Associations between C-reactive protein levels and cognition during the first 6 months after acute psychosis

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Abstract

Objective: Inverse relationships between the C-reactive protein (CRP) levels and cognitive performance in acute psychosis have been demonstrated. We aimed to investigate how the serum level and initial change of CRP in acutely admitted patients with psychosis was correlated with cognitive performance during a 6-months follow-up period.

Methods: The study is part of a pragmatic, randomised trial comparing four different second-generation antipsychotic drugs, and consists of 208 acute phase patients recruited at admittance for psychosis. This study reports data for all groups collectively, and does not compare treatment groups. Measurements of CRP and cognitive performance were conducted at baseline (T1) and after 4 weeks on average after inclusion (T2). Cognition was also assessed after 3 months (T3) and 6 months (T4) of follow-up.

Results: Global cognition improved during the follow-up period of 6 months, especially in the T1 – T2 interval. The different cognitive subdomains showed different time-dependent profiles of improvement, with memory and attention improving significantly also in the later phases. Reduction of the CRP level during the initial follow-up interval (T1 – T2) was associated with increased overall cognitive performance in the T2 – T4 interval, but not in the T1 – T2 interval. For the cognitive subdomains, we found an inverse association between change in CRP level and verbal abilities (T2 – T4 interval), and attention (T2 – T3 interval). Conclusion: These findings indicate that initial changes in the serum level of CRP in the acute phase of psychosis may predict cognitive function in later phases of the disease.

Trial registration

ClinicalTrials.gov ID; URL: http://www.clinicaltrials.gov/:NCT00932529

Significant outcomes

- Global cognition and several cognitive subdomains continued to improve beyond the initial phase of acute psychosis treatment and into the later phase of follow-up.
- Reduction of the C-reactive protein (CRP) level in the initial acute phase was associated with delayed improvement of global cognition. Inverse associations between CRP levels and cognitive subdomains were found for learning, verbal abilities, and attention.

Limitations

- There was considerable attrition in the study during follow-up.
- CRP was the only inflammatory marker measured in the study.

Introduction

Cognitive dysfunctions are core features of schizophrenia that detrimentally affect functional outcome (1–3). The neurobiological disturbances involved in cognitive dysfunctions are, however, largely unknown. Abnormal myelination, white matter changes, and
immunological processes, including low-grade inflammatory responses, have been suggested as possible mechanisms (4). Many studies have indicated that the cognitive impairments seem to stabilize after the first episode of psychosis (5,6), although there have also been some findings suggesting cognitive improvements (7–10). The inconsistent literature might at least in part be explained by differences in the patient samples, the duration of follow-up, and the cognitive test batteries. Taken together, recent findings indicate that cognitive dysfunction is not always irreversible and can be dynamic, especially in the acute phases (11,12). Importantly, current treatment options in psychosis, including psychosocial interventions and antipsychotic medications, have few if any beneficial effects on cognitive performance (4,13–17). Thus, this central area of dysfunction in psychosis is in need of a better understanding and novel treatment approaches.

Inflammation has been the focus of recent studies addressing the pathophysiology of psychotic disorders. Immune abnormalities in the blood, cerebrospinal fluid, and central nervous system, including immune cell numbers, inflammatory markers, and antibody titers, have been demonstrated in schizophrenia (18–23). There is increasing evidence for underlying inflammatory mechanisms relevant to cognitive functioning (4,24–26). Indeed, neuroinflammation with white matter pathology has been demonstrated in the early stages of psychosis (27), and it has been suggested that these changes can lead to both structural and functional dysconnectivity and cognitive dysfunction (21). Low-grade elevation of the CRP, a well-characterized and standardised marker of inflammation (28), has been found in some studies in schizophrenia (29–35). An inverse association between the serum levels of CRP and cognitive function has been reported (18,36,37). However, these studies are predominantly cross-sectional and include patients in the chronic phase. This might restrict the generalisability of the results, and longitudinal studies with repeated cognitive assessments are scarce.

We have recently shown an inverse association between the serum level of CRP and cognitive performance in the acute phase of psychosis (11). What remains unresolved, however, is whether the levels and change of CRP in the initial phase of acute psychosis influence cognition in later phases. The main aim of this study was therefore to investigate how the CRP level in the first acute phase of psychosis correlates with cognitive function during a 6 months follow-up.

