C-Reactive Protein Levels in Schizophrenia: A Review and Meta-Analysis

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Abstract

There is an impression in the literature that schizophrenia is associated with increased inflammation, including abnormal blood levels of the acute phase reactant C-reactive protein (CRP). We performed a meta-analysis of blood CRP levels to estimate the overall effect size, as well as a pooled analysis of the prevalence of an elevated CRP level in patients with schizophrenia and related disorders. We identified articles by searching PubMed, PsycInfo, and ISI, and the reference lists of identified studies. Eight studies met the inclusion criteria for the meta-analysis, and five studies were included in the pooled analysis. CRP levels were significantly increased in patients compared to controls (effect size=0.45, 95% confidence interval 0.34–0.55, p<0.001). There was a 28% prevalence of an elevated CRP level in patients with schizophrenia and related disorders. Our results support a growing body of literature that schizophrenia is associated with increased inflammation, although many studies did not control for potential confounding factors such as BMI and smoking. Given the high prevalence of elevated CRP, metabolic syndrome, and premature cardiovascular mortality, our findings also suggest that measurement of blood CRP levels may be germane to the clinical care of patients with schizophrenia and related disorders.

Key Words: Schizophrenia, CRP, Meta-Analysis

Introduction

Converging lines of evidence support an association between immune system dysfunction and inflammation in schizophrenia. Inflammation is the complex response to injury or tissue destruction, and involves activation and recruitment of immune cells, and increased blood supply and vascular permeability. There is evidence for abnormal levels of acute phase proteins—plasma proteins synthesized by the liver in response to inflammation—in patients with schizophrenia, including haptoglobin, α1-antitrypsin, and C-reactive protein (CRP) (1-5). Cytokines, signaling molecules of the immune system that exert effects in the periphery and the brain, are key regulators of inflammation. Cytokines, particularly interleukin-6 (IL-6), are the primary inducers of acute phase proteins, including CRP. There is an increased prevalence of aberrant cytokine levels, including increased IL-6 levels, in drug-naive patients with first-episode psychosis and acutely relapsed patients with schizophrenia (6), as well as first-degree relatives of patients with schizophrenia (7).

CRP is an acute phase protein that is produced by hepatocytes. Normal CRP levels are <3 mg/L, and the high-sensitivity CRP (hs-CRP) assay has a lower limit of detection of 0.1 mg/L. The measurement of CRP is useful in the diagnosis and monitoring of many acute and chronic inflammatory conditions, including infections, periodontal disease, chronic

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lung disease, and obesity and the metabolic syndrome, which can cause elevations of hs-CRP in the range of 3–10 mg/L (8). High-sensitivity CRP levels >10 mg/L are often suggestive of an underlying infection, some inflammatory diseases, or cancer, but are also seen in some otherwise healthy subjects (8). A recent meta-analysis found that hs-CRP was an independent predictor of cardiovascular disease (9), the leading cause of mortality in patients with schizophrenia and related disorders (10). Consistent with this observation, the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial found that—among patients with an elevated hs-CRP—statin therapy decreased vascular events by 50%, even in the absence of elevated total cholesterol (11).

We performed a meta-analysis of blood CRP levels to estimate the overall effect size and pooled analysis of the prevalence of an elevated CRP level in patients with schizophrenia and related disorders.

