Thesis

BETTER UNDERSTANDING OF C-REACTIVE PROTEIN AND LEUKOCYTES IN PSYCHIATRIC INPATIENTS WITH AFFECTIVE DISORDERS: A BIOPSYCHOSOCIAL APPROACH

submitted by

Felix Paul Kölblinger

in partial fulfillment of the requirements for the degree of

Doktor der gesamten Heilkunde (Dr. med. univ.)

at the

Medical University of Graz

executed at the **University Department of Psychiatry and Psychotherapeutic Medicine**

under the supervision of

Nina Dalkner, Research Prof.in Priv.-Doz.in Mag.a rer.nat. Dr.in rer.nat.

Elena Schönthaler, Dr. in scient.med MSc

Graz, 18.08.2024

Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, 18.08.2024 *Felix Kölblinger m.p.*

Acknowledgements

First and foremost, I want to thank both of my thesis supervisors Nina Dalkner and Elena Schönthaler for giving me the opportunity of writing my thesis as a publication and letting me have a big part in both the planning and conduction of the study. Further thanks go to the coauthors of the paper who, with their insight and perspective, helped me refine it. Thank you for supporting me every step of the long way to peer-review with your wealth of knowledge and experience.

I also want to thank my family, especially my parents for supporting me both emotionally and financially throughout my medical degree, always listening to my struggles and helping me overcome them.

Then, I want to thank my friends, without them I would have never even considered medicine, though now I can't imagine doing anything else. So, thank you for planting that idea in my head.

I thank my colleagues, for sharing the highs and lows of med school with me, you made it one of the best times of my life.

Last but not least a big thank you to everyone who took the time to participate in the study.

Zusammenfassung

Hintergrund: Affektive Erkrankungen (AD) sind mit inflammatorischen Prozessen in Verbindung gebracht wurden, allerdings konnten die ursächlichen Mechanismen noch nicht vollständig aufgedeckt werden. Es wird jedoch vermutet, dass demographische, somatische, Lebensstil und Persönlichkeits Parameter Inflammationsparameter in AD vorhersagen könnten.

Ziel: Biopsychosoziale und persönlichkeits Faktoren identifizieren, welche zur Inflammation in Personen mit affektiven Erkrankungen beitragen, gemessen an zwei Parametern: C-Reaktives Protein (CRP) und Leukozyten.

Methoden: Diese Beobachtungsstudie untersuchte 186 Patient*Innen mit der Diagnose einer affektiven Erkrankung. Dazu wurden demografische Parameter, Serum Entzündungsmarker, somatische Variablen, psychologische Fragebögen und Lebensstil Parameter verwendet. Hierarchische Regressionsanalysen wurden verwendet um Inflammationsparameter anhand von demographischen, somatischen, Lebensstil und Perönlichkeits Parametern vorherzusagen.

Ergebnisse: In den hierarchischen Regressionsanalysen konnte 33.8% der Varianz im C-Reaktiven Protein durch den Body-Mass-Index, somatische Medikation (z.B. Antidiabetika), Alter, Bildungsstand und Alter bei Diagnosestellung der affektiven Erkrankung erklärt werden. Bei Leukozyten konnten 20.1% der Varianz durch rauchen, Ernährung, metabolisches Syndrom und antiinflammatorische Medikation (z.B. nichtsteroidale Antirheumatika) erklärt werden. Andere psychiatrische Variablen zeigten keine Signifikanz.

Konklusion: Metabolische Komponenten erscheinen wichtig, vor allem da es Hinweise auf einen metabolischen Subtyp affektiver Erkrankungen gibt. Lebensstilmodifikationen und Psychoedukation sollten verwendet werden um MetS in AD zu verhindern oder es zu behandeln.

Abstract

Background: Affective disorders (AD) have been linked to inflammatory processes, although the underlying mechanisms of this relationship are still not fully elucidated. It is hypothesized that demographic, somatic, lifestyle, and personality variables predict inflammatory parameters in AD.

Aim: To identify biopsychosocial factors contributing to inflammation in AD measured with two parameters, C-reactive protein (CRP) and leukocytes.

Methods: This observational study investigated 186 hospital inpatients diagnosed with AD using demographic parameters, serum inflammatory markers, somatic variables, psychological questionnaires, and lifestyle parameters. Hierarchical regression analyses were used to predict inflammatory markers from demographic, somatic, lifestyle, and personality variables.

Results: Analyses showed that 33.8% of the variance of CRP was explained by body mass index and other somatic medication (e.g. anti-diabetics), age and education, and age of affective disorder diagnosis. For leukocytes, 20.1% of the variance was explained by smoking, diet, metabolic syndrome (MetS), and anti-inflammatory medication (e.g. non-steroidal anti-inflammatory drugs). Other psychiatric or behavioural variables did not reach significance.

Conclusion: Metabolic components seem important, with mounting evidence for a metabolic affective disorder subtype. Lifestyle modifications and psychoeducation should be employed to prevent or treat MetS in AD.

Keywords: Affective disorders; C-reactive protein; Leukocytes; Metabolic syndrome; Health behaviour; Personality

Disclosure of previous Publications

This work was written as an academic paper, with the intention of using its final, published version as Diploma-Thesis.

It was published online in the “World Journal of Clinical Cases”:

Kölblinger, F., Schönthaler, E. M., Baranyi, A., Stross, T., Fellendorf, F. T., von Lewinski, D., Queissner, R., Reininghaus, E. Z., & Dalkner, N. (2024). Better understanding of c-reactive protein and leukocytes in psychiatric inpatients with affective disorders: A biopsychosocial approach. *World journal of clinical cases*, *12*(19), 3824–3836. https://doi.org/10.12998/wjcc.v12.i19.3824

Angabe bereits erfolgter Publikationen

Diese Arbeit wurde als wissenschaftlicher Artikel verfasst, dessen Peer-Reviewte Veröffentlichung als Diplomarbeit eingereicht wird.