Material and methods

The study is part of a pragmatic, randomised trial comparing four different second-generation antipsychotics in the treatment of psychosis (Fig. 1). Importantly this study reports data for all treatment groups collectively, and does not compare treatment groups. We have previously published cross-sectional comparisons of treatment groups, and no differences were found (11). The main objective of the present study was to investigate overall associations between longitudinal changes in CRP and cognition in the whole group. The clinical sample and methods have been described in detail elsewhere (38).

Clinical sample

The sample consists of 208 consecutive, acute phase patients recruited at admittance for psychosis, who underwent CRP measurements and cognitive assessment. The project was designed and approved by the Ethics committee with two phases: The first was the quality assurance phase from admission to discharge or 6 weeks at the latest, and was approved by the Ethics Committee without the requirement of informed consent as this phase included only elements of best clinical practice. At admission all psychotic patients admitted to the hospital for symptoms of acute psychosis were consecutively included, if they were to use the hospital’s standard antipsychotic medication regimen, and could cooperate with clinical assessments of condition. This phase should assure that psychosis patients were offered best-quality guideline-concordant treatment for psychosis. The second phase (research phase) was based on informed consent provided at discharge or after 6 weeks at the latest. This included invitation to visits and tests at 3, 6, 12, and 24 months after admission. In this part of the project there were procedures beyond usual clinical standard, such as collections of data for use in psychiatric basic research within genetics and brain functioning.

The recruitment period was from March 2004 until February 2009 at Haukeland University Hospital, Bergen, Norway, with a catchment population of about 400 000. The study was approved by the Regional Committee for Medical Research Ethics, and by the Norwegian Social Science Data Services. The study was publicly funded and did not receive any financial or other support from the pharmaceutical industry.

All adult patients were eligible for participation if they were acutely admitted to the emergency ward for symptoms of active psychosis, as determined by a score of ≥4 on one or more of the items Delusions, Hallucinatory behaviour, Grandiosity, Suspiciousness/persecution, or Unusual thought content in the Positive and Negative Syndrome Scale (PANSS) (39) and were candidates for oral antipsychotic drug therapy. All eligible patients met the International Statistical Classification of Diseases and Related Health Problems (ICD)-10 diagnostic criteria (http://apps.who.int/classifications/icd10/browse/2010/en) for schizophrenia, schizoaffective disorder, acute and transient psychotic disorder, delusional disorder, drug-induced psychosis, major depressive disorder with psychotic features, bipolar disorder except manic psychosis. Manic psychosis was excluded based on a priori expectation that these patients would not be able to cooperate with the assessments in the acute phase.

Figure 1. Estimated mean level and change in global cognitive score over time, with standard deviations to display individual variation (N=181).
抗精神病药物治疗在几个小时内未见改善和在患有药物引起的精神症状的患者中包括，患者理解并能使用口抗精神病药物，患有躁狂性精神病，或者因其他行为或心理原因与精神状态有关，可被考虑进行电击治疗，或者被苛刻在过期时接受氯丙嗪治疗。

患者被排除在研究之外，如果他们在研究中无法使用抗精神病药物，或因其他原因而未受骗，或对精神疾病有一定程度的了解，患者能与患者治疗合作并接受患者治疗，但未理解患者使用抗精神病药物或患者在患者使用抗精神病药物前接受了氯丙嗪治疗。患者因药物引起的精神病被包括只在当条件在几日内没有改善时，当抗精神病药物治疗没有被判断出来时。

患者在基线（T1：N=208，基线；T2：N=103）后进行了首次随访（平均4周后；T2后第2次随访3个月后；T3：N=43，第3次随访后6个月；T4：N=35）。这一时期对应于治疗的急性期，期间最大精神症状的减少被观察到，而治疗反应被预期在大多数患者（40%）。

### Clinical and biochemical assessments

合格的患者接受PANSS结构化临床访谈，以确定病史，包括那些被培训和与内应者可靠性相关的临床部门，外应者可靠性（0.92）。此外，加利福尼亚抑郁症量表和精神分裂症（41），以及精神疾病和药物使用量表（42）被使用，并且被评定根据临床全球印象-严重性（43），以及全球评估-分版评估，版本分数（44）。使用病史数据是基于从参与者获得的。