Method

Study Selection

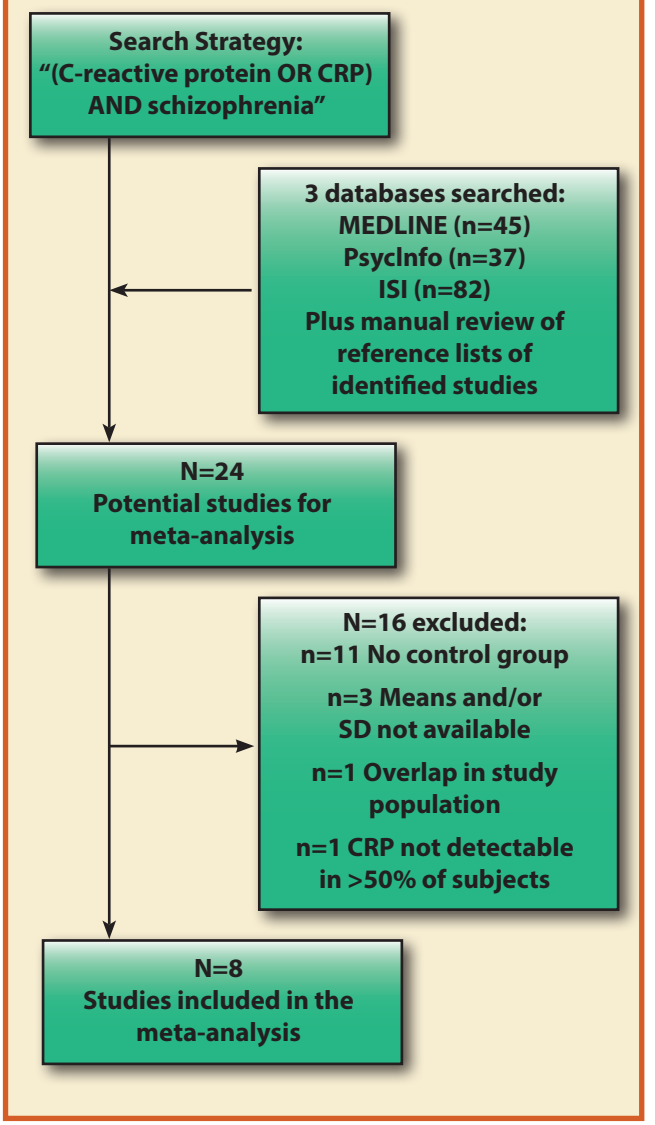
Studies of CRP levels in schizophrenia published after 1990 were systematically searched using MEDLINE (PubMed), PsycInfo (via Ovid), and ISI (Science and Social Science Citation Index) in July 2011. The primary search strategy was "(C-reactive protein OR CRP) AND schizophrenia." Limiting results to studies in English identified 45 articles from PubMed, 37 for PsycInfo, and 82 for ISI. From these sources, plus a manual review of reference lists from identified studies, we found a total of 24 potential studies for inclusion, which are described in Table 1 (1, 12-34).

The inclusion criteria were: 1) cross-sectional studies of blood CRP levels in patients with schizophrenia or related psychotic disorders (including schizophreniform disorder, brief psychotic disorder, psychotic disorder not otherwise specified, delusional disorder, and schizoaffective disorder) and healthy controls; and, 2) studies published in English. The exclusion criteria were: 1) studies without a control group; 2) studies that did not present mean and standard deviations (SDs) for CRP levels (after attempting to contact the study authors); 3) CRP concentrations were not detectable in >50% of subjects; 4) significant overlap in study population with another study; and, 5) genetic studies related to CRP.

In a secondary analysis, we also pooled data from a convenience sample of four studies that reported the prevalence of an elevated CRP level in patients with schizophrenia and related disorders (17, 18, 26, 34), plus a fifth study that provided this information after contacting the authors (20).

After independent searches, review of study methods by two authors (BJM and NC), and attempts to contact the authors, eight studies met the inclusion criteria (1, 15, 19, 20, 23, 31-33). There was universal agreement on the included studies. Sixteen studies were excluded due to: no control group (n=11), group means and/or standard deviations for CRP levels not available (n=3), significant study population overlap (n=1), and CRP concentrations were not detectable in >50% of subjects (n=1). A flow chart summarizing the study selection process is presented in Figure 1.

Figure 1 Flow Chart of the Study Selection Process for the Meta-Analysis



Data Extraction and Meta-Analysis

Data were extracted (sample size, mean, and standard deviation for subjects with schizophrenia and controls) for CRP levels. One author (BJM) extracted all data, which were independently verified by another author (NC). We then calculated effect size estimates (Hedges' g) for CRP levels in

