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Caroline Wendzel April 13, 2020

# C-Reactive Protein as a Biomarker for Anhedonia in Treatment-Resistant Depression: A Clinical Approach

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An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
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Abstract

C-Reactive Protein as a Biomarker for Anhedonia in Treatment-Resistant Depression: A Clinical Approach

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Although depression is one of the most common and debilitating illnesses worldwide, less than half of depressed patients respond to first-line antidepressant or psychotherapy treatment (Congio et al., 2020). Patients who do not respond to treatment are defined as treatment-resistant. Treatment resistance is associated with high rates of anhedonia (Lally et al., 2014), or a decrease in the ability to feel pleasure, and decreased motivation to pursue rewarding activity. Anhedonia is thought to be related to decreased connectivity in the corticostriatal network of the brain, and this decreased connectivity is also associated with inflammation (Felger, 2017). The purpose of the study was to assess C-reactive protein, an inflammatory marker, as a biomarker for anhedonia in patients with TRD. We hypothesized that patients with higher CRP levels would correlate with those with higher baseline anhedonia scores, that CRP values would positively predict anhedonia scores, and that CRP would uniquely predict anhedonic symptoms as compared to non-anhedonic symptoms. We analyzed 263 TRD patients' baseline CRP levels and baseline anhedonic and non-anhedonic symptoms, as measured by the Beck Depression Inventory II. We ran both Spearman's rho correlations and multiple regression analyses, with age, sex, BMI and whether or not a patient was diagnosed with inflammatory or inflammation-associated conditions as covariates. Although our hypotheses were incorrect when examining the overall sample, when we split the file into two groups based on whether or not a patient had an inflammatory or inflammation-associated condition, we found that CRP had a significant main effect on the variance in anhedonic scores, non-anhedonic scores, and total BDI in the non-inflammatory group, suggesting that CRP may be an indicator of depressive symptoms in patients without inflammatory conditions, but not for those with inflammatory conditions. This finding suggests that medical screening could be particularly important in determining when to use CRP as a biomarker for depression.

# C-Reactive Protein as a Biomarker for Anhedonia in Treatment-Resistant Depression: A Clinical Approach

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Table of Contents

# C-Reactive Protein as a Biomarker for Anhedonia in Treatment-Resistant Depression: A Clinical Approach

## Introduction

Depression is one of the leading causes of illness and disability worldwide (World Health Organization, 2017), with 10-15% of the population affected each year. Despite its prevalence, only 50% of people receive treatment for this condition (Al-Harbi, 2012) and of those who receive treatment, less than 50% respond to first line antidepressant or psychotherapy treatment (Congio et al., 2020). Patients who do not respond to treatment are defined as treatment-resistant, or treatment-refractory. Although there is disagreement surrounding the amount and types of treatments a patient needs to fail in order to be classified as treatment-resistant, the most common definition includes patients who fail to respond to at least two clinically adequate trials (6-8 weeks) (Voineskos, Daskalakis, & Blumberger, 2020) of antidepressants (antidepressants administered for an adequate length of time at an adequate dose) (Al-Harbi, 2012). These treatment-resistant depression (TRD) patients tend to have lower health-related quality of life, greater healthcare resource utilization, and greater impairment in work and activity productivity, as compared to both the general population and depressed individuals who are not treatment-resistant (Jaffe, Rive & Denee, 2019). Thus, TRD causes a substantial burden not only to the patients themselves but also to the healthcare system. Because TRD only affects some depressed patients, and not others, it is theorized that TRD may have a unique etiology that requires unique treatment (Al-Harbi, 2012), leading scientists to investigate different symptom dimensions of depression to see if certain symptoms are more prevalent in TRD than other forms of depression.

