e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(2); 944-953

Review Article

# C-Reactive Protein and Depression: A Systematic Review on the Correlation between the Two Factors

**Kajal Gupta[1], Nidhi Choudhary[2], Hritu Singh[3], Swati Agarwal[4]**

[1]Assistant Professor, Microbiology, RKDF MCH & RC, Bhopal
[2]Associate Professor, Department of Dermatology, Venereology and Leprosy, RKDF MCH & RC, Bhopal
[3]Professor & Head, Department of Psychiatry, RKDF MCH & RC, Bhopal
[4]Associate Professor, Biochemistry, RKDF MCH & RC, Bhopal

**Received: 29-12-2022 / Revised: 10-01-2023 / Accepted: 20-02-2023**
**Corresponding author: Dr. Swati Agarwal**
**Conflict of interest: Nil**

**Abstract**

**Background:** Researchers have recently become interested in the potential link between increased C-reactive protein (CRP) levels and depression because there is evidence to suggest that these levels may affect the onset and progression of this mental health disease. As part of this systematic review, we analysed studies that looked at the connection between CRP levels in the body and the occurrence of depression in patients.

**Methods:** The phrases "Anxiety," "C-reactive protein," "Depression," "Depressive Disorders," and "Inflammation" were thoroughly searched for in the databases PubMed, Web of Science, and Embase. The investigation produced 482 initial publications and restricted the search to articles published in the English language between 2010 and 2022.

**Results:** Twelve papers were chosen for the review's assessment. Five studies—three of which were systematic reviews that looked at several studies—did not find any conclusive links between changes in CRP levels and the prevalence of depression or any other related diseases. There were some relationships between the two factors that were noted in the remaining 7 trials.

**Conclusion:** Although the majority of the clinical trials we chose for our review showed some sort of evidential correlation between elevated CRP levels and incidence of depressive disorders in the population under study, it was not possible to determine with certainty whether the two are directly or indirectly related. Therefore, we believe that more research and testing are necessary in this area.

**Keywords:** Anxiety, C-reactive protein, Depression, Depressive Disorders, Inflammation.



## Introduction

A frequently used indicator of inflammation in the human body is C-reactive protein (CRP) [1]. Its levels in the blood can reveal the existence and severity of a number of medical problems, including infections, autoimmune diseases, and chronic illnesses like heart disease, stroke, and diabetes. This protein is produced by the liver in response to inflammation. Because there is evidence to suggest that elevated CRP levels may

contribute to the onset and course of this mental health disease, researchers have recently become interested in the potential link between CRP levels and depression [1-3]. Millions of people worldwide are afflicted by the prevalent and crippling mental health illness known as depression.

It is marked by enduring unhappiness, hopelessness, and loss of interest in once-enjoyable activities. Depression can result in both mental and physical symptoms, including adjustments to eating, sleep, and energy levels [4]. Although the precise causes of depression are unclear, research indicates that a number of genetic, environmental, and physiological factors may play a role in its emergence [4].

The potential contribution of inflammation to the onset of depression has been the subject of one of the most fascinating lines of investigation into this correlation [5-8]. Depression is one of the many physical and mental health issues that chronic low-grade inflammation has been related to. Studies have revealed that patients with depression typically have greater levels of CRP in their blood compared to those without the disorder [9–11]. CRP is regarded as a trustworthy marker of inflammation in the body.

There are various possibilities, albeit it is not yet apparent exactly how high CRP levels might be related to depression. Some scientists think that inflammation may affect how neurotransmitters work in the body, causing alterations in brain chemistry that worsen depression. Others contend that inflammation may heighten oxidative stress, which harms brain tissue and fuels sadness [12].

Hence, by the means of this systematic review, we aimed to analyse studies that looked at the correlation between CRP levels in the human body and the incidence of depression in individuals.

## Materials and Methods

### Protocol employed

The PRISMA guidelines for systematic review were followed in the preparation of this systematic review (figure 1) [13].

### Review hypotheses

We used 12 pertinent papers that satisfied the necessary inclusion/exclusion criteria to determine the current state of knowledge/research that assessed the relationship between CRP levels in the human body and the prevalence of depression in people as part of this systematic review.

### Inclusion criteria

For full-text screening, articles that included pertinent information for the review's aims, which covered all age groups, were chosen. Studies that investigated the correlation between C-reactive protein and depression in humans, used validated measures for both C-reactive protein and depression, reported correlation coefficients or provide sufficient information to calculate them and were published in peer-reviewed journals or other reputable sources were considered for inclusion in the review.