Table 1 Studies of CRP in Schizophrenia

Study (Ref #)	Assay	hsCRP	Antipsychotic	Location	Included Meta-Analysis	Included Pooled Analysis	Comment
Akanji 2009 (1)	CIA	Yes	Yes	Kuwait	**Yes**	No	
Baptista 2007a (12)	ELISA	No	Yes	Venezuela	No	No	No control group
Baptista 2007b (13)	Turbidimetric method	No	Yes	Venezuela	No	No	No control group
Baptista 2007c (14)	Turbidimetric method	No	Yes	Venezuela	No	No	No control group
Carizzo 2008 (15)	ELISA	No	Yes	Venezuela	**Yes**	No	Control group=first-degree relatives
Diaz 2010 (16)	Immunonephelometry	No	Yes	Spain	No	No	No control group
Dickerson 2007 (17)	ELISA	No	Yes/No	US	No	**Yes**	No control group
Fan 2007 (18)	Immunonephelometry	No	Yes	US	No	**Yes**	No control group
Fawzi 2011 (19)	Turbidimetric method	Yes	No	Egypt	**Yes**	No	Males only
Fernandez-Egea 2009 (20)	ELISA	No	No	Spain	**Yes**	**Yes**	
Henderson 2009 (21)	Not stated		Yes	US	No	No	No control group
Hope 2009 (22)	ELISA	Yes	Yes/No	Norway	No	No	Overlaps w/Hope 2010
Hope 2010 (23)	ELISA	Yes	Yes/No	Norway	**Yes**	No	
Kim 2011 (24)	Turbidimetric method	Yes	Yes	US	No	No	No control group
Loffler 2010 (25)	Turbidimetric method	Yes	Yes	Germany	No	No	Means and/or SD not available
Mazzarello 2004 (26)	Not stated		Yes	Italy	No	**Yes**	Means and/or SD not available
Meyer 2009 (27)	ELISA	No	Yes	US	No	No	No control group
Ohaeri 1992 (28)	SRI	No	Yes	Nigeria	No	No	No control group
Ohaeri 1993 (29)	SRI	No	Yes/No	Nigeria	No	No	Not detectable in >50% of samples
Perron 2007 (30)	Advia 1650 test kit	Yes	Yes	France	No	No	Not
Sarandol 2007 (31)	Immunonephelometry	Yes	Yes	Turkey	**Yes**	No	
Severance 2009 (32)	ELISA	Yes	Yes	US	**Yes**	No	
Shcherbakova 1999 (33)	Immunonephelometry	No	Yes/No	Russia	**Yes**	No	Males only
Vuksan-Cusa 2010 (34)	Turbidimetric method	No	Yes	Croatia	No	**Yes**	No control group

CIA=Chemoluminescent Immunometric Assay
SRI=Single Radial Immunodiffusion

patients with schizophrenia versus controls in each study, and these data are included in Table 2. We calculated effect size estimates, as it was not feasible to use absolute values of CRP due to the heterogeneity in assay methods and concentrations across the different studies. Random effects pooled effect size estimates and 95% confidence intervals were calculated using the method of DerSimonian and Laird. The random effects model is more conservative than the fixed effects model, as it yields a lower Type I error rate and wider confidence intervals, and its use was supported by significant heterogeneity between studies (35). P-values were considered statistically significant at the $\alpha=0.05$ level. The statistical analyses were performed in Stata 10.0 (StataCorp LP, College Station, TX).

For descriptive purposes, we also extracted, when available, data on the prevalence of an abnormal CRP level (and the associated cutoff value) in patients with schizophrenia and related disorders in each study, from which the mean overall prevalence was calculated. In each of these studies, an abnormal CRP was defined as >5 mg/L (which is equivalent

Table 2 Effect Size Estimates For Individual Studies

Study (Ref #)	Schizophrenia Mean	Schizophrenia N	Schizophrenia SD	Control Mean	Control N	Control SD	Hedges' g	95% CI Lower	95% CI Upper
Akanji 2009 (1)	0.62	207	7.78	0.33	165	2.88	0.05	-0.16	0.25
Carizzo 2008 (Clozapine) (15)	5.20	29	5.00	3.20	23	2.60	0.48	-0.08	1.03
Carizzo 2008 (Olanzapine) (15)	4.90	29	2.90	3.60	11	1.90	0.48	-0.23	1.18
Fawzi 2011 (19)	3.30	200	1.40	1.40	200	0.70	1.71	1.48	1.94
Fernandez-Egea 2009 (20)	0.21	50	0.28	0.20	50	0.18	0.04	-0.35	0.43
Hope 2010 (22)	0.87	187	1.29	0.78	239	1.23	0.07	-0.12	0.26
Sarandol 2007 (31)	0.19	40	0.21	0.28	35	0.47	-0.25	-0.71	0.20
Severance 2009 (32)	7.32	10	3.45	7.31	10	4.14	0.00	-0.87	0.88
Shcherbakova 1999 (33)	22.00	15	5.60	4.30	12	3.50	3.11	1.98	4.23

to both 5 µg/mL and 0.5 mg/dL). Of note, in the study by Fernandez-Egea et al. (20), CRP values were originally reported in mg/L, but it was confirmed with the authors that the correct units were mg/dL (Fernandez-Egea, personal communication). The study by Mazzarello et al. (26) reported CRP values in mg/mL. We unsuccessfully attempted to contact the authors to confirm that the correct units were mg/dL. Excluding this study, however, did not significantly change the results.