Die Arbeit wurde online im „World Journal of Clinical Cases“ veröffentlicht:

Kölblinger, F., Schönthaler, E. M., Baranyi, A., Stross, T., Fellendorf, F. T., von Lewinski, D., Queissner, R., Reininghaus, E. Z., & Dalkner, N. (2024). Better understanding of c-reactive protein and leukocytes in psychiatric inpatients with affective disorders: A biopsychosocial approach. *World journal of clinical cases*, *12*(19), 3824–3836. https://doi.org/10.12998/wjcc.v12.i19.3824

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Abbreviations

AD	affective disorders
BD	bipolar disorder
CMD	cardiometabolic disease
CRP	C-reaktive protein
CVD	cardiovascular disease
DT	dark triad
HDL	high-density lipoprotein
MDD	major depressive disorder
MetS	metabolic syndrome
TG	triglycerides

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Publication

The following part is the article published in the World Journal of Clinical Cases to be used as the diploma thesis. All citations of the article are to be done by citing from the World Journal of Clinical Cases.

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2024 July 6; 12(19): 3824-3836

DOI: 10.12998/wjcc.v12.i19.3824

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Observational Study

Better understanding of c-reactive protein and leukocytes in psychiatric inpatients with affective disorders: A biopsychosocial approach

Felix Kölblinger, Elena MD Schönthaler, Andreas Baranyi, Tatjana Stross, Frederike T Fellendorf, Dirk von Lewinski, Robert Queissner, Eva Z Reininghaus, Nina Dalkner

Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade C
Scientific Significance: Grade B

P-Reviewer: Hosak L, Czech Republic

Received: February 27, 2024
Revised: May 7, 2024
Accepted: May 27, 2024
Published online: July 6, 2024
Processing time: 122 Days and 19 Hours

Felix Kölblinger, Elena MD Schönthaler, Andreas Baranyi, Tatjana Stross, Frederike T Fellendorf, Robert Queissner, Eva Z Reininghaus, Nina Dalkner, Clinical Department of Psychiatry and Psychotherapeutic Medicine, Medical University of Graz, Graz 8036, Austria

Dirk von Lewinski, Clinical Department of Cardiology, Medical University of Graz, Graz 8036, Austria

Corresponding author: Elena MD Schönthaler, MSc, Doctor, Researcher, Clinical Department of Psychiatry and Psychotherapeutic Medicine, Medical University of Graz, Auenbruggerplatz 31, Graz 8036, Austria. elena.schoenthaler@medunigraz.at

Abstract

BACKGROUND

Affective disorders (AD) have been linked to inflammatory processes, although the underlying mechanisms of this relationship are still not fully elucidated. It is hypothesized that demographic, somatic, lifestyle, and personality variables predict inflammatory parameters in AD.

AIM

To identify biopsychosocial factors contributing to inflammation in AD measured with two parameters, C-reactive protein (CRP) and leukocytes.

METHODS

This observational study investigated 186 hospital inpatients diagnosed with AD using demographic parameters, serum inflammatory markers, somatic variables, psychological questionnaires, and lifestyle parameters. Hierarchical regression analyses were used to predict inflammatory markers from demographic, somatic, lifestyle, and personality variables.

RESULTS

Analyses showed that 33.8% of the variance of CRP was explained by body mass index and other somatic medication (*e.g.* anti-diabetics), age and education, and age of affective disorder diagnosis. For leukocytes, 20.1% of the variance was explained by smoking, diet, metabolic syndrome (MetS), and anti-inflammatory medication (*e.g.* non-steroidal anti-inflammatory drugs). Other psychiatric or

behavioural variables did not reach significance.

CONCLUSION
Metabolic components seem important, with mounting evidence for a metabolic affective disorder subtype. Lifestyle modifications and psychoeducation should be employed to prevent or treat MetS in AD.

Key Words: Affective disorders; C-reactive protein; Leukocytes; Metabolic syndrome; Health behaviour; Personality

Core Tip: Somatic and psychological variables may affect inflammation in affective disorders (AD). In 186 inpatients with AD, C-reactive protein (CRP) and leukocytes were measured. CRP relates to somatic variables (*e.g.*, body mass index), age, education, and age of diagnosis. Leukocytes relate to smoking, diet, and somatic variables (*e.g.*, metabolic syndrome). Lifestyle modifications and psychoeducation on MetS is needed in individuals with AD to prevent symptom deterioration.

Citation: Kölblinger F, Schönthaler EM, Baranyi A, Stross T, Fellendorf FT, von Lewinski D, Queissner R, Reininghaus EZ, Dalkner N. Better understanding of c-reactive protein and leukocytes in psychiatric inpatients with affective disorders: A biopsychosocial approach. *World J Clin Cases* 2024; 12(19): 3824-3836
URL: https://www.wjgnet.com/2307-8960/full/v12/i19/3824.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i19.3824