### Exclusion criteria

The breadth of our systematic investigation excluded studies that were seminar presentations, academic articles, opinion pieces, or possessed incomplete data. Also, studies that used animal or in vitro models, did not report correlation coefficients or provide sufficient information to calculate them or were not published in peer-reviewed journals were excluded from the scope of our systematic review.

### Search strategy

A comprehensive search was conducted using the databases PubMed, Web of Science, and Embase, using the keywords "Anxiety", "C-reactive protein",

"Depression", "Depressive Disorders" and "Inflammation". The search was limited to articles published in the English language between 2010 and 2022.

### Data selection and coding

Two reviewers extracted data from the selected articles using a standardized data extraction form separately. The data which was extracted included the various types of variable characteristics such as author, year of publication, country, type of publication, key findings, and conclusions. This data extracted was then compared for ascertaining consistency, with disagreements between the reviewers being resolved by a third independent re-viewer wherever required.

Then in the final step, the synthesized data was assessed for quality using a specific validated tool.

### Risk of bias assessment

The studies we picked, which are included in figure 2, were assessed for bias using the RoB-2 method [14].

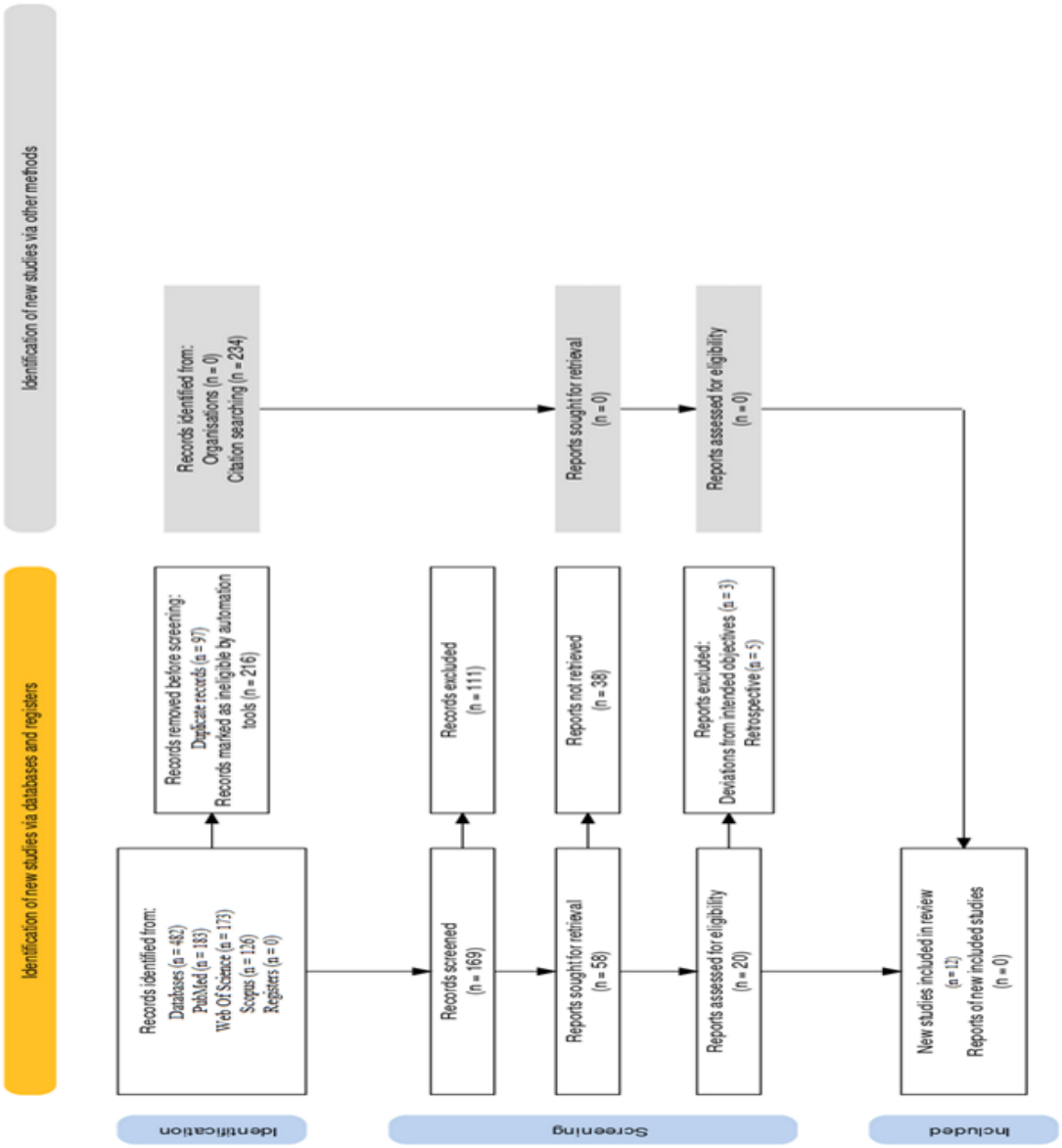


**Figure 1: Protocol representing the selection of articles for the review**

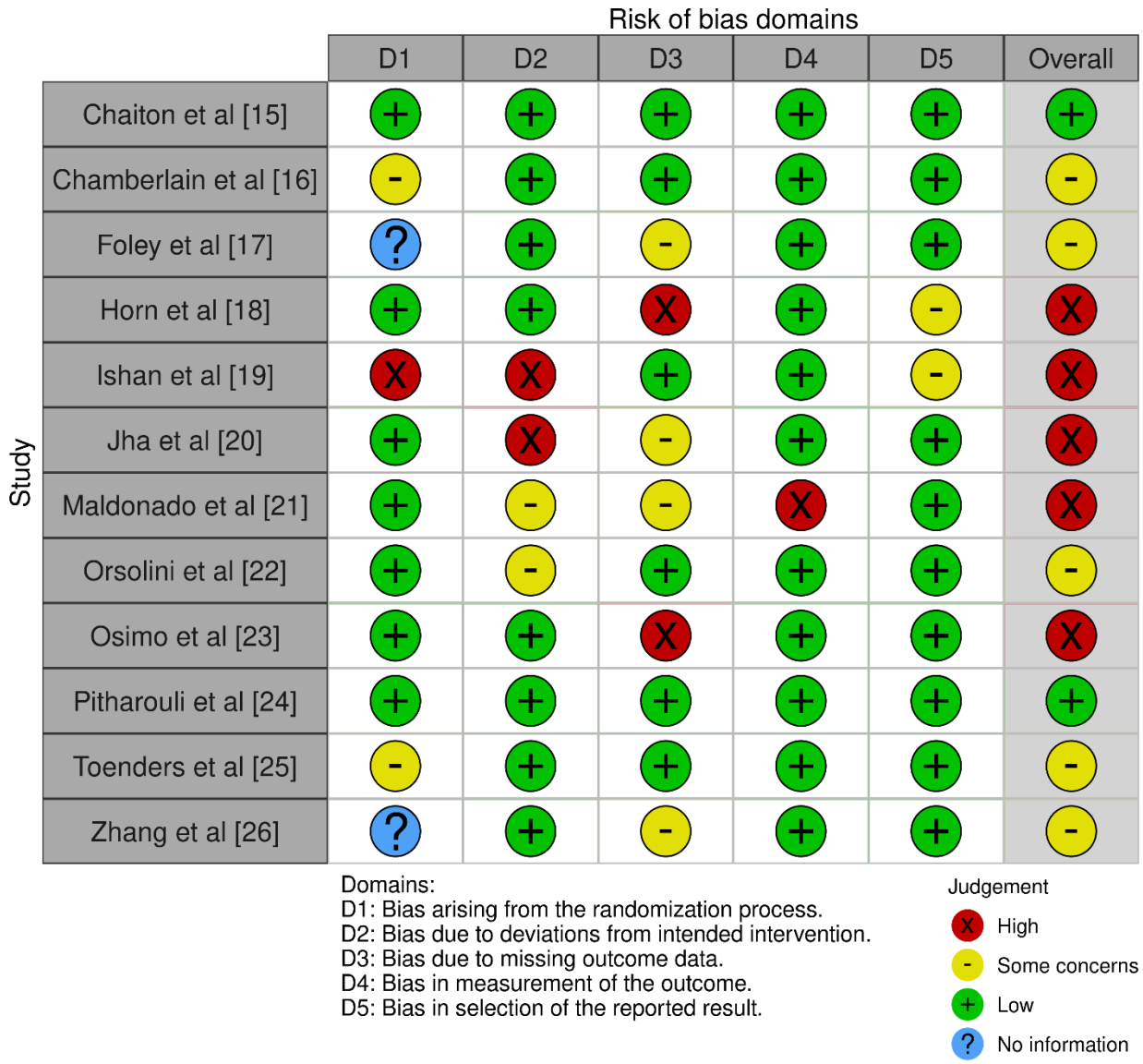


**Figure 2: RoB-2 tool for risk of bias assessment**

## Results

The first screening was conducted by reviewing the titles and abstracts of the 482 papers. Out of these, 169 papers were initially selected based on their relevance to the research question. 111 publications that were similar or duplicates of one another were removed to ensure that the final selection contained distinct papers. This left us with 58 papers.