Results

The meta-analysis included a total of 767 patients with schizophrenia and related disorders and 745 controls. CRP levels were significantly increased in patients compared to controls, with an effect size (ES) of 0.45, 95% confidence interval (CI) 0.34–0.55, p<0.001 (see Table 2 and Figure 2). There was also significant heterogeneity between studies (I^2 [the variation in effect size attributable to heterogeneity]=95.6%, p<0.001). In a sensitivity analysis, the effect size for the difference in CRP levels between patients and controls was no longer significant after removal of the study by Fawzi et al. (19) (ES=0.10, 95% CI -0.02–0.22, p=0.10). Furthermore, the heterogeneity in the effect size estimate was not attributable to any single study (i.e., the heterogeneity remained significant after separate removal of each individual study).

Among the five studies in the convenience sample, comprising 576 patients, there was a 28% prevalence of an elevated CRP level in patients with schizophrenia and related disorders, which is shown in Table 3. As noted above, excluding the study by Mazzarello et al. (26) did not significantly change the prevalence (27.2%).

Table 3 Prevalence of Abnormal CRP* in Patients with Schizophrenia

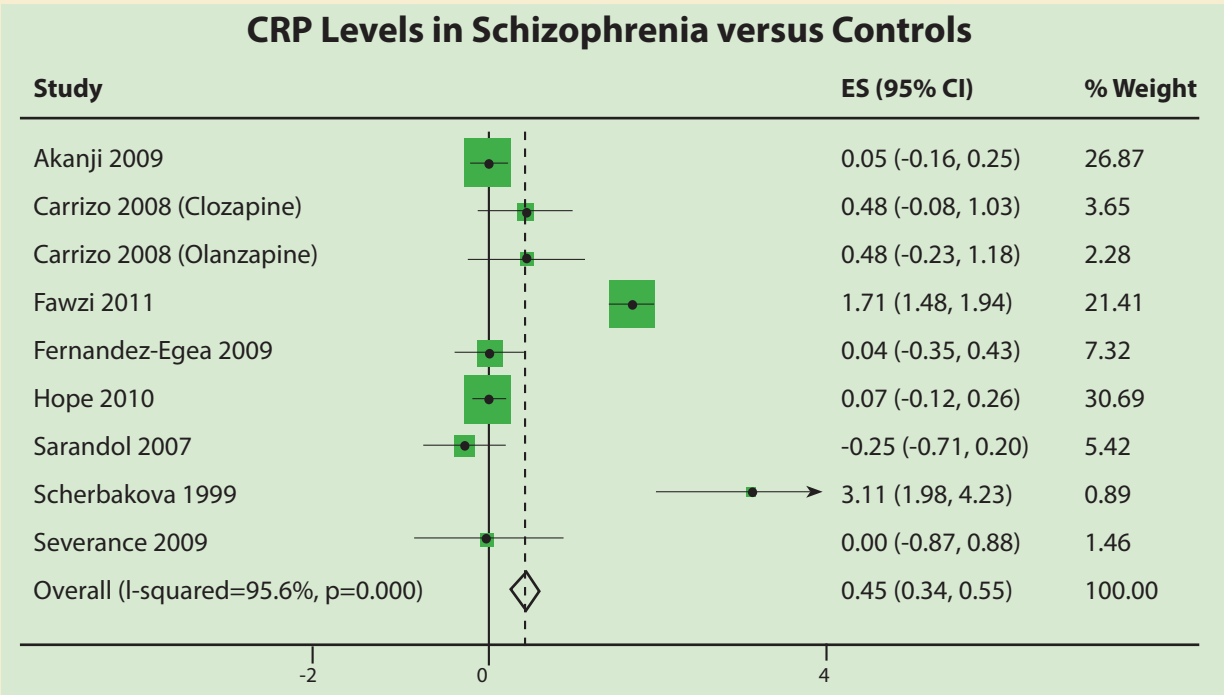
Study	Cutoff	N	Abnormal CRP Yes	Abnormal CRP %
Dickerson 2007	5 µg/mL	413	127	30.8
Fernandez-Egea 2009	0.5 mg/L†	50	4	8.0
Fan 2007	0.5 mg/dL	26	5	19.2
Mazzarello 2004 (Group 1)	0.5 mg/mL§	11	7	63.6
Mazzarello 2004 (Group 2)	0.5 mg/mL§	13	4	30.8
Vuksan 2010	5 mg/L	63	14	22.2
TOTAL		576	161	28.0

*In each of these studies, an abnormal CRP was defined as >5 mg/L (which is equivalent to both 5 µg/mL and 0.5 mg/dL); †In this study CRP values were reported in mg/L, but it was confirmed with the authors that the correct units were mg/dL (Fernandez-Egea, personal communication). §In this study, CRP values were reported in mg/mL. We unsuccessfully attempted to contact the authors to confirm that the correct units were mg/dL. Excluding this study, however, only slightly changed the prevalence of an abnormal CRP (27.2%).