Out of these investigations, anhedonia has emerged as one of the primary dimensions of depression associated with treatment-resistance (Lally et. al., 2014). Anhedonia is one of the

main criteria for major depressive disorder in the DSM-V (American Psychiatric Association, 2013), and is broadly defined as a decrease in the ability to feel pleasure, and decreased motivation to pursue rewarding activity. Patients with higher overall anhedonia scores report lower rates of depression remission, and those who do remit in overall depression often retain their anhedonic symptoms (Craske et al., 2016). Anhedonic symptoms are also an indicator of poor long-term outcomes, including suicide (Craske et al., 2016). Anhedonic symptoms in depression have been linked to reductions in reward sensitivity, reduced willingness to expend effort in pursuit of reward, and disruptions in goal-directed reasoning (Cooper, Arulpragasam, & Treadway, 2018). These symptoms are the thought to be related to decreased connectivity in the corticostriatal network of the brain, particularly between the supplementary motor area (SMA) and anterior cingulate cortex (ACC), as these areas has been linked to reduced motivation, and decreased striatal activity. Activity in the SMA in particular has been associated with effort minimization (Cooper, Arulpragasam, & Treadway, 2018). This decreased functional connectivity is not only significantly associated with anhedonia (Felger, 2017) but has also been associated with inflammation. Inflammation is measured through markers in the blood, and levels of these markers are often found in increased numbers in TRD patients in particular (Osimo et al., 2019).

The purpose of this study to investigate one type of inflammatory marker in particular, C-Reactive Protein (CRP), as a potential biomarker of anhedonia. Anhedonia is currently assessed through self-report and clinician-administered assessments. These assessments generally have good levels of validity and reliability (see Wang & Gorenstein, 2013), but can be prone to bias and error, due to their reliance on human judgment. Because of this, scientists have been investigating more objective measurements of psychopathology to use alongside the current

assessments. An example of such an objective measurement is a biomarker, or a biological indicator of a disease or pathological condition. CRP is an excellent candidate as a biomarker for anhedonia, specifically. An acute phase reactant protein secreted by the liver, CRP is released in response to an increase in cytokines in the blood, and is considered a marker of inflammation in the body (Ridker, 2009). According to a recent meta-analysis **(**Osimo et al., 2019), about 27% of patients diagnosed with depression (including both unipolar and bipolar depression, and treatment-resistant varieties) have low-grade inflammation (CRP > 3mg/L) and 58% of patients have elevated CRP (CRP > 1mg/L but < 3mg/L). Taking all of this into account, it is reasonable to hypothesize that elevated CRP levels will be linked to higher self-report scores of anhedonia in patients with treatment-resistant depression. We thus hypothesize that will see patients with higher CRP levels correlate with those with higher baseline anhedonia scores, indicating a positive relationship between CRP and anhedonia. We further hypothesize that CRP values will positively predict anhedonia scores, and that CRP will uniquely predict anhedonic symptoms as compared to non-anhedonic symptoms.

## Methods

### Participants

Data was collected from Emory University's Treatment-Resistant Depression clinical research program in Atlanta, Georgia. The TRD program is a consultative program to which outside psychiatrists refer their patients with TRD. The clinic provides extensive diagnostic evaluation and treatment planning, as well as neuromodulation and experimental treatment services. This study includes data from patients' pre-treatment (intake) diagnostic and assessment appointment.

In total, our study included 263 participants. 108 of the participants were male (41.1% of the sample), and 155 (58.9% of the sample) were female, consistent with known gender distributions of depression diagnoses. There were 231 Caucasian participants, 21 Black participants, eight Asian or Pacific Islanders, one American Indian, and two whose races were unavailable, yielding percentages of 87.8%, 8.0%, 3.0%, 0.4%, and 0.8%, respectively. There were two (0.8% of the sample) Spanish, Hispanic and/or Latino participants. The participants ranged in age, with the youngest participant 20 at the time of intake, and the oldest participant 90. The average age of participants was 52.9, with a standard deviation of 16.9. Participants had an average BMI of 28.8, with a standard deviation of 7.7. The lowest BMI was 15.8 and the highest was 71.7. 187 (71.1% of) patients had some sort of inflammatory medical condition (See Table 1), or condition associated with inflammation; 76 (28.9% of) patients did not. Determining whether a condition was inflammatory or inflammation-associated was done through a literature search, and included conditions defined as inflammatory (ex. autoimmune disorders such as rheumatoid arthritis) and conditions consistently shown in the literature to be associated with inflammation (ex. hypertension, hyperlipidemia). Analyses were run both including and excluding affected patients.