The second screening was conducted by reviewing the titles and abstracts of the remaining 58 papers. Based on this review, 46 more papers were dropped due to their lack of relevance or not meeting the inclusion/exclusion criteria. After the second screening, the final selection comprised 12 papers that satisfied the necessary inclusion and exclusion criteria. These 12 papers primarily included in-vitro experiments, literature reviews, and comparative evaluations. 12 studies analysing the impact of CRP on the incidence of

depression/depressive disorders in patients were selected after the application of the relevant inclusion/exclusion criterion. Their various characteristics, such as study design, sample size and outcomes are represented in table 1.

**Table 1: Details of studies included in the investigation**

| Study author | Year | Sample size | Design | Outcome observed |
|---|---|---|---|---|
| Chaiton *et al* [15] | 2010 | 1535 adolescents | Observational study | The findings refuted any link between teenage CRP elevation and depression symptoms. |
| Chamberlain *et al* [16] | 2019 | 102 patients | Non-interventional study | Patients with major depressive disorders (MDD) and particularly those who were treatment-resistant have higher CRP levels. Adversity in childhood and particular depressive and anxious symptoms were other characteristics connected to higher CRP. |
| Foley *et al* [17] | 2021 | 84 patients | Case control study | Higher depression severity, weariness, state anxiety, stress, a worsened quality of life, and both physical and psychological symptoms of depression were all linked to elevated CRP (>3mg/L). |
| Horn *et al* [18] | 2018 | 26 studies | Systematic review/meta-analysis | No significant correlation was reported between CRP and depressive disorders in nearly half of the studies (13) that underwent meta-analysis. |
| Ishan *et al* [19] | 2021 | 86 patients | Case control study | According to the findings, bipolar disorder patients' C-reactive protein levels were marginally higher than those of controls. However, in this analysis of bipolar disorder, no such strong connection of demographic characteristics was found. |