Discussion

We found a significant increase in CRP levels in patients with schizophrenia and related disorders compared to controls, with a small-to-medium effect size of 0.45 (an effect size of 0.50 is considered medium). This finding provides further evidence for an association between inflammation and schizophrenia. Several hypotheses regarding an immune-cytokine basis for the pathophysiology of schizophrenia have been postulated (37-39). A recent meta-analysis found that serum levels of IL-1β, IL-6, and TGF-β may be state-related markers for acute psychosis, as they were elevated in acutely relapsed inpatients and first-episode psychosis, but normalized with antipsychotic treatment (6). Since IL-6 and, to a lesser extent, IL-1β are known inducers of CRP, it is reasonable to hypothesize that CRP levels would be increased in patients with an acute relapse of psychosis. The results of several studies in this paper are consistent with this prediction. Shcherbakova et al. (33) found significantly increased CRP

Figure 2 Meta-Analysis of CRP Levels in Schizophrenia



levels in acutely relapsed males compared to controls. In two studies, Ohaeri et al. (28, 29) found significant decreases in CRP levels following resolution of acute psychosis. Finally, Mazzarello et al. (26) found higher mean CRP levels among patients with an episodic illness course compared to continuously ill subjects. However, only one of the identified studies considered for the meta-analysis (21) simultaneously measured blood CRP and cytokine levels; the authors found that CRP levels were significantly positively correlated with IL-6 ($r=0.48$, $p<0.00001$). Given these associations, future studies of CRP should concomitantly measure other cytokines and consider effects of clinical status on inflammatory markers.

If future studies replicate the association between elevated CRP and schizophrenia, further work addressing the following questions would be required to establish the CRP response as a biological marker for the psychoses. Is the CRP response specific to the psychoses or is it a severity index for other psychiatric disorders? There is some evidence for abnormal CRP levels in both major depression (40) and bipolar disorder (23, 34). Is CRP a state-dependent or trait-dependent marker of psychosis? As noted above, there is some preliminary evidence that CRP is a state-dependent marker for acute psychosis; but, there is a need for prospective, longitudinal studies to examine the extent to which CRP varies with illness acuity and with acute exacerbations of schizophrenia within individuals. Are polymorphisms in the gene for CRP associated with schizophrenia? One case-control study in an Armenian population did not find an association between genetic variants of CRP and schizophrenia (41). What is the theoretical basis for linking the CRP response to the psychoses?

Regardless of whether the immune-cytokine hypothesis of schizophrenia is correct, we also found a high (28%) prevalence of an elevated CRP level in patients with schizophrenia and related disorders. A recent meta-analysis found that hs-CRP was an independent predictor of cardiovascular disease (9), the leading cause of mortality in patients with schizophrenia and related disorders (10). Of note, however, none of the studies in our convenience sample used the hs-CRP assay. Metabolic syndrome, an important risk factor for cardiovascular disease incidence and mortality (42), is highly prevalent in patients with schizophrenia and related disorders (43). Four studies included in the meta-analysis reported significant associations between CRP levels and components of the metabolic syndrome. Fawzi et al. (19) found higher mean CRP levels in a subsample of patients with central obesity (waist circumference >94 cm) compared to age- and sex-matched patients with waist circumference <94 cm. In two other studies, CRP levels were significantly positively correlated with body mass index (BMI) and waist circumference (15) and waist-to-hip ratio (1). In the study by Carizzo et al. (15), CRP levels were significantly negatively correlated with HDL levels. Lastly, in the study by Shcherbakova et al. (33), a CRP level >5 mg/L was significantly associated with the metabolic syndrome. Taken together, CRP may represent an important biomarker of patients with schizophrenia at

risk for cardiovascular disease. While this risk is most likely mediated by obesity and metabolic syndrome, for some patients CRP may be an independent risk factor for cardiovascular disease (11).