对于分析CRP，一份血样被收集来自患者在空腹状态的08:00和10:00 h在早晨基线（T1）后4周随访（T2）。实验室使用了之前分析CRP方法在2005年1月，因此仅可用数据在使用这一修订后在目前的工作中。CRP水平被测量通过Tina-quant C-反应性蛋白（Latex）方法从Roche Modular P® (Mannheim, Germany)，该方法测量CRP水平>1 mg/l。
the tests was the one that obtained a satisfactory relationship with the RBANS (50). Raw scores for the neuropsychological variables were converted to \( t \)-scores using the best available norms from corresponding manuals (when available) or published papers. The final summary score based on the mean \( t \)-scores across the five cognitive domains defined the overall cognitive function \( t \)-score. Neuropsychological assessment by cognitive domain and time are shown in Table 1.

### Statistical analyses

Descriptive statistics (mean, standard deviation, frequency) and independent sample-\( t \)-test were analysed with SPSS version 24.0. The program Mplus 8 (51) was used to analyse the level and change in variables with latent growth curve and time contrast models (52). The standard linear change assumption was tested based on the goodness of fit measures, residual results, and plots of the observed and estimated change model were used to decide the change pattern. If this assumption was not met, piecewise growth was explored. If the model indicated one piece based on two measurements only, this part is a difference score model (53). Some residuals had to be set as constant to fit such a model. The models were evaluated based on their goodness of fit measures, as follows: threshold values in comparative fit index and Tucker-Lewis index beyond 0.95; root mean error of approximation (RMSEA) < 0.05 as close fit, RMSEA < 0.08 as fair fit, and RMSEA < 0.10 as a mediocre fit (52). Model fit measures were presented for unconditional level and change models, but not for prediction models, as these models solely are predictions with statistical significant and non-significant relations and not structural models. The estimator was set to maximum likelihood with robust standard errors (MLR) to account for non-normality in data (54). The full information maximisation likelihood (FIML) method uses all available data under the assumption that missing data are random (‘Missing at Random’) (51,54). Thus, the level and change results are estimated and not observed values based on all observations. After analysing the variables separately, level and change in CRP were related to levels and changes in neuropsychological scales. A sensitivity analysis was performed for CRP levels <10 mg/l.

Finally, we controlled for confounders, known to have impact on both CRP level and cognition, as metabolic syndrome, smoking, being antipsychotic medication-naive, illicit drug use, and educational level (11).

### Results

The study included 208 patients with data in one or more of the outcome variables. At baseline, there were CRP measurement for 158 patients and cognitive assessments for 169 patients and a total of 123 patients had both measurements. In total, 181 patients had observations on cognitive performance and 169 on CRP at any time point. The demographic and clinical characteristics are shown in Table 2. The patients that were tested only at baseline were not statistically different from those with follow-up data for the clinical or demographic characteristics at baseline, with the exception of a higher PANSS negative subscale score in patients with baseline test only compared to those with two or more visits [independent samples \( t \)-test: \( p = 0.034 \); mean difference 2.2 points; 95\% confidence interval (CI): 0.2–4.2], and fewer years of education (independent samples \( t \)-test: \( p = 0.027 \); mean difference, 0.8 years; 95\% CI: 0.10–0.6).

| Table 2. Baseline demographics and clinical characteristics (\( N = 208 \)) |
|-----------------|-------|-----|
| Characteristics | \( N \) | % |
| Male            | 143   | 68.8 |
| Antipsychotic drug naive | 92  | 44.2 |
| Alcohol abuse last 6 months | 22  | 10.6 |
| Illicit drug use last 6 months | 139  | 66.8 |
| Current tobacco smoking | 103  | 49.5 |
| Diagnosis*      |       |     |
| Schiz and related | 106  | 53.2 |
| Drug-induced    | 28    | 14.1 |
| Affective       | 23    | 11.6 |
| Acute psychosis | 17    | 8.5  |
| Other           | 25    | 12.5 |