INTRODUCTION

Affective disorders (AD) are mental illnesses characterized by episodic or persistent mood and activity changes[1]. The most common AD is major depressive disorder (MDD) with a prevalence of 3.15%[2] followed by bipolar disorder (BD) with an estimated one-year prevalence of 1.21%[3]. The latter comprises at least two recurrent (hypo)manic episodes, though often combined with depressive episodes[1]. Life expectancy for people suffering from AD is significantly shortened compared to the general population, with a life expectancy 14.0 years or 10.1 years shorter for men or women with MDD, respectively[4], and 12.9 years of potential life lost for people with BD[5]. As shown by the "Global Burden of Disease Study", AD is a leading cause of the global burden of disease, which highlights the importance of research in this field[6]. De Hert *et al*[7] points out that the increased mortality rates are only partly due to suicides and accidents, but rather due to non-infectious diseases. It is therefore necessary to investigate the link between depression and physical health. Somatic comorbidities are very common in people with AD and pose a major challenge for outcome and progression[8]. Notably, obesity-associated comorbidities such as the metabolic syndrome (MetS) and its related cardiometabolic diseases (CMD) have been associated with AD. MetS is a cluster of cardiometabolic risk factors, consisting of central obesity, measured by waist circumference above 94 cm for males and 80 cm for females, high blood pressure, lower high-density lipoprotein (HDL), raised triglycerides (TG), and elevated blood sugar. These lead to increased insulin resistance, which may further progress into diabetes mellitus type 2 and cardiovascular diseases (CVD) such as atherosclerosis[9]. Approximately one third of MDD and BD patients fulfil the criteria for MetS, compared to less than one fifth of the mentally healthy general population, making MetS a common and important additional health risk in AD[10,11,12].

Given the high prevalence of MetS in AD, which is accompanied by a concurrent chronic low-grade inflammatory component[13], the relationship between metabolic dysregulation and inflammatory processes in the context of AD becomes evident. Indeed, de Melo *et al*[14] point to low-grade inflammation as a common denominator and possible explanation for the close relationship between AD and MetS. With regard to inflammation, increased biomarkers of C-reactive protein (CRP) and leukocytes have been detected in patients with AD compared to healthy controls[15-19].

Recent research has shown that there are multiple shared pathways and factors contributing to the bidirectional relationship of AD and MetS, including inflammatory and hormonal pathways as well as lifestyle behaviour[14,20]. Another possible link and mediating factor, between AD, MetS, and inflammation is personality, which stems from the both positive and negative effects that personality traits have on health behaviour[21-23] and health parameters in general[22]. Additionally, there is evidence for personality traits affecting health not only through health behaviour but also *via* biomarkers (*e.g.*, CRP), independently of behaviour[24]. Specifically, some of the "Big Five" personality traits have been linked to AD[25] and AD outcome[26]. Nevertheless, personality traits like the Dark Triad (DT) traits, which are known to have a health deteriorating effect[23] have rarely been investigated in the context of AD, MetS, and inflammation.

The DT are three overlapping but distinct personality traits. They consist of Machiavellianism, characterized by manipulative behaviour, psychopathy, characterized by impulsive and reckless behaviour, and a lack of anxiety and empathy, as well as narcissism, which is characterized by entitlement, grandiosity, and self-deception[27]. The DT have been shown to predict health behaviour and disease in multiple studies[23,28,29] and may thus influence both AD and inflammation. For instance, while psychopathy is negatively associated with health behaviour and positively associated with disease (*e.g.* depression, obesity), results for Machiavellianism are ambiguous, and results for narcissism tend to

show a more positive effect on health[23,28,29], although narcissism seems to be associated with higher leukocyte counts [30].

The abovementioned factors show the complexity of the connection between AD, personality, inflammation, and further diseases such as CMD. Notably, there is evidence on the relationships between AD and inflammation[15,17], AD and MetS[11,12], MetS and inflammation[13], personality and AD[23], personality and criteria of MetS[23], as well as personality and inflammation[24]. Although this network of interactions between diseases, inflammation, health behaviour, and personality traits is known, to our knowledge, no study has yet investigated these factors altogether. Thus, our aim was to set up a model including demographic variables (*e.g.*, age), somatic variables (*e.g.*, MetS, serum TG), psychiatric variables (*e.g.*, number of affective episodes), health behaviour (*e.g.*, smoking), personality (DT), and inflammatory markers (CRP, leukocytes) in individuals with AD. We hypothesized that demographic variables, somatic variables, psychiatric variables, health behaviour, and the DT are unique predictors of CRP and leukocytes as representants of inflammatory markers in the population of psychiatric inpatients with AD.

MATERIALS AND METHODS

Sample

A total of 233 inpatients were recruited between November 2021 and May 2023 at the Clinical Department of Psychiatry and Psychotherapeutic Medicine, Medical University of Graz. Inclusion criteria required participants to be of legal age (18 years) and to have an AD diagnosis according to International Classification of Diseases-10[31], which was confirmed by mental health professionals at our clinic. Exclusion criteria were a known diagnosis of a chronic inflammatory disease or an acute inflammation at the time of routine blood sampling. All participants gave written informed consent before inclusion. Seven patients were excluded because of missing CRP or leucocytes in routine blood work and another 40 because of current or chronic inflammation. Finally, data from 186 individuals [77 (41.4%) males, 106 (57.0%) females, 3 (1.6%) diverse] were included in all analyses. On average, participants had an age of M = 42 years (standard deviation (SD) = 15.47). This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Graz (No. 33-632 ex 20/21).

Materials

This study was part of a large-scale study "health-protective and harmful moderating effects of the DT traits in individuals with affective disorders and mentally healthy individuals" examining DT traits and health behaviour in people with AD and mentally healthy people. Self-report questionnaires were carried out online in German language *via* the online survey tool LimeSurvey (Version 3.40).

Socio-demographic questionnaire: Sociodemographic variables age, sex, and education level, as well as psychiatric and somatic variables (*e.g.*, diagnoses, number of affective episodes, age of diagnosis, medication) were assessed *via* a self-constructed questionnaire.