| Jha *et al* [20] | 2019 | 220 patients | Randomised control trial | In contrast to men, females showed a lower decline in depression scores throughout tests when their initial CRP levels were higher. |
| Maldonado *et al* [21] | 2018 | 154 patients | Observational study | When salivary CRP levels were low, there was a positive correlation between acculturative stress and state anxiety symptoms. CRP attenuated this link between acculturative stress and state anxiety. |
| Orsolini *et al* [22] | 2022 | 56 studies | Systematic review/meta-analysis | Majority of the studies found a positive correlation between higher CRP values and depressive disorders in individuals. |
| Osimo *et al* [23] | 2019 | 1561 patients | Longitudinal cohort study | Comparatively to subjects with chronically lower levels of CRP, those who exhibited |

| | | | | |
|---|---|---|---|---|
| | | | | rising CRP levels growing up had a greater risk of depression/depressive disorders at the age of 18. |
| Pitharouli *et al* [24] | 2021 | 26894 patients | Case control study | In comparison to control participants, patients with depression had CRP levels that were considerably higher. |
| Toenders *et al* [25] | 2022 | 109 studies | Systematic review/meta-analysis | With the exception of one study, increased CRP levels were not linked to the beginning or progression of depression in any of the studies that were chosen. |
| Zhang *et al* [26] | 2019 | 75 patients | Randomised control trial | Depression test scores, along with other variables, were all higher in the participants with high CRP levels. |

The observations mentioned in the 12 studies [15-26] examining the impact of CRP on depression were mixed in nature. In some studies, elevated levels of CRP were found to be associated with increased risk for depression, while other studies found no significant relationship between CRP levels and depression.

