
Intake of contraceptive medication		.320 (.084, .538)	.182	.028		-.187 (-.420, .044)	-.171	.189
Step 2	.320				.211			
ELM		.012 (-.008, .034)	.083	.323		.010 (-.019, .038)	.113	.399
rMDD		.266 (.093, .433)	.246	.004		.181 (.009, .378)	.269	.042
Step 3	.322				.215			
rMDD*ELM		-.018 (-.069, .030)	-.100	.512		-.016 (-.076, .056)	-.140	.551

Note. *n*(CRP) = 122. *n*(IL-6) = 66. ELM=early life maltreatment (sum score, mean-centered). rMDD=major depressive disorder in remission. CI = 95% confidence intervals based on 1000 bootstrap samples (percentile method).

Table 4

Correlations of CRP and IL-6 with different disorder characteristics in rMDD patients.

r (p)	Number of episodes	Onset age	Number of suicidal attempts	BDI sum score	Time since last episode	Intake of SSRI/SSNRI	Intake of other antidepressants
CRP	-.104 (.407)	.007 (.955)	-.144 (.249)	-.089 (.479)	.067 (.595)	.227 (.067)	-.017 (.890)
IL-6	-.019 (.463)	.482 (.005)	-.067 (.370)	-.031 (.440)	-.421 (.016)	.228 (.127)	-.142 (.240)

Note. Sub-sample of women with rMDD: *n*(CRP) = 76 and *n*(IL-6) = 35. Pearson *r* and point-biserial correlation coefficients (two-tailed tests). Analyses controlled for severity of early life maltreatment as well as current DSM-IV axis I disorder, BMI, age, and intake of contraceptive medication.