Inflamed Depression: The link between Depression and Inflammation expressed by CRP and IL-6 markers in the elderly population

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Summary

Even though various interventions for the treatment of depression have been developed, around 30% of depressed individuals do not respond to the treatment which indicates that there is a gap in understanding the underlying mechanisms of this disorder (Leighton et al., 2018).

One potential biological mechanism may be inflammation, as depressed individuals often have heightened inflammatory responses such as heightened levels of Interleukin-6 (IL-6) and C-reactive protein (CRP). The current paper, therefore, aims at investigating to what extent heightened inflammatory responses can be explained by depression. The hypotheses that depression will be associated with higher levels of CRP, as well as higher levels of IL-6, were determined through the review of existing literature.

Two longitudinal data sets from The Swedish Adoption/Twin Study of Aging and OCTO-Twin study were used (N=474, M_{age}=79, 63% female). Two sets of linear regression models were run for each inflammatory marker: CRP and IL-6. The analyses yielded no significant results regarding the prediction of CRP and IL-6 from depression. However, the exploratory analyses revealed significant effects of age, smoking, and BMI on the inflammatory markers, suggesting that inflammation can be better explained by these factors than depressive symptoms as observed in the elderly population.

Causal conclusions are extremely challenging to draw due to unknown confounding variables as well as the possibility of reversed directionality with inflammation posing greater risks for the development of depression rather than the other way around. Keeping in mind the rise of disabilities following depression, as well as the crisis of Sars-CoV-2 which imposes great risks for the older population as well as potential risks for depressed individuals, future research should continue exploring the topic of the bi-directional link of depression and inflammation in order to develop novel approaches for the prevention, diagnosis, and treatment of the issues.

Introduction

Depression is the second leading cause of disability, with an estimation of 8-12% prevalence in the population (World Health Organization, 2017). It is associated with an increased risk of mortality by 50% due to deaths by suicide, unintentional injuries, and subsequent health conditions (Gilman et al., 2017). Even though pharmacological and psychological interventions have been developed, around 30% of depressed individuals do not respond to the treatment which indicates that there is a gap in understanding the pathogenesis of this disorder (Leighton et al., 2018). This illustrates the need to expand the knowledge which could be implemented in novel therapeutic approaches.

Over the last few decades, there has been a growing amount of literature proposing that depression is linked to physical health. It has been argued that depression is associated with a higher incidence of various chronic diseases such as dementia, Type II diabetes, autoimmune and cardiovascular diseases, metabolic syndrome, and is linked to worse predicted outcomes (McIntyre et al., 2007; Wolkowitz et al., 2010). The "inflammatory hypothesis" has been proposed as a possible underlying mechanism, relating depression to physical health and the immune system in particular (Penninx et al., 2013). Depressed individuals often have heightened inflammatory responses such as heightened levels of Interleukin-6 (IL-6) and C-reactive protein (CRP) that are theorised to be due to the dysregulation of the immune system (Beurel et al., 2020). Indeed, Matthews and his colleagues (2010) concluded that higher depression scores were associated with higher levels of pro-inflammatory markers and vice versa. However, this was done in a not representative sample, and in order to draw the conclusions regarding causality, more research is required.

If depression could potentially be a predisposing factor for inflammation, the current health crisis of Sars-CoV-2 and the vulnerability of depressed individuals highlights the urgent need of exploring this topic (World Health Organization, 2020; Lamontagne et al., 2020). Studies regarding the immune system responses in COVID-19 and possible links to depression are emerging: contrasting effects of elevation or suppression of immunity are similar to processes seen in depression (Lamontagne et al., 2020); increased levels of IL-6 that are associated with chronic stress are also linked to the poorer outcomes of COVID-19 patients (Wu et al., 2020); high depression rates in Sars -CoV-2 patients are reported not only during the treatment process but also after being the discharge from the hospital, adding to a possible bi-directional association of depression and immune system, as well as health in general (Yuan et al., 2020).

Taking into account the burden posed by depression and possible vulnerabilities associated with it, this paper will aim to investigate the research question: to what extent heightened inflammatory responses can be explained by depression.

To investigate the aforementioned research question the following section will explore the existing literature on 1) depression and immune system, 2) biochemical abnormalities in depression associated with inflammation, and 3) psychosocial and lifestyle factors contributing to inflammation in depression. Following the literature review, hypotheses will be explored and analyses investigating the longitudinal data will be presented.