\( * \) number of patients; Antipsychotic drug naive, no life-time exposure to antipsychotic drugs before index admission; Alcohol abuse or dependence according to the Clinical Drug and Alcohol Use Scales (CDUS/CAUS), patients with no illicit drug use could be included in the category alcohol use last 6 months; Schiz and related, schizophrenia and related disorders; Schizophrenia, schizoaffective disorder, acute polymorphic psychotic disorder with symptoms of schizophrenia, acute schizophrenia-like psychotic disorder, delusional disorder; Acute psychosis, acute psychosis other than those categorised under Schizophrenia and related; Affective, bipolar and unipolar depression; Other, miscellaneous psychotic disorders.

CDSS, the Calgary Depression Scale for Schizophrenia; CGI, the Clinical Global Impression, severity of illness scale; CRP, C-reactive protein (mg/l); GAF-F, the Global Assessment of Functioning, split version, Functions scale; PANSS, the Positive and Negative Syndrome Scale; RBANS, the Repeatable Battery for the Assessment of Neuropsychological Status.

All diagnoses are according to ICD-10.

*Patients with missing diagnoses are not included in the list. According to the naturalistic design, patients were included on the basis of the presence of active psychosis as determined by the PANSS, and not based on diagnosis.

### Levels and changes in cognitive performance

The mean and individual levels and changes in cognitive subdomains are presented in Table 3. The mean level of global cognitive performance increased over time in a non-linear manner, being most pronounced in the T1–T2 interval (Fig. 1). The figure also shows more individual change variation in the T1–T2 interval than in the later intervals. Statistically significant improvements over time were also found for verbal abilities,
learning and attention in the T1–T2 interval, and for memory and attention in the T2–T4 interval, respectively. Individual differences in change (standard deviation) were also present. Some patients improved their performance, whereas others showed decline. The goodness of fit measures showed close fit between model and data for global cognitive performance, verbal abilities and learning scales, while the other three scales were based on saturated models and thereby giving no fit measures (please see Supplementary Table 1).

The relationship between levels and changes in CRP and cognition

The mean change in CRP from T1 to T2 was not statistically significant (0.52 mg/l/ month, \( p = 0.652 \), baseline mean level: 3.99 mg/l, SD = 8.32). However, the individual variation in change was statistically significant (SD = 12.13, \( p = 0.031 \)). In the total sample, a reduction in the CRP level from T1 to T2 was associated with an increase in global cognitive performance in the T2–T4 interval, whereas no such association was found between CRP and cognition during the T1–T2 interval (Table 4). Patients with most reduction in CRP also were the patients with most improvement in global cognitive performance, illustrated with a steeper increase in their performance, compared to those with a smaller reduction or an increase in CRP (Fig. 2).

For the cognitive subdomains, we observed a statistically significant association between reduction of the CRP level and increase in verbal abilities for the T2–T4 interval and in attention for the T2–T3 interval (Table 4).

For patients with CRP <10 mg/l (\( N = 191 \)), the results remained unchanged regarding the association between changes in global cognitive performance (T2–T4), verbal abilities (T2–T4), and attention (T2–T3), and CRP level changes. However, we also found additional statistically significant associations in this sub-sample compared to the total sample (Table 4).

A separate model for the sub-sample of patients diagnosed within the schizophrenia spectrum showed that change in CRP level did not predict T2–T4 change in the global cognitive performance as was found in the total sample (\( b = -0.01, p = 0.208 \)). Two new statistically significant associations were found between change in CRP level and attention in the T1–T2 interval (\( b = 0.12, p = 0.045 \)) and in the T3–T4 interval (\( b = 0.03, p = 0.026 \)).

Finally, the models were adjusted for the covariates metabolic syndrome, smoking, being medication naïve, illicit drug use, and the educational level. The association between baseline CRP level and global cognitive performance for the whole follow-up remained essentially unchanged. Baseline CRP level and visuospatial performance in the T3–T4 interval was no longer statistically significant (\( p = 0.120 \)), whereas a statistically significant association was found between CRP baseline level and this subdomain in the T1–T2 interval (\( b = 0.66, p = 0.018 \)). CRP level change and verbal abilities in the T2–T4 interval was no longer statistically significant associated (\( p = 0.067 \)), while such an association was found in the T1–T2 interval (\( b = -0.09, p = 0.039 \)). Additional statistically significant associations were found between CRP baseline level and attention in the T3–T4 interval (\( b = 0.31, p < 0.001 \)), and CRP level change and attention in the T1–T2 interval (\( b = 0.12, p = 0.045 \)), and in the T3–T4 (\( b = 0.03, p = 0.026 \)), respectively.