Anthropometric and somatic markers: Assessment for MetS followed the criteria for MetS as proposed by the international diabetes foundation in 2006[32]. Although there are newer, less stringent, criteria available[33], we felt that in the context of inflammation a stricter approach is prudent. The presence of MetS was presumed if waist circumference was above the cut-off point for europids (≥ 94 cm for males and ≥ 80 cm for females) and at least two additional criteria were fulfilled. Waist circumference was measured between the ribs and hip bones. Blood pressure was measured using a "boso medicus uno" blood pressure monitor. Additionally, height and weight were queried to calculate body mass index (BMI). The required metabolic (TG, HDL-cholesterol and plasma glucose) and inflammatory parameters (CRP and leukocytes) were obtained from routine blood tests. Further, somatic comorbidities (*e.g.* arterial hypertension) and medication were queried. Psychiatric (*e.g.* anti-depressants) and somatic medication (*e.g.* diabetes treatment, proton pump inhibitors) were assessed separately. For somatic medication, it was further differentiated between treatment of hypertension, cholesterol, and TG, as well as anti-inflammatory medication (*e.g.* glucocorticoids).

Patient Health Questionnaire (PHQ-9): To assess the current severity of depression as a psychiatric parameter, the Patient Health Questionnaire (PHQ-9)[34] was used. It consists of nine items rated on a four-point Likert scale, ranging from (0) = "never" to (4) = "nearly every day" (total score range = 0-27; *e.g.*, "Over the past two weeks, how often have you been bothered by feeling tired or having little energy?"). Sufficient internal consistency was given, as proposed by Cronbach's α (α = 0.85).

Mediterranean diet score: To measure the adherence to a Mediterranean diet, which has been previously shown to have health-promoting effects, the Mediterranean diet score[35] was administered. It includes 14 items, with higher scores indicating greater adherence to the Mediterranean diet. Items are presented as questions (*e.g.*, "How many servings of nuts do you consume per week?") and rated on a dichotomous or four-point scale with a maximum of one point per question. Scores were calculated by building the sum of the items (maximum score = 14). Sufficient internal consistency was given, as proposed by Cronbach's α (α = 0.48).

Pittsburgh sleep quality index: To measure sleep quality as a health behaviour, the Pittsburgh sleep quality index[36] was used. It contains 19 items, presented as questions (*e.g.*, "During the past month, how would you rate your sleep quality overall?") and rated on a four-point Likert-scale, yielding seven component scores rated 0-3 (maximum score: 21),

with higher scores indicating worse sleep quality. Sufficient internal consistency was given, as proposed by Cronbach's α (α = 0.73).

Multidimensional Health Behaviour Inventory: To measure the utilization of medical check-ups, physical activity, diet independent of the Mediterranean diet, and smoking, the respective scales of the Multidimensional Health Behaviour Inventory (MHBI)[37] were used. Rated on a five-point Likert-scale ranging from (1) = "never" to (5) = "always", items are presented as questions (*e.g.*, "How often do you exercise vigorously?"). Subscales used were check-up (nine items), diet (13 items), physical activity (four items), and one item of substance use. Sufficient internal consistency was given, as proposed by Cronbach's α (check-up: α = 0.74; diet: α = 0.72; physical activity: α = 0.78; substance: α = 0.72).

Short DT: To examine the DT, the Short DT[38] was administered. This questionnaire contains 27 items on three scales (narcissism, Machiavellianism, and psychopathy) presented as statements (*e.g.*, "Most people can be manipulated"). Each item is graded on a five-point Likert-scale, with final scores for each scale being calculated by averaging the corresponding item scores. Sufficient internal consistency was given, as proposed by Cronbach's α (narcissism: α = 0.61; Machiavellianism: α = 0.74; psychopathy: α = 0.74).

Statistics

All analyses were conducted in IBM SPSS Statistics 29. To determine significant differences and associations between the demographic, somatic, psychiatric, health behaviour, and DT variables regarding CRP and leukocytes, *t*-tests, Spearman correlation analyses, and Pearson correlation analyses were applied. Due to possible type-I errors in response to multiple testing, the Benjamini-Yekutieli false discovery rate was applied to all correlation analyses[39]. Subsequently, two hierarchical regression analyses predicting CRP and leukocytes from demographic, somatic, psychiatric, health behaviour, and DT variables were conducted. To prevent suppression effects, only variables which previously showed significant associations with CRP and/or leukocytes and were not part of a significantly associated syndrome (*e.g.*, waist circumference in MetS) were included. Since the order of entering the variables into the hierarchical regression analyses could not be derived from literature, simple linear regression analyses for each predictor block (*e.g.*, somatic parameters) predicting CRP and leukocytes were conducted prior to the main analysis. Derived from these preliminary simple regressions, predictors were entered stepwise in a descending order according to the highest $R^2_{(adj)}$ in the hierarchical regression. All assumptions for the statistical tests were fulfilled. Hypotheses were tested two-sided at an α-level of 0.05. Data and analysis scripts can be accessed *via* https://doi.org/10.17605/OSF.IO/WGRXD.

RESULTS

Descriptive analyses

Results of the sample-related and psychometric analyses are displayed in Table 1. We excluded 21 more outliers deviating more than three SD in the variables CRP, TG, plasma glucose, and psychopathy (n = 165).

Differences and associations between study variables and primary outcome inflammatory parameters

Participants, who identified themselves as diverse gendered (n = 3) were excluded to administer point-biserial Pearson correlation analyses. For the demographic variables, there was a significant association between CRP, age (r = 0.26, P < 0.001), and education (r = -0.23, P < 0.01), indicating that individuals higher in age and lower education levels demonstrated higher CRP levels. All other associations did not reach statistical significance (P > 0.052).