Literature review

Depression and Immune system

The immune system serves as a basis of protection from various infections or injuries which result in the inflammatory response. Two distinct types of the immune system exist: the innate immune system and adaptive immune system (Beurel et al., 2020). The innate adaptive system provides rapid, first-line responses with the use of myeloid and lymphoid cells, which are also defined as white blood cells (Turvey & Broide, 2010). These white blood cells, in turn, activate cytokines (interleukins or/and chemokines) and initiate the adaptive immune response. The adaptive immune system is composed of T and B lymphocytes that interact with specific antigens and can provide an immunological memory which if the same antigen is found again, would result in a rapid immune response (Murphy et al., 2012; Troubat et al., 2021). Both of these systems work together to ensure that homeostasis is maintained, however, overactivation or suppressed activation of these systems might lead to various diseases (Beurel et al., 2020).

The dysregulation of the central immune system in depression refers to neuroinflammation which is analyzed using cytokines and other immune responsive cells such as microglia and astrocytes as markers. A significant amount of evidence in several meta-analyses indicates that in depressed individuals, levels of proinflammatory cytokines and acute-phase proteins are increased which supports the dysregulation of immune response in depression (Dowlati et al., 2010; Howren et al., 2009; Köhler et al., 2017; Beurel et al., 2020). The chronically activated proinflammatory concentrations of CRP, IL-6, and tumor necrosis factor (TNF) in blood and CSF have an effect on CNS which can, in turn, result in dysregulation of the activity of neurotransmitters and neurodevelopmental systems, and lead to pathological effects in various organ systems (Nemeroff, 2020; Halaris, 2019). Moreover, important to

mention is that the relationship between inflammation and depression is bi-directional (Euesden et al., 2017). An aforementioned longitudinal study over the seven years explored the link between depressive symptoms and CRP in women. It was concluded that more severe depressive symptoms led to higher levels of CRP, and at the same time, higher CRP levels led to more depressive symptoms in women even when adjusting for body mass index, medications, and health covariates (Matthews et al., 2010). This finding informs the hypothesis for the current study that higher depression scores will predict inflammatory levels of CRP measured in the Swedish Twin Register studies. By investigating this hypothesis, the question of whether the findings by Matthews and his colleagues (2010) can be replicated in a different sample will be examined.

In addition to the increased pro-inflammatory markers found in depression, a finding of decreased anti-inflammatory cells is also evident (Syed et al., 2018). This suggests that depressed individuals are immunocompromised because the levels of natural killer cells, T helper cells, and lymphoproliferative cells are significantly lower compared to healthy individuals (Reiche et al., 2005; Nemeroff, 2020). In a recent study, the possible immunosuppression following depression was researched by exposing the plasma of depressed individuals to peripheral blood mononuclear cells from not depressed individuals which, as predicted, led to the immunosuppression (Syed et al., 2018).