A separate model for the sub-sample of patients diagnosed within the schizophrenia spectrum showed some differences. Change in CRP did not predict T2–T4 change in the global score as it did in the total sample (\( b = 0.01, p = 0.208 \)), whereas change in CRP was found to be associated with change in attention for the T1–T2 (\( b = 0.12, p = 0.045 \)) and T3–T4 (\( b = 0.03, p = 0.026 \)) intervals, respectively.

In the schizophrenia group, the inclusion of covariates showed that higher CRP baseline level was related to lower baseline level in global cognitive performance (\( b = 0.26, p = 0.036 \)). CRP baseline level was found to be associated with verbal abilities in the T1–T2 interval (\( b = 0.64, p = 0.016 \)). In addition, CRP level change was found to be associated with verbal abilities in (\( b = -0.09, p = 0.024 \)) and learning in the T1–T2 interval (\( b = -0.04, p = 0.009 \)). The model with the attention outcome variable did not converge, even after increasing the number of iterations.

**Discussion**

The main finding of the present study was that the global cognitive performance continued to improve from the initial phase (baseline to 4 weeks) of acute psychosis to the later phase (4 weeks to 6 months), and was predicted by the reduction of the CRP level as observed during the initial phase (baseline to 4 weeks) of the

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**Table 3. Levels and changes in global cognition and cognitive subdomains over time**

<table>
<thead>
<tr>
<th>Scale</th>
<th>T1 Level (I)</th>
<th>Change T1–T2 (S1)</th>
<th>Change T2–T4 or change T2–T3 (S2)*</th>
<th>Change T3–T4 (S3)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>( p )</td>
<td>Mean</td>
</tr>
<tr>
<td>Global performance</td>
<td>38.3</td>
<td>7.6</td>
<td>0.000</td>
<td>2.9</td>
</tr>
<tr>
<td>Verbal abilities</td>
<td>40.1</td>
<td>8.4</td>
<td>0.000</td>
<td>6.0</td>
</tr>
<tr>
<td>Visuospatial abilities*</td>
<td>47.3</td>
<td>12.1</td>
<td>0.000</td>
<td>1.4</td>
</tr>
<tr>
<td>Learning</td>
<td>35.8</td>
<td>8.1</td>
<td>0.000</td>
<td>2.9</td>
</tr>
<tr>
<td>Memory*</td>
<td>38.1</td>
<td>12.1</td>
<td>0.000</td>
<td>1.2</td>
</tr>
<tr>
<td>Attention*</td>
<td>29.7</td>
<td>9.0</td>
<td>0.000</td>
<td>3.5</td>
</tr>
</tbody>
</table>

*Three change factors had to be estimated: S1: T1–T2; S2: T2–T3; and S3: T3–T4.

The time unit for change is months. T1, baseline; T2, 4 weeks; T3, 3 months; T4, 6 months. S1: change from T1–T2; S2: change from T2–T4 if supported by data; and S3: change T3–T4. Change in the T3–T4 interval was estimated if a linear change from T2–T4 was not supported. In these models, S2 consists of the change between T2–T3.

Group mean and individual differences (standard deviation, SD) for both level and change are reported. Statistical \( p \)-values are presented for individual differences at baseline level (T1 Level), and mean change and individual differences in change (standard deviation).

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treatment. Similar associations were found for several of the cognitive subdomains. These findings might indicate a prolonged effect of inflammatory processes on cognition after an acute psychosis, stretching beyond the initial phase.