**Procedure**

All information was obtained during a pre-treatment visit to the Emory TRD clinic (i.e., "baseline"). Most patients were taking psychotropic medications or engaged in therapy at the time of intake. Patients self-reported demographic information (including age, race, ethnicity, and medical history). The patients' height and weight were collected either on the day of intake or shortly thereafter. In rare cases where it was not possible to obtain actual height and weight, doctors estimated participants' height and weight, and these were used for BMI calculations.

Alternatively, patients were asked to provide estimates of their weight and height, and these numbers were used for BMI calculations (doctors' estimates took precedence over patients'). High-sensitivity C-Reactive protein (hsCRP) was measured as part of the clinic's routine blood draws. The samples were processed at Emory Medical Labs, using a Beckman Coulter AU Analyzer.

**Measures**

*Self-report Anhedonia* Participants completed the Beck Depression Inventory-II (BDI-II). The BDI-II (Beck, Steer, Ball, & Ranieri, 1996) is a 21-question self-report scale measuring depression within the last two weeks, with a Likert scale ranging from 0-3, with 3 being the highest severity. Scores can range from 0-63. Ratings of 1-10 are considered "normal", 11-16 are considered "mild mood disturbance", 17-20 are considered "borderline clinical depression", 21-30 are considered "moderate depression", 31-40 are considered "severe depression", and over 40 are considered "severe depression." The BDI has good validity and reliability, (Wang & Gorenstein, 2013), and is a quick, easy, and cost-effective way for patients to provide their own perspective on their symptoms, making it a convenient and effective tool for clinical studies and clinical use.

To quantify anhedonia, we used the previously-validated BDI-II anhedonic subscale (see Pizzagalli, Jahn & O'Shea, 2005 and Joiner, Brown, & Metalsky, 2003). The subscale is a summed score of questions #4 (loss of pleasure), #12 (loss of interest), #15 (loss of energy) and #21 (loss of interest in sex), with scores ranging from 0 to 12. The remaining 17 questions were grouped into a "BDI non-anhedonic subscale," with scores ranging from 0 to 51. Both the anhedonic subscale and the non-anhedonic subscale were converted to means for ease of analysis.

**Analytic Plan**

Consistent with prior studies, the distribution of CRP values was significantly skewed (kurtosis = 17.12, SE = .30). CRP values were thus log-transformed to normalize their distribution, as seen in past studies (Kohler-Forsberg et al., 2017; Uher et al., 2014; Jokela, et al., 2015). We first looked at the sample as a whole, using Spearman's rho correlations to identify possible correlations between the anhedonia subscale mean, the BDI non-anhedonic subscale mean, the BDI total score, and CRP, with age, gender, BMI, and whether or not a patient had an inflammatory or inflammation-associated medical condition as covariates. In a recent meta-analysis (Majd, Saunders, & Engeland, 2020), age, gender, and BMI were the most common covariates used in studies of TRD; older age and female gender have been associated with higher rates of TRD (Gronemann et al., 2020), and higher BMI has been associated with greater levels of inflammation in the body (Majd, Saunders, & Engeland, 2020), hence their inclusion as covariates. Because CRP is a marker of inflammation in the body, it is important to distinguish between CRP potentially related to anhedonia and inflammation associated with other medical conditions, hence inflammatory medical condition's inclusion as a covariate. To assess the degree to which anhedonia scores for patients change depending upon their CRP values, we ran a multiple linear regression, with anhedonia as the dependent variable, CRP as the predictor variable, and age, gender, BMI, and whether or not a patient had an inflammatory or inflammation-associated medical condition as covariates. We then ran this same regression analysis with the non-anhedonic symptoms as the dependent variable, as well as with the BDI total as the dependent variable, to determine if CRP had differing effects on non-anhedonic scores or the BDI total. We examined partial regression plots for each variable. Then, in order to see the ways in which the group of patients with inflammatory or inflammatory-associated

conditions and those without compare, we split the sample into two groups—patients with inflammatory conditions (Group 1, n = 187) and patients without inflammatory conditions (Group 2, n = 76), and we ran multiple linear regressions for each group, with the same variables. All calculations, graphs, and correlations were done using IBM SPSS Version 26.