For somatic parameters, *t*-tests showed a significant difference in CRP between MetS [$M_{(with\ MetS)}$ = 2.47, $SD_{(with\ MetS)}$ = 1.83, $M_{(with\ out\ MetS)}$ = 1.32, $SD_{(with\ out\ MetS)}$ = 1.34; t (73.47) = -3.96, P < 0.001], intake of blood pressure treatment [($M_{(treatment)}$ = 2.37, $SD_{(treatment)}$ = 1.77, $M_{(no\ treatment)}$ = 1.52, $SD_{(no\ treatment)}$ = 1.51; $t_{(160)}$ = -2.72, P <0 .01], and intake of somatic medication [$M_{(treatment)}$ = 2.10, $SD_{(treatment)}$ = 1.79, $M_{(no\ treatment)}$ = 1.42, $SD_{(no\ treatment)}$ = 1.41; t(104.12) = -2.54, P < 0.05]. Moreover, Pearson correlation analyses indicated that CRP was significantly positively associated with waist circumference (r = 0.39, P < 0.002), TG (r = 0.31, P < 0.001), systolic blood pressure (r = 0.25, P < 0.001), diastolic blood pressure (r = 0.26, P < 0.001), fasting plasma glucose (r = 0.29, P < 0.001), and BMI (r = 0.41, P < 0.001), as well as significantly negatively associated with HDL cholesterol (r = -0.28, P < 0.001). This indicates that individuals with MetS, blood pressure treatment, other somatic medication, higher waist circumference, TG, blood pressure, plasma glucose and/or lower HDL cholesterol exhibit greater CRP levels. Regarding leukocytes, there was a significant difference between the presence of MetS [$M_{(without\ MetS)}$ = 7.26, $SD_{(without\ MetS)}$ = 1.50, $M_{(without\ MetS)}$ = 6.33, $SD_{(without\ MetS)}$ = 1.68; t (160) = -2.95, P < 0.01], intake of cholesterol treatment [$M_{(treatment)}$ = 7.59, $SD_{(treatment)}$ = 1.79, $M_{(no\ treatment)}$ = 6.59, $SD_{(no\ treatment)}$ = 1.63; t(160) = -2.29, P < 0.05], intake of blood pressure treatment [$M_{(treatment)}$ = 7.43, $SD_{(treatment)}$ = 1.94, $M_{(no\ treatment)}$ = 6.52, $SD_{(no\ treatment)}$ = 1.55; t(160) = -2.74, P < 0.01], and intake of anti-inflammatory medication [$M_{(treatment)}$ = 8.03, $SD_{(treatment)}$ = 1.40, $M_{(no\ treatment)}$ = 6.61, $SD_{(no\ treatment)}$ = 1.65; t(160) = -2.52, P < 0.01] in leukocytes, respectively. Finally, correlation analyses showed that leukocytes are positively associated with TG (r = 0.21, P < 0.01), and negatively associated with HDL cholesterol (r = -0.25, P < 0.01). This indicates that individuals with MetS, cholesterol treatment, blood pressure treatment, anti-inflammatory medication, elevated TG, and/or decreased HDL cholesterol exhibit greater leukocyte levels.

Regarding psychiatric variables, a significant positive association between the age of diagnosis and CRP was observed (r = 0.23, P < .01), indicating that a higher age at AD diagnosis is related to higher CRP levels. All other associations remained non-significant (P > 0.190).

Table 1 Descriptive and psychometric characteristics of the study population, *n* (%)

Variable	
Demographic variables	
Age (years), mean ± SD	41.82 ± 15.82
Sex	
Female	98 (59.4)
Male	64 (38.8)
Diverse	3 (1.8)
Education	
No formal education	1 (0.6)
Compulsory schooling	19 (11.5)
Apprenticeship	63 (38.2)
High school diploma	52 (31.5)
University diploma	30 (18.2)
Other school diploma	0 (0)
Somatic variables	
Somatic comorbidities (yes)	48 (29.1)
Metabolic syndrome (yes)	51 (30.9)
Somatic medication (yes)	61 (37.0)
TG treatment (yes)	15 (9.1)
Cholesterol treatment (yes)	16 (9.7)
Antihypertensive treatment (yes)	30 (18.2)
Anti-Inflammatory treatment (yes)	9 (5.5)
C-reactive protein (mg/L), mean ± SD	1.67 ± 1.58
Leukocytes (10^9/L), mean ± SD	6.70 ± 1.66
TG (mg/dL), mean ± SD	127.52 ± 68.69
HDL cholesterol (mg/dL), mean ± SD	58.56 ± 18.61
Plasma glucose (mg/dL), mean ± SD	88.93 ± 12.71
Systolic blood pressure (mmHg), mean ± SD	124.11 ± 13.69
Diastolic blood pressure (mmHg), mean ± SD	80.41 ± 9.96
Waist circumference (cm), mean ± SD	87.75 ± 14.95
BMI (kg/m^2), mean ± SD	25.57 ± 5.23
Psychiatric variables	
Type of AD	
Single-episode unipolar depression	27 (16.4)
Recurrent unipolar depression	109 (66.1)
Bipolar disorder	22 (13.3)
Cyclothymia/dysthymia	2 (1.2)
Other	5 (3.0)
Psychiatric comorbidities (yes)	83 (50.3)
Psychiatric medication (yes)	165 (100)
Antidepressants (yes)	150 (90.9)
FDR (yes)	70 (42.4)