The stability of cognitive dysfunctions in patients with psychosis has been debated for decades. Most studies have suggested stability or decline in cognitive functioning (55–58). A study of first-episode schizophrenia spectrum disorders and controls with follow-up intervals of 1-year and 3-years showed that, although patients performed worse than controls at any given time, the follow-up intervals of 1-year and 3-years showed that, although patients performed worse than controls at any given time, the cognitive performance of the patients improved in a similar way as the controls in all domains, except for verbal and visual memory, which showed greater improvement in controls (6). Another longitudinal study demonstrated improvement of general cognitive function, working memory, and verbal learning after 12 weeks, but these changes were mediated by improvements in both positive and negative symptoms (59).

There is substantial evidence that inflammatory processes are involved in the cognitive performance in psychosis (23,60,61). Oxidative stress and inflammation have been suggested to be associated with specific aspects of cognitive functioning in first-episode psychosis patients (62). Of particular interest, several studies have shown a link between CRP and cognitive function (25,29,37,63,64). CRP levels have been associated with cognitive impairments in both positive and negative symptoms (59).

Table 4. Baseline level and changes over time in cognitive performance predicted by baseline and change in C-reactive protein (CRP) level

<table>
<thead>
<tr>
<th>Table 4. Baseline level and changes over time in cognitive performance predicted by baseline and change in C-reactive protein (CRP) level</th>
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<tbody>
<tr>
<td><strong>Global performance</strong></td>
</tr>
<tr>
<td><strong>CRP level T1</strong></td>
</tr>
<tr>
<td>T1</td>
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<tr>
<td>T1−T2</td>
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<tr>
<td>T2−T4</td>
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<tr>
<td><strong>Verbal abilities</strong></td>
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<td>T1</td>
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<tr>
<td>T1−T2</td>
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<td>T2−T4</td>
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<tr>
<td><strong>Visuospatial abilities</strong></td>
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<td>T1</td>
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<td>T1−T2</td>
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<tr>
<td>T2−T3</td>
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<tr>
<td>T3−T4</td>
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<tr>
<td><strong>Learning</strong></td>
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<td><strong>Memory</strong></td>
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<td>T2−T3</td>
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<td>T3−T4</td>
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<td><strong>Attention</strong></td>
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<td>T1</td>
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<tr>
<td>T1−T2</td>
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<td>T2−T3</td>
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<td>T3−T4</td>
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</table>

The table presents results for all patients (i.e. total sample) and patients with CRP <10 mg/l (i.e. subsample). The time unit for change is months. Relations are given by unstandardised and standardised regression weights (b and β).
functioning of general intellectual ability, abstract reasoning, memory, working memory, semantic memory, learning abilities, attention, mental flexibility, and processing speed (25). In another, longitudinal study, CRP levels did not predict changes in cognitive performance (65), but this study included chronic phase patients with an average illness duration of 22.5 years, who are likely to have a lesser potential for inflammation related cognitive improvements.

Taken together, the present study supports a link between inflammation and cognitive performance in schizophrenia. Our study shows that early low-grade inflammation can predict cognitive improvement in later phases. Some studies have suggested that low-grade inflammation as indicated by elevated CRP levels is related to cerebral microstructural disintegration, involving frontal lobe executive functions (66). It has been suggested that increased levels of CRP can increase blood–brain barrier permeability, which might lead to inflammatory-related cognitive impairment (67). As neuroinflammation has been demonstrated to be associated with white matter pathology (27), any psychosis-related inflammation could, in principle, have a negative impact on brain tissue components of relevance to cognition, and the reversibility of such effects would likely include more slow regenerative processes.

There are some limitations to this study. First, attrition was substantial, but generally not related to any of the baseline characteristics except a higher PANSS negative subscale score and lower educational level in those patients tested only at baseline. As negative symptoms have been found to correlate with cognitive dysfunctions (12), those with the most pronounced cognitive difficulties may have dropped out during follow-up.

It is, however, difficult to predict how any selective dropout might have biased our results. Furthermore we used statistical methods that reduce the effect of missing data (68), and give improved statistical power and generalisability to the results, as all information in the data set is taken into consideration, rather than using the listwise deletion method that gives a net sample based on intact data in all variables under the assumption of missingness to be completely at random. However, the FIML method does not rule out the possibility of missingness to be non-random. The study included several models for different outcome variables, but accounted for, although many relevant factors were included in the analyses. Finally, the cognitive test battery at the T3 follow-up was more comprehensive but assessed the same cognitive domains as the test battery at T1, T2, and T4. We have no reason to suspect that this difference could have influenced the results.