## Results

### CRP and Anhedonia, All Subjects

No significant correlation was found between CRP and anhedonia in the overall sample. However, when we ran multiple regression analysis on the overall sample, we found that the model produced significant results, explaining 6.0% of the variance in anhedonia scores ($F(5, 257) = 3.28$, $p < 0.05$, $R^2 = .060$, $R^2_{adjusted} = .042$). Age ($\beta = -.213$, $p < 0.05$) and whether or not a patient was inflammatory ($\beta = -.143$, $p < 0.05$) were both significant contributors to the model; however, CRP, BMI, and gender were not.

### CRP and Anhedonia in Patients With/Without Inflammatory Med. Conditions

When we split the file into patients with inflammatory conditions (Group 1, n =187) and patients without inflammatory conditions (Group 2, n = 76). We found a positive correlation between CRP and anhedonia ($r_s = .24$, $p < 0.05$) (see Figures 1 and 2) in Group 2. Positive correlations were also found between CRP and non-anhedonic scores ($r_s = .29$, $p < 0.05$) (see Figures 3 and 4) and CRP and total BDI score ($r_s = .28$, $p < 0.05$). In Group 1, no significant correlation was found between CRP and anhedonia, non-anhedonic scores, or BDI total.

Multiple regression analysis of both groups, with anhedonia as the dependent variable, CRP as the predictor, and age, gender, and BMI as covariates, yielded significant results for both groups. We found that the Group 1 model explained 5.2% of the variance in anhedonia scores ($F(4, 182) = 2.50$, $p < 0.05$, $R^2 = .052$, $R^2_{adjusted} = .031$), and that the Group 2 model explained 15.5%

of the variance in anhedonia scores ($F (4, 71) = 3.25$, $p < 0.05$, $R^2 = .155$, $R^2_{adjusted} = .107$). In other words, we found that our predictor variables explained more of the variance in anhedonia scores in patients *without* inflammatory conditions than in those with inflammatory conditions. Upon further analysis, we found that CRP specifically contributed significantly to the Group 2 ($\beta = .351$, $p < 0.05$), but not Group 1 model. Age contributed significantly to both the Group 1 ($\beta = -.168$, $p < 0.05$) and Group 2 model ($\beta = -.263$, $p < 0.05$). BMI and gender did not contribute significantly to either model. We then computed an interaction between CRP and whether or not a patient had an inflammatory medical condition (holding covariates constant) in the overall sample. The model explained 7.2% of the variance in anhedonia scores in all patients ($F (6, 256) = 3.31$, $p < 0.05$, $R^2 = .072$, $R^2_{adjusted} = .050$). However, the interaction did not contribute significantly to the model; whether or not a patient was inflammatory did contribute significantly ($\beta = -.266$, $p < 0.05$), as did age ($\beta = -.212$, $p < 0.05$).

We then ran a multiple regression analysis of the overall sample, with non-anhedonic symptoms as the dependent variable, and CRP as the predictor, and age, gender, BMI and whether or not a patient had inflammatory conditions as covariates. The model was significant, explaining 20.7% of the variance in non-anhedonic symptoms ($F (5, 257) = 13.42$, $p < 0.05$, $R^2 = .207$, $R^2_{adjusted} = .192$). In particular, whether or not a patient had inflammatory conditions or not significantly contributed ($\beta = -.172$, $p < 0.05$), as did age ($\beta = -.406$, $p < 0.05$) and gender ($\beta = .153$, $p < 0.05$). We then ran the interaction between CRP and whether or not a patient had an inflammatory condition in the overall sample, with non-anhedonic symptoms as the dependent variable, CRP as the predictor, and all other covariates constant. The model was significant ($F(6, 256) = 11.79$, $p < 0.05$, $R^2 = .217$, $R^2_{adjusted} = .198$), explaining 21.7% of the variance in non-anhedonic scores. However, the interaction was not significant. Splitting the sample yielded a

significant model in Group 1 ($F(4, 182) = 10.70$, $p < 0.05$, $R_2 = .190$, $R_{2\ adjusted} = .173$) and Group 2 ($F(4, 71) = 7.35$, $p < 0.05$, $R_2 = .293$, $R_{2\ adjusted} = .253$) but yielded a significant main effect for CRP in Group 2 only ($\beta = .292$, $p < 0.05$). Gender was also significant in Group 2 ($\beta = .292$, $p < 0.05$) but not Group 1. Age was significant in both Group 2 ($\beta = -.403.$, $p < 0.05$) and Group 1 ($\beta = -.389$, $p < 0.05$).