We believe that ours is the first meta-analysis of blood CRP levels in patients with schizophrenia and related disorders. An important strength of our study was the relatively large sample size (767 patients and 745 controls). There are also several limitations of the present study. Only a relatively small number of studies met the inclusion criteria for the meta-analysis. The two samples with the largest effect sizes for CRP levels in patients with schizophrenia versus controls were all male (19, 34). We were not able to stratify data on CRP levels by sex in the meta-analysis. Furthermore, many studies were excluded because either the absence of a control group or summary data on mean CRP levels was not available. These studies would have otherwise been included in the meta-analysis, and their influence on the results is uncertain. Our results should be interpreted with caution in light of significant heterogeneity across studies. Many of the studies published in the literature—and three of the studies included in this meta-analysis (15, 20, 26)—did not use the hs-CRP assay that is now the standard in most of medicine. However, in a sensitivity analysis, the between-study heterogeneity was still significant when only the studies that used the hs-CRP were included. We also note that the effect size for the difference in CRP between patients and controls was no longer significant after removal of the study by Fawzi et al. (19), although there was still a trend for increased CRP (p=0.10). This was the second largest study in the meta-analysis (comprising over 25% of the patients and controls), and the authors controlled for many potential confounding factors, including age, education, smoking, BMI, and physical activity.

Another limitation is that many individual studies did not control for potential confounding factors known to influence CRP levels, particularly BMI and smoking (36). The effects of antipsychotic medications are also another important potential confound of this association. One study of drug-naive patients with a first episode of nonaffective psychosis did not find elevated CRP levels compared to well-matched controls (20), although these patients did have significantly increased levels of the pro-inflammatory cytokine IL-6. By contrast, another well-matched study found significantly increased CRP levels in drug-naive and drug-free patients with schizophrenia compared to controls (19), and there was no significant difference in CRP levels between drug-naive and drug-free patients (Fawzi, personal communication). Furthermore, different antipsychotic medications may have different effects on CRP levels. Longitudinal studies have shown significant changes in CRP levels over time in patients treated with clozapine, olanzapine, and quetiapine, but not other antipsychotic medications, although effects may depend on baseline CRP levels (25, 27).

The relationship between CRP levels and clinical features has been explored in several studies. Two studies, one using a continuous measure of CRP (19) and another that dichotomized CRP levels as normal (≤0.50 mg/dL) and elevated (>0.50 mg/dL) (18), found that elevated CRP was a significant predictor of both PANSS total and negative symptoms. By contrast, another study (17) did not find any association between dichotomized CRP and PANSS scores, but elevated CRP (>5.0 mg/μL) was associated with more severe cognitive impairment in that study. By contrast, Akanji et al. (1) found the highest mean CRP levels among patients in remission (Clinical Global Impression [CGI] score=1), compared to patients with either mild-to-moderate (CGI=2–4) or severe (CGI=5–7) illness, although potential confounding factors were not addressed in that comparison. In that study, higher CRP levels were also associated with catatonic features and the absence of a family history of psychosis. In general, the differences in clinical correlations present in the published literature may reflect the smaller sample size of the individual studies, diagnostic heterogeneity, and differences in assay methodology.

Clinical trials of antipsychotic augmentation with nonsteroidal anti-inflammatory agents (NSAIDs) also support an association between inflammation and clinical features in schizophrenia. Four trials of adjunctive NSAIDs in acutely relapsed patients with schizophrenia showed significant improvement in total symptoms (44-47), and baseline levels of inflammatory markers were a significant predictor of response to NSAIDs in two studies (45, 48). One potential mechanism for these associations is that inflammation alters tryptophan metabolism, resulting in increased levels of the NMDA receptor antagonist kynurenic acid, resulting in glutamatergic dysfunction and symptoms of psychosis (49). Further investigation of the relationship between CRP and clinical features in schizophrenia is warranted.

Future studies of CRP in schizophrenia should utilize the hs-CRP assay, concomitantly measure other cytokines, consider the effects of clinical status, control for potential confounding factors, and explore the relationship between CRP and clinical features. Given the significant increase in CRP levels, and high prevalence of elevated CRP, metabolic syndrome, and premature cardiovascular mortality, these findings suggest that measurement of blood CRP levels may be germane to the clinical care of patients with schizophrenia and related disorders. In the future, consistent replications of abnormal hs-CRP in well-controlled studies would suggest that treatment with statins for some patients with schizophrenia may result in both improvement in psychotic symptoms

and decreased risk of cardiovascular morbidity and mortality (11). Additionally, the signal-to-noise ratio of treatment trials of adjunctive anti-inflammatory agents in schizophrenia may be increased by stratifying patients based on CRP level. Taken together, our results provide further evidence for an association between inflammation and schizophrenia.

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