Age of first affective symptoms, mean ± SD	26.87 ± 15.93
Age of AD diagnosis, mean ± SD	32.66 ± 14.08
Number of affective episodes, mean ± SD	10.90 ± 16.49
Depression severity (PHQ-9 score), mean ± SD	16.19 ± 6.52
Health behaviour variables, mean ± SD	
Dietary behaviour, mean ± SD	38.73 ± 7.96
Mediterranean diet, mean ± SD	6.61 ± 2.05
Smoking, mean ± SD	2.88 ± 1.88
Participation in medical check-ups, mean ± SD	25.12 ± 6.60
Physical activity, mean ± SD	10.45 ± 4.05
Sleep quality, mean ± SD	10.92 ± 4.72
Personality variables	
Narcissism, mean ± SD	2.09 ± 0.62
Machiavellianism, mean ± SD	2.39 ± 0.72
Psychopathy, mean ± SD	1.67 ± 0.61

Smoking: Item from the Multidimensional Health Behaviour questionnaire ("How often do you smoke?"; Range 1-5, higher values indicate higher smoking frequency). FDR: First-degree relatives with severe psychiatric disorders (*e.g.*, schizophrenia); AD: Affective disorder; TG: Triglycerides; PHQ-9: Patient Health Questionnaire-9; HDL: High-density lipoprotein; BMI: Body mass index.

With regards to health behaviours, only dietary behaviour (r = -0.27, P < 0.001) and smoking (r = 0.27, P < 0.001) were significantly related to leukocytes, indicating that a healthier diet and more smoking is associated with decreased leukocyte levels. All other associations between health behaviours, CRP, and leukocytes did not reach statistical significance (P > 0.05). Similarly, none of the DT showed a significant relationship with CRP or leukocytes (P > 0.367).

Prediction of inflammatory parameters by study variables

For the stepwise hierarchical prediction of CRP, three preliminary simple linear regressions (block 1: Demographic variables, block 2: Psychiatric variables, block 3: Somatic variables) were performed to determine the order of entering the predictor blocks. These linear regression analyses indicated that somatic variables explain most variance in CRP ($R^2_{(adj)}$ = 0.18), followed by demographic variables ($R^2_{(adj)}$ = 0.11), and psychiatric variables ($R^2_{(adj)}$ = 0.05), which were thus entered into the hierarchical regression analysis in the according order. Within the hierarchical regression analysis, six more outliers deviating more than three SD were found in CRP and thus excluded (n = 155). In total, all predictors were able to explain 33.8% of the variance in CRP. The somatic parameters entered in a first step accounted for 25.2% of the variance, with other somatic medication and BMI contributing significant unique variance to the prediction of CRP. The inclusion of demographic variables explained another 4.1% of the variance, with age and education providing a significant, unique contribution to the prediction of CRP. Finally, the inclusion of psychiatric variables represented by the age of diagnosis accounted for 4.5% of incremental variance in CRP. The regression statistics including unstandardized and standardized β-weights, standard errors, 95% confidence intervals and R^2-changes can be found in Table 2.

For the stepwise hierarchical prediction of leukocytes, two preliminary simple linear regressions (block 1: Somatic variables, block 2: Health behaviours) were performed to determine the order of entering the predictor blocks. Similar to the prior analysis, only variables, which were previously shown to be significantly associated with leukocytes were examined. These linear regression analyses indicated that health behaviour variables explain most variance in leukocytes ($R^2_{(adj)}$ = 0.10), followed by somatic variables ($R^2_{(adj)}$ = 0.07), which were thus entered into the hierarchical regression analysis in the according order. Within the hierarchical regression analysis, one more outlier deviating more than three SD was found in the leukocytes and thus excluded (n = 154). In total, all predictors were able to explain 20.1% of the variance in leukocytes. The health behaviour parameters entered in a first step accounted for 11.5% and the inclusion of somatic variables explained another 8.6% of the variance, with all variables explaining significant unique variance in leukocytes. The regression statistics including unstandardized and standardized β-weights, standard errors, 95% confidence intervals and R^2-changes can be found in Table 3.

DISCUSSION

The current study examined the role of CRP and leukocytes as indicators of inflammation in AD. Although the significance of inflammation and inflammatory markers for AD is still not clear, there is evidence for a positive association between CRP and affective symptoms[40], as well as treatment resistance[40,41]. In line with these findings, a potential

Table 2 Somatic, demographic, and psychiatric variables predicting C-reactive protein levels in individuals with affective disorders within hierarchical regression analysis

Variable	B	95% $CI_{(B)}$		SE_B	β	R^2	ΔR^2
		LL	UL				
Step 1						0.25	0.25[c]
Constant	-1.90[c]	-0.89	-0.9	0.5	0.08		
Metabolic syndrome	0.23	-0.31	0.76	0.27	0.08		
Somatic medication	0.45[a]	0.06	0.84	0.2	0.17		
BMI	0.10[c]	0.05	0.14	0.02	0.3		
Step 2						0.29	0.04[a]
Constant	-1.1	-2.32	0.13	0.62			
Metabolic syndrome	0.16	-0.38	0.69	0.27	0.06		
Somatic medication	0.26	-0.16	0.69	0.21	0.1		
BMI	0.08[c]	0.04	0.13	0.02	0.33		
Age	0.02[a]	0	0.03	0.01	0.18		
Education	-0.19[a]	-0.35	-0.04	0.08	-0.18		
Step 3						0.34	0.05[b]
Constant	-1.42[a]	-2.63	-0.21	0.61			
Metabolic syndrome	0.14	-0.37	0.66	0.26	0.05		
Somatic medication	0.33	-0.08	0.74	0.21	0.12		
BMI	0.09[c]	0.04	0.14	0.02	0.37		
Age	-0.01	-0.03	0.01	0.01	-0.09		
Education	-0.22[c]	-0.37	-0.07	0.08	-0.21		
Age of diagnosis	0.03[c]	0.01	0.05	0.01	0.34		

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
BMI: Body mass index; CI: Confidence interval; LL: Lower limit; UL: Upper limit; SE: Standard error.

subtype of MDD with a distinct inflammatory component has been identified[40]. Leukocytes are also associated with symptom severity in MDD[42], while for BD, a deviation from mean leukocyte counts correlates with specific symptoms and their severity, differing by gender[43,44].