We ran the same regression analyses with the BDI Total as the dependent variable, which yielded similar results as the analyses run with non-anhedonic scores as the dependent variable.

**Discussion**

Our results suggest that CRP values are not uniquely associated with anhedonic symptoms as measured by the BDI-II; rather, CRP values are broadly associated with depressive symptoms. Although we did not find a significant interaction between CRP values and whether or not a patient had an inflammatory or inflammation-associated condition, CRP had a significant main effect on the variance in anhedonic scores, non-anhedonic scores, and total BDI in the non-inflammatory group, in each of our regression analyses, with small to moderate effect sizes, suggesting that CRP may be an indicator of depressive symptoms in patients without inflammatory conditions, but not for those with inflammatory conditions. This finding suggests that medical screening could be particularly important in determining when to use CRP as a biomarker for depression. If implemented, this could lead to a reduction in healthcare costs, and would add further credibility to the emerging field of precision medicine.

Previous studies have found significantly higher CRP values in treatment-resistant depression patients compared to non-TRD depressed patients (Congio et al., 2020; Chamberlain et al., 2019); these high levels of inflammation unique to TRD suggest that inflammation may contribute to treatment non-response in depression. Because our results found that CRP predicted

variance in depressive symptoms only in patients without inflammatory or inflammation-associated medical conditions, our results suggest that this theory may be most relevant in subgroups of TRD patients without (other) significant inflammatory conditions.

BMI was not a significant covariate in any of our analyses, while gender as a covariate produced mixed results; however, age was found to be a consistently significant covariate in the overall sample, influencing all dependent variables tested, and was most often significant in Group 2. In all analyses, betas were negative, indicating an inverse relationship with age and depressive symptomology.

**Limitations**

Although our original hypothesis, that anhedonia would prove to be more positively associated with CRP than other depressive symptomology, was not supported, this does not necessarily imply that there is no unique connection between CRP and anhedonia. The outcome of measurement for anhedonia was based upon one self-report measure (the BDI-II); in the future, it would be worthwhile to include multiple measures of outcome, including both clinician-administered and self-report scales, to better measure the targeted construct. Furthermore, post-hoc correlation analyses found that all of the BDI items correlated heavily, suggesting that the assessment instrument may not be well-designed for anhedonia severity that is independent of other symptoms of depression. It would also be helpful to include more diverse measures of depressive symptoms and non-anhedonic symptoms, as these constructs also relied upon only one measure (the BDI-II).

Increasing our sample size would also likely increase the accuracy of our predictions.

Missing data, and lack of control for potentially confounding variables, such as patients' current medication and therapy use, could also have skewed our data.

### Future Directions

In the future, we would like to see if CRP's association with depressive symptomology in patients without inflammatory or inflammation-associated disorders is specific to patients diagnosed with TRD, or if this effect is generalizable to other subtypes of depression or other psychological disorders. We would also like to analyze additional inflammatory markers, such as IL-6, to see if our results are specific to CRP or to inflammatory markers more broadly. Finally, it would be worthwhile to more precisely define and categorize "inflammatory conditions" in patients, to examine if there are specific conditions within this category that may be influencing results more than others.

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**Table 1**

*Inflammatory Conditions/Conditions Associated with Inflammation*

| | | | | | |
|---|---|---|---|---|---|
| Hypertension | Crohn's disease | COPD | Asthma | Arthritis (type unspecified) | Diabetes (type unspecified) |
| Hashimoto's Disease | Hyperlipidemia | Sarcoidosis | Parkinsonism | Lupus | Migraine |
| Ulcerative colitis | Obstructive sleep apnea | Polycystic ovary syndrome | Reflex neurovascular dystrophy | Cancer (type unspecified) | GERD |
| Thyroid disease (general) | Fibromyalgia | Autoimmune disease (unspecified) | Renal insufficiency | Stress-induced cardiomyopathy | Psoriatic arthritis |
| Hypothyroidism | Chronic pain | Chronic pancreatitis | Hypercholesterolemia | Bronchiectasis | Dementia |
| Thyroid disease (general) | Sjogren's syndrome | HIV+ | Psoriasis | Idiopathic cardiomyopathy | Endometriosis |
| Tourette's Syndrome | | | | | |