For example, in a study conducted by Zhang *et al* [26], participants with higher levels of CRP were found to have a greater likelihood of developing depression over time. On the other hand, the study by Toenders *et al*. [25] found no significant association between CRP levels and mental issues in a sample of patients with cardiovascular disease.

Several studies [16,22] reported that demographic factors, such as age, gender, and race/ethnicity on the correlation being investigated in this review. Some studies found a stronger relationship between CRP and depression in women [18,20], while others found no gender differences [17,22,25]. Additionally, some studies [16,20,23] investigated the temporal relationship between CRP and depression, finding that higher baseline CRP levels predicted future depression, while others [17,21,25,26] found no predictive effect. All in all, the results of the 12 studies [15-26] on the impact of CRP on depression were inconsistent and suggest a complex relationship between these two factors. Further studies is needed to fully understand the role of CRP in depression and to identify potential subgroups of individuals who may be most susceptible to the effects of elevated CRP levels on depression.

## Discussion

Even while there is a growing body of knowledge about the link between CRP levels and depression, much more study is still required to completely understand this association. Currently, there is insufficient data to draw any firm conclusions about the link between elevated CRP levels and depression or the likelihood that treating inflammation will automatically relieve depressive symptoms. Though more research in this area is necessary, the evidence that has so far surfaced points to a possible causal relationship between depression and CRP levels. When it comes to the topic of our systematic review, the 12 research [15–26] that were chosen for the review all looked into the connection between CRP levels and depression, and the findings were conflicting. While other research found no conclusive correlation, some have discovered that higher CRP levels are linked to an increased risk for depression.

After adjusting for potential confounders such age, sex, and body mass index, Pitharouli *et al*case-control's study [24], which included a substantial number of patients with a lifetime diagnosis of depression, revealed a strong correlation between CRP levels and depression. Depression is one of the many physical and mental health issues that chronic low-grade inflammation has been related to. Some scientists think that inflammation may affect how neurotransmitters work in the body, causing alterations in brain chemistry that worsen depression [24]. Others contend that inflammation may heighten oxidative stress, which harms brain tissue and fuels depression [15–21].

The AHA and CDC have established specific CRP parameters as indicators of inflammation levels [27]. The following thresholds apply: 1 = "low," 1-3 = "mid," and >3 mg/L = "high." Our findings are consistent with prior meta-analyses [28–30] that showed depression patients to have higher mean levels of CRP than controls. Our study adds to the body of knowledge by identifying the proportion of depressed patients who exhibit inflammation-related symptoms.

Inflammation has also been associated to dementias [31], schizophrenia [32], and diabetes mellitus [33]. Numerous research [34–36] that have been published indicate that inflammation is a major predictor of greater all-cause mortality. In order to decrease overall health-related mortality and morbidity, routine CRP testing in depressed individuals as well as the identification and treatment of inflammation-related causes are recommended. Public health initiatives that lessen inflammation may lower the mortality and morbidity of a variety of diseases.

Some people with depression may not benefit from anti-inflammatory drugs [37]. Researchers may use CRP measurement to choose the most suitable participants for clinical trials of medications for depression. We now know of studies that test novel anti-inflammatory drugs against specific pathways. Recruitment for one of these trials examining sirukumab's efficacy and safety in the treatment of depression has come to an end.

In an RCT, tocilizumab is being investigated for the treatment of depression [38]. Patients having CRP concentrations ≤ 3 mg/L served as the subjects for these two investigations. According to secondary analyses of existing RCTs, mAb against certain inflammatory cytokines may be helpful for treating depression [39–40]. Before being taken into consideration in psychiatric therapeutic practise, anti-inflammatory drugs must successfully complete conclusive efficacy trials.

We did not analyse the various effects of excluding versus correcting for specific variables, such as chronic illnesses or medication use, which could be said to be one of the major limitations of our review. The class of antidepressant employed in some of the trials chosen for the evaluation may also have an impact on the outcomes.

## Conclusion

The connection between CRP levels and depression is an area of ongoing research, and more work is needed to fully understand the relationship between these two conditions. The results of previous studies have been mixed, with some studies finding a significant association between elevated CRP levels and increased risk for depression, and others finding no significant association.

However, the evidence for the link between the two factors is still up for debate. Hence, further research into this regard is warranted, as it could lead to new and innovative approaches to the treatment of this debilitating mental health condition.

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