In this study, we were particularly interested in relevant variables that could predict the levels of CRP and leukocytes. Our hypotheses stated that demographic variables, somatic variables, psychiatric variables, health behaviour, and the DT are able to predict CRP and leukocytes in a well-diagnosed sample of patients with AD. The results of the regression models showed that age, use of somatic medication, higher BMI, and age of diagnosis positively predicted CRP, while higher educational attainments negatively predicted CRP. In total, these variables explained a third of the observed variance. Use of anti-inflammatory medication, MetS, and smoking positively predicted leukocytes, whereas better diet was a negative predictor. These variables explained a fifth of the variance in leukocytes. No other psychiatric, behavioural, or personality variables had any significant influence on CRP or leukocytes. These findings are discussed below.

Demographic variables

The demographic variables sex, age, and education are controlled for in most studies examining inflammation because of their well-known effect on inflammatory markers[45,46], which was confirmed in this investigation for age and education. Education has a significant effect on CRP, which has been demonstrated to mainly stem from worse health behaviours like bad diet, smoking, and less exercise in people with low educational attainment[47]. These behaviours predispose for CVD and further MetS, which is linked to AD through various pathways[14] and might be an etiological factor, as proposed by the metabolic genesis hypothesis of AD[48,49]. We found no significant association between sex, CRP, and leukocytes. This might be due to a higher baseline of inflammation compared to general population that is shared by the sexes in inpatients with AD.

Table 3 Health behaviour and somatic variables predicting leukocyte levels in individuals with affective disorders within hierarchical regression analysis

Variable	B	95% $CI_{(B)}$		SE_B	β	R^2	ΔR^2
		LL	UL				
Step 1						0.1	0.12[c]
Constant	7.93[c]	6.67	9.2	0.64			
Dietary behaviour	-0.05[b]	-0.08	-0.02	0.02	-0.24		
Smoking	0.18[b]	0.05	0.3	0.06	0.21		
Step 2						0.18	0.09[c]
Constant	5.72[c]	4.04	7.39	0.85			
Dietary behaviour	-0.04[b]	-0.07	-0.02	0.01	-0.22		
Smoking	0.16[a]	0.04	0.28	0.06	0.19		
Metabolic syndrome	0.76[b]	0.27	1.25	0.25	0.23		
Anti-inflammatory medication	1.09[a]	0.11	2.07	0.5	0.16		

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
CI: Confidence interval; LL: Lower limit; UL: Upper limit.

Somatic medication

The prediction of CRP by intake of somatic medication is expected when considering that all medication has an indication (a corresponding illness) it is prescribed to treat. Somatic medication, in this case, might thus be seen as a stand in for illnesses, not directly classified as inflammatory, and thus not excluded prior to calculations done in this study. Anexample for this is arterial hypertension, which has been shown to be positively associated with CRP levels in previous research[50,51]. Antihypertensive medication, which was also positively associated with CRP in our study, seems to lower CRP levels[52], though the magnitude of this effect seems to differ by class[53], and might not always restore CRP levels to baseline[54].

BMI, MetS, and anti-inflammatory medication

Together with somatic medication, BMI explained a fourth of the variance in CRP. Previous research has shown that higher BMI is a significant predictor of CRP in patients with MDD[55], as well as inflammatory cytokines in BD[56], suggesting that a higher BMI contributes to inflammation in AD. Regarding MetS, our results are partly in line with previous research[57,58]. We found a significant association between MetS and CRP in patients with AD, which is contrary to previous research. However, MetS was not a significant predictor of CRP in patients with AD in our model, which is in line with previous research. This might be due to the MetS criteria used in this study[32], which include central obesity. Central obesity is linked to higher BMI, thus creating an overlap between MetS and BMI. With multiple shared inflammatory pathways, one of which is adipose tissue[14], the relationship between AD and MetS is so close, a recent review has even proposed that MetS might be considered a part of a depressive syndrome[59]. MetS has also been shown to lead to longer disease duration in late-onset MDD, with abdominal obesity and lipid dysregulation as important factors[60]. This might indicate that adipose tissue contributes above other MetS factors to the inflammatory state implicated in both pathophysiology and progression of both AD and MetS. Moreover, MetS and anti-inflammatory medication served as predictors for the individual leukocyte level. The relationship between MetS and leukocyte count has long been known. Previous research has also shown that for leukocytes, contrary to CRP, MetS itself is the decisive factor, with the effect of obesity being dependent on the presence of MetS[61]. Our results support this theory regarding inpatients with AD. A different study found that leukocyte count correlates with BMI only in obese and insulin resistant individuals, in the absence of other MetS components[62]. This points to insulin resistance as a possible mediating factor. One might expect anti-inflammatory drugs to relate to lower leukocyte counts and while some do, others like aspirin, as shown in animal models, might increase them[63], and in the case of glucocorticoids even lead to leucocytosis[64]. Considering this, grouping all anti-inflammatory medication into one variable might have led to predicting higher leukocyte counts in our model.

Psychiatric variables

Age of diagnosis was the only psychiatric variable to show significant association with CRP and explained 4.5% in the variance. This might indicate that in later AD diagnoses, the role of inflammation is more prominent, possibly by way of MetS, the prevalence of which increases with age[65]. This explanation is supported by a study that found an association

between age of onset and CRP for men with MDD, postulating either a vascular or metabolic etiology for late onset MDD [66]. In our sample, other psychiatric variables showed no association with CRP and none with leukocytes. Most other studies investigating disease severity and CRP in MDD found an association between these variables[40], whereas it has previously also been shown, that BMI, but not mood episodes predict CRP in BD[56]. The association between disease severity and CRP found by other studies may possibly be mediated by metabolic factors, which are in turn affected by behavioral changes during severe mood episodes. Further, a recent study has shown that the association between CRP and depression severity does not persist when controlling for confounding variables like BMI and waist circumference [67].