# Figures

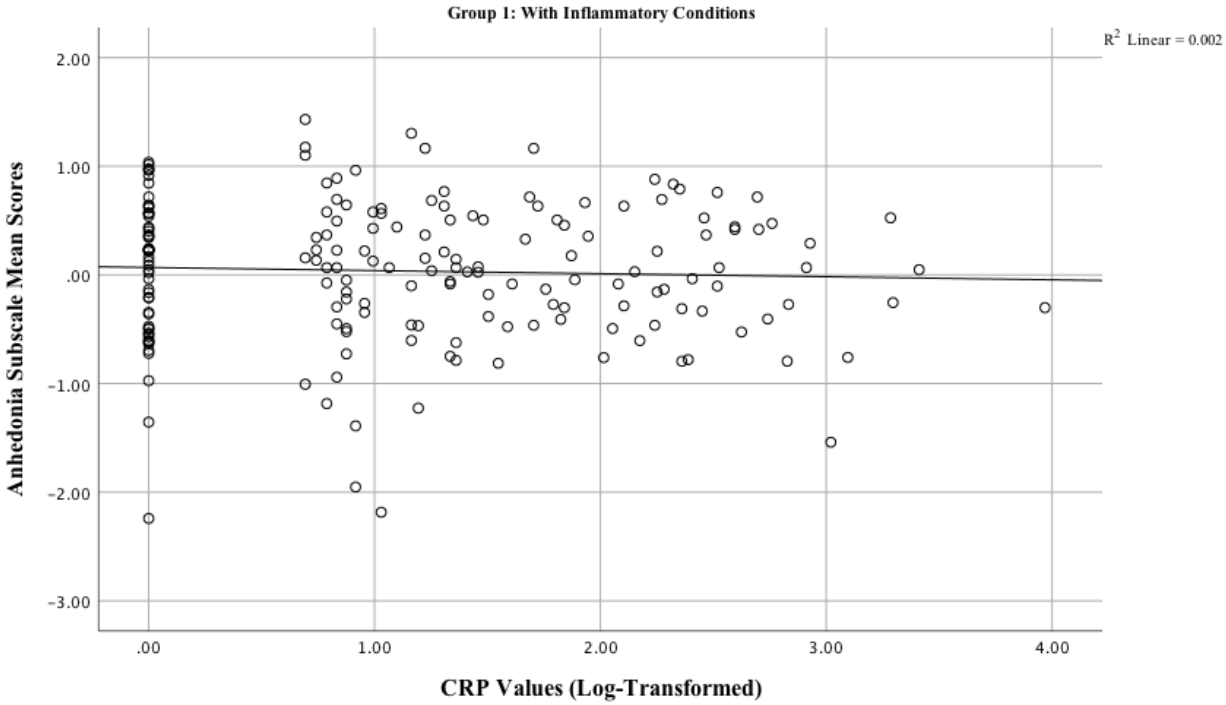


*Figure 1.* Correlation between CRP and Anhedonia Symptoms in Patients with Inflammatory or Inflammation-Associated Medical Conditions.