We have shown that initial changes in the serum level of CRP in the acute phase of psychosis may predict cognitive function in later phases of the disease. These findings create an opportunity for future RCT research efforts to develop more individualised treatments with add-on anti-inflammatory agents (69). Some efforts have already been made in this field of research, but the results are mixed. A double-blind, randomised, placebo-controlled, add-on study with Celecoxib, a cyclo-oxygenase-2 inhibitor showed significant effect on the total PANSS score and the cognition factor of PANSS scale in patients with schizophrenia (70). N-acetyl cysteine significantly improved working memory compared to placebo in patients with psychosis, however, these preliminary data require replication (71). A double-blind, randomised study with minocycline treatment was associated with improvement in negative symptoms and executive functioning in early phase schizophrenia (72), whereas another study with add-on minocycline treatment showed improvement in negative symptoms, but not in cognition (73). Aspirin given as add-on treatment in another study reduced the total and positive PANSS score, but did not affect cognitive function (74). Finally, omega-3 fatty acid (ethyl eicosapentaenoic acid) add-on treatment did not affect cognition, positive or negative symptoms (75). Possible explanations for the equivocal findings might at least in part be related to small, unselected samples both with and without signs of an increased inflammatory status, with predominantly chronic phase psychosis, and with anti-inflammatory agents under investigation typically of low anti-inflammatory potency (76). Therefore, a more targeted approach might be to investigate more potent anti-inflammatory agents, for example, corticosteroids, in selected samples with signs of low-grade inflammation as determined by, for example, elevated CRP levels.

Acknowledgements. The authors thank research nurses Ingvild Helle and Marianne Langeland at the Research Department, Division of Psychiatry, Haukeland University Hospital for their contributions. We also wish to thank the Division of Psychiatry, Haukeland University Hospital for financial support, and the Clinical Departments for enthusiasm and cooperation. Authors’ Contributions: All authors made substantive intellectual contributions to the being exploratory, we did not adjust for multiple testing. The high number of tests could theoretically result in statistical type I error. However, we find it very unlikely that such a high number of statistically significant findings could be the result of chance.

According to the naturalistic design, patients were included on the basis of the presence of active psychosis as determined by the PANSS, and not based on diagnosis. Hence all patients were psychotic and in need of antipsychotic medication. The lack of specific diagnosis for nine patients probably reflects that some patients may have dropped out or been discharged before the treating clinician were able to make a proper diagnostic evaluation. This is clearly a limitation, but the direction of any influence on our results is difficult to predict.

Moreover, CRP was the only inflammatory marker that was measured, at baseline and the first follow-up (T2). Further measurements during the follow-up period would have allowed for analyses of associations between potential later changes in the CRP level and cognitive performance. We are also aware of the limitation that other factors potentially confounding the relationship between CRP and cognition might exist that we have not accounted for, although many relevant factors were included in the analyses. Finally, the cognitive test battery at the T3 follow-up was more comprehensive but assessed the same cognitive domains as the test battery at T1, T2, and T4. We have no reason to suspect that this difference could have influenced the results.

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study. F.F. designed the study, contributed to the statistical analyses and interpretations of the data, and wrote the first draft of the manuscript. E.-M.L. collected data and contributed to interpretations of the data and drafting the manuscript. R.G. contributed to the statistical analyses and interpretations of the data and contributed to the drafting of the manuscript. R.A.K. collected data and contributed to interpretations of the data and drafting of the manuscript. V.M.S. was the co-designer of the project and contributed to the interpretations of the data and drafting of the manuscript. H.A.J. designed the project, assisted in data collection and contributed to interpretations of the data and drafting of the manuscript. E.J. was the co-designer of the project, collected data, contributed to the statistical analyses, and co-drafted the manuscript. All authors have read and given final approval of the latest version of the manuscript.

**Statement of interest.** E.-M.L. has received honoraria in relation to the development of the Norwegian version of the RBANS by Pearson Assessment. E.J., F.F., R.G., V.M.S., R.A.K. and H.A.J. report no conflicts of interest related to the present work.

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**Ethical standards.** The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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