Diet and smoking

We found that diet and smoking served as predictors of leukocytes. This relationship is well known for smoking and may be explained through an inflammatory response in reaction to radicals in cigarette smoke[68,69]. Previous studies have shown that diet, especially the Mediterranean diet, influences leukocytes. Specifically, dietary fibre and antioxidant content may be the principal moderators of the inverse relationship between Mediterranean diet and leukocytes[70]. In our study, it wasn't adherence to the Mediterranean diet that predicted leukocytes, but broader aspects of good dietary behaviour, as queried by the dietary behaviour subscale of the MHBI.

Personality variables

Contrary to our assumptions and previous research[23], the DT did not affect any inflammatory markers examined in this study. A possible explanation for DT not influencing inflammation in our sample is a difference in distribution of DT components compared to the general population. Means for all three subscales were lower by about 0.5 points compared to the validation samples[38].

Limitations

Results of this study are limited to individuals with AD. Moreover, due to the cross-sectional nature of the study, causality of the results cannot be determined. Although all patients were treated at the Clinical Department of Psychiatry and Psychotherapeutic Medicine, no external ratings were obtained, limiting the evaluation of depression severity to self-assessments. However, results derived from questionnaire data in this study may also be susceptible to self-report bias. Thus, future studies should employ additional external ratings (*e.g.*, the Hamilton Depression Scale[71] or the Montgomery Åsberg Depression Rating Scale[72] to measure depression severity). Moreover, generalizability of the results is limited to individuals with AD and mentally healthy individuals. Finally, we only used CRP and leukocyte levels as indicators of inflammation. However, there might be other important inflammatory markers, which should be investigated in future studies (*e.g.*, cytokines, serum amyloid A).

CONCLUSION

We examined the relationship between multiple influences on inflammation (CRP/leukocytes) in the context of AD. It could be shown that age, education, BMI, medication for somatic diseases, and age of diagnosis predicted CRP levels, and that MetS, anti-inflammatory medication, diet, and smoking predicted leucocyte levels. Understanding the connections between CRP/leukocytes and AD becomes especially important when considering their links to metabolic dysregulation, particularly in the form of MetS. This comorbidity is both common and perilous in AD. Our results further underline this relationship, as the only significant psychiatric variable age of AD diagnosis itself seems to be linked to a vascular or metabolic subtype of MDD. This emphasizes the importance of somatic variables in the chronic low-grade inflammation present in AD. We suggest that MetS parameters should always be considered when planning treatment of patients with AD. Metabolic lifestyle modification (diet, exercise) should be applied wherever possible, in combination with medication for MetS components where needed, to reduce inflammatory burden on the body and prevent or treat MetS, which vastly limits potential healthy years, while also possibly lengthening AD duration. Therapeutical interventions in AD should incorporate learning about a healthy lifestyle and motivating for lifestyle modifications.

ACKNOWLEDGEMENTS

We kindly thank the participants of this study.

FOOTNOTES

Author contributions: Kölblinger F was responsible for conceptualization, formal analysis, investigation, data curation, writing-original draft, writing-review and editing; Schönthaler E was responsible for conceptualization, methodology, software, validation, formal analysis, investigation, data curation, writing-original draft, writing-review, editing, visualization, supervision and project administration; Baranyi A was responsible for conceptualization, methodology, writing-review and editing; Stross T was responsible for software, formal analysis, data curation, writing-review and editing; Fellendorf F was responsible for writing-review and editing; von Lewinski D was responsible for conceptualization, methodology, writing-review and editing; Queissner R was responsible for

methodology, writing-review and editing; Reininghaus E was responsible for resources, writing-review and editing; Dalkner N was responsible for conceptualization, methodology, validation, investigation, resources, writing-original draft, writing-review, editing, supervision, and project administration.

Institutional review board statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Graz (EK-number: 33-632 ex 20/21).

Informed consent statement: Informed consent was obtained from all participants prior to study inclusion.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: Data and analysis scripts can be accessed *via* https://doi.org/10.17605/OSF.IO/WGRXD.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country of origin: Austria

ORCID number: Elena MD Schönthaler 0000-0002-9645-4503; Frederike T Fellendorf 0000-0001-7215-3848; Eva Z Reininghaus 0000-0001-5964-4087; Nina Dalkner 0000-0001-7716-3674.

S-Editor: Luo ML
L-Editor: A
P-Editor: Zhao YQ

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Personal Contribution

This diploma thesis project was integrated in a bigger project titled *The Moderating Effect of the Dark Triad Traits in the Relationship Between Affective Disorders and Health Behaviours* at the Medical University of Graz, Division of Psychiatry and Psychotherapeutic Medicine.

In the process of this thesis, I recruited psychiatric inpatients treated at the Division of Psychiatry and Psychotherapeutic Medicine, obtaining written informed consent prior to inclusion.

Additionally to the original study protocol, I measured the hip-circumference of participants, obtained the health parameters necessary solely for this study (e.g., C-reactive protein, Leukocytes) and did data curation on my own. I further did data entry for the data of participants of the whole project and obtained missing parameters from medical records.

I did data analysis with SPSS under supervision and wrote the first draft of the paper independently. In addition, I was responsible for incorporating the coauthors comments during the review process.

The article was finally published on July 6th, 2024.

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