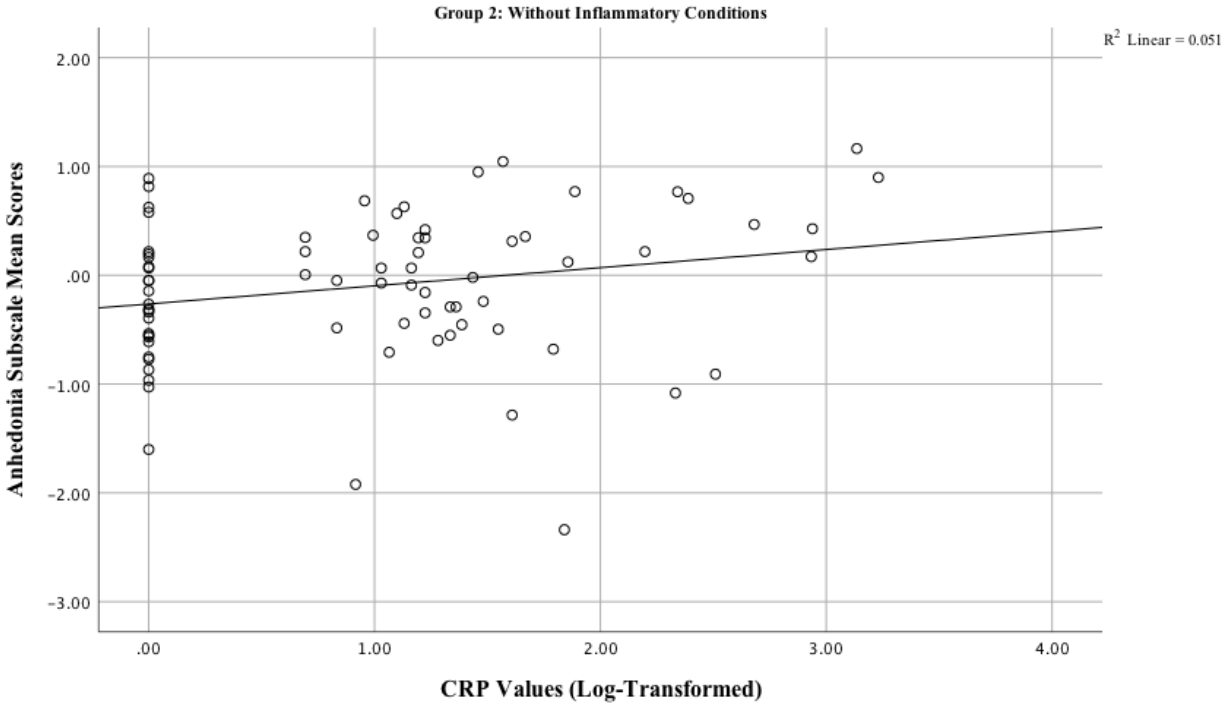


*Figure 2.* Correlation between CRP and Anhedonia Symptoms in Patients without Inflammatory or Inflammation-Associated Medical Conditions.

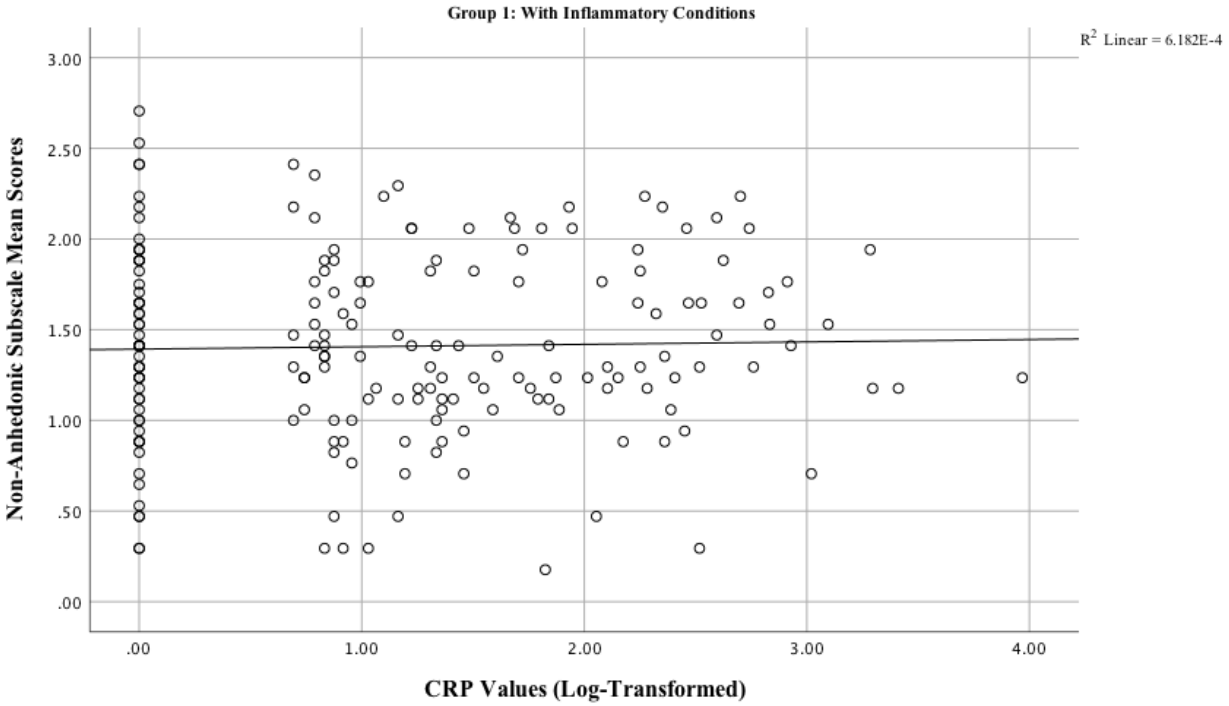


*Figure 3.* Correlation between CRP and Non-Anhedonic Symptoms in Patients with Inflammatory or Inflammation-Associated Medical Conditions

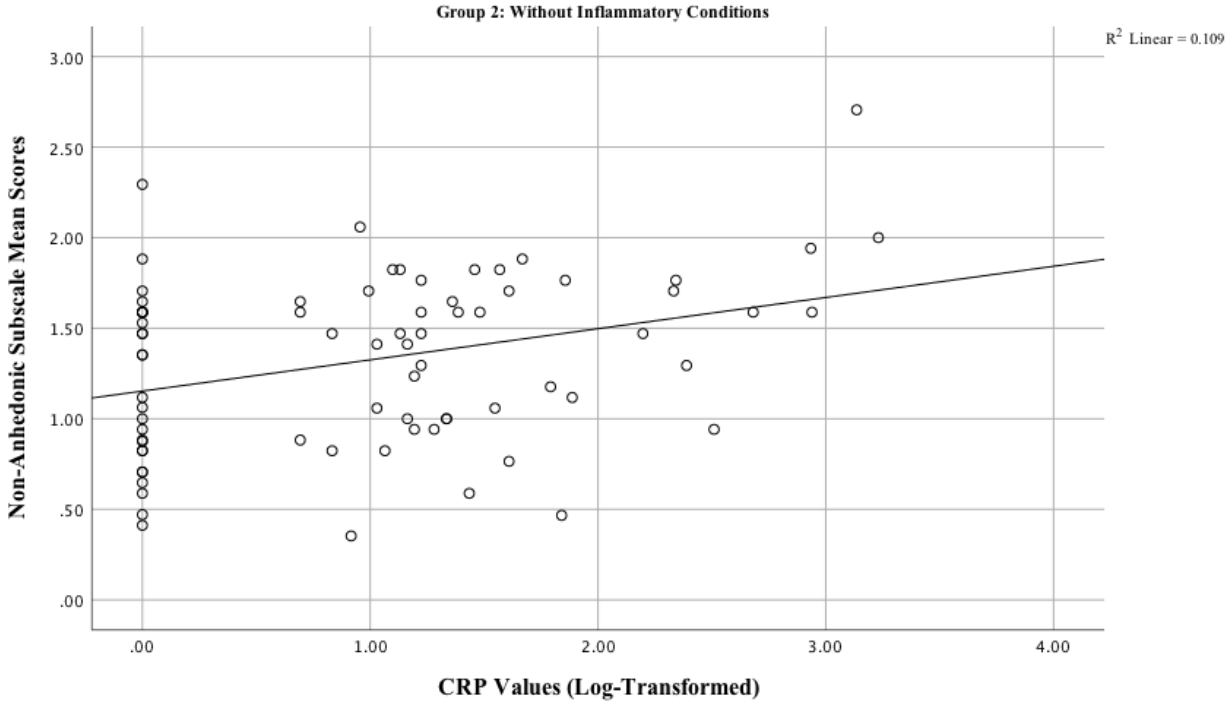


*Figure 4.* Correlation between CRP and Non-Anhedonic Symptoms in Patients without Inflammatory or Inflammation-Associated Medical Conditions.