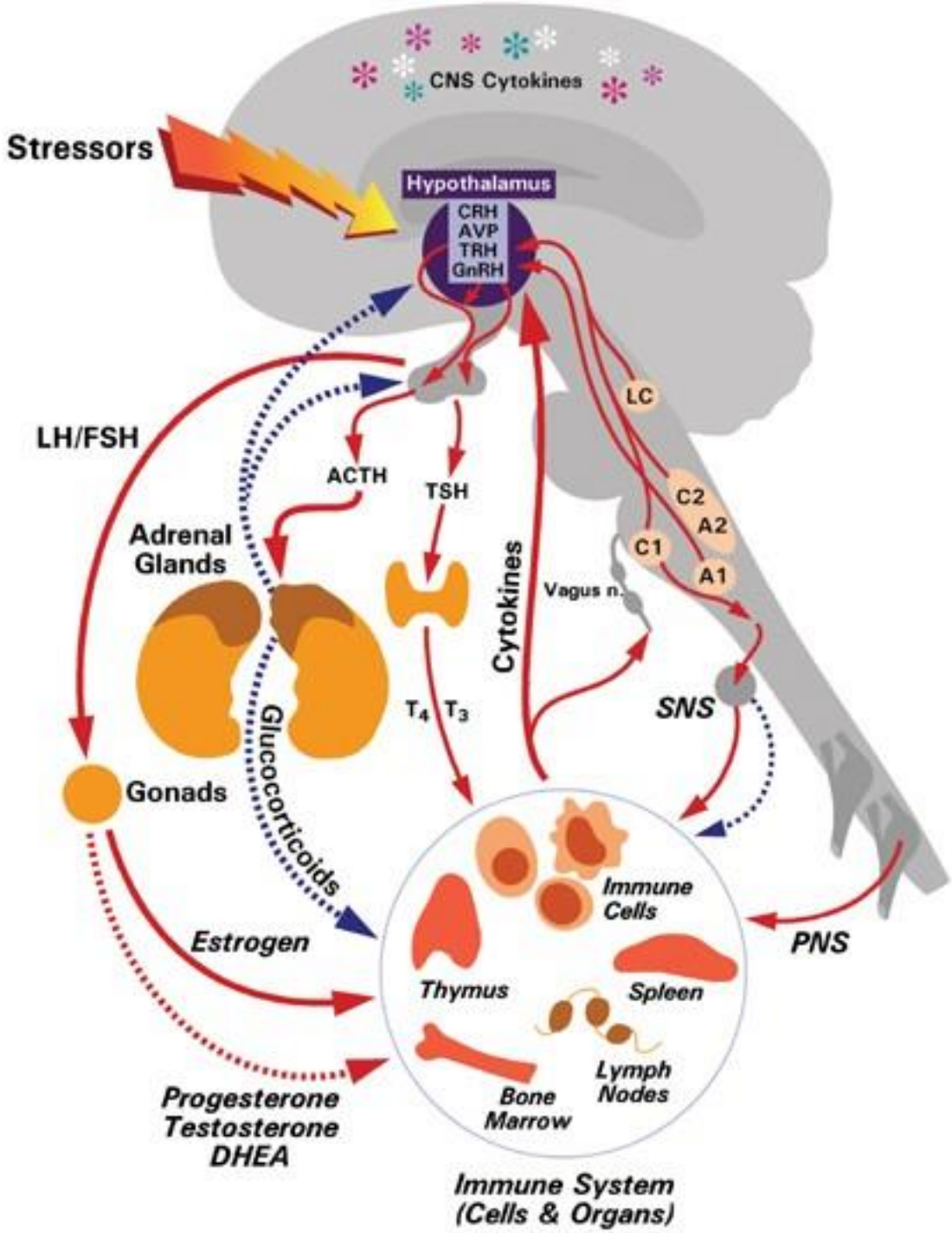
Together these findings indicate the vulnerability and susceptibility of the immune system in depressed individuals which might have an effect on various diseases and have to be taken into account throughout the prevention, diagnosis, and treatment processes.

Inflammation and biochemical abnormalities in depression

A vast amount of evidence is emerging that suggests biochemical abnormalities in depression such as dysregulated inflammasome pathway (Fleshner et al., 2017); induced kynurenine pathway which catabolizes tryptophan and results in depleted serotonin production; amplified permeability of blood-and-brain barrier (Beurel et al., 2020), and changes in the microbiome (Rogers et al., 2016) that are linked to inflammation. However, due to the limited scope of this paper, only the mechanism of the hypothalamic-pituitary-adrenal (HPA) axis in depression will be briefly discussed.

Figure 1

Schematic figure depicting immune-nervous system connections



It has been proposed that the underlying mechanism of inflammation associated with depression is the dysregulation of the HPA axis and the function of glucocorticoids (Blume et al., 2011). HPA axis controls the responses to various types of stressors by regulating the production of adrenocorticotropin which releases cortisol. Normally, elevated levels of cortisol would reduce the activity of the HPA axis through negative feedback. However, the sensitivity to glucocorticoids in depression is thought to be reduced, therefore, cortisol no

longer reduces the HPA activity effectively, leading to the overactivation of the HPA axis (Beurel et al., 2020).

The ‘wear and tear’ and the continued activation of the HPA axis are closely related to the allostatic load (AL) which is associated with the prolonged exposure to various stressors and inability to maintain the stability of the homeostasis (McEwen & Stellar, 1993). It has been suggested that the AL reaches the final stage when dysregulation of various physiological responses (e.g., immune, cardiovascular, or metabolic) results in tertiary (disordered, ill, or morbid) outcomes (Juster et al., 2013). Various behaviors such as alcohol and substance use, unhealthy diet, and sleep disturbance have been described as increasing risks for AL. However, the cumulative factors involved in AL and following illnesses interact in a non-linear way, therefore it is difficult to determine how and when the tertiary outcomes will develop (Suvarna et al., 2020).

While there is still no clear consensus in the literature regarding the inflammatory response and comorbidities found in depression, since glucocorticoid-resistance and HPA axis dysregulation has been found in many depressed individuals, it has been hypothesized to be one of the core mechanisms, associated with hyperactive stimulation of pro-inflammatory cytokines such as IL-6 in depressed individuals (Perrin et al., 2019; Maes et al., 2011).

Psychosocial and lifestyle factors associated with inflammation in depression

Stress

As mentioned earlier, various environmental stressors and factors affect neuroimmune circuits, resulting in an increased risk for depression and inflammation (Berk et al., 2013). For instance, one of the most prominent factors is childhood trauma associated with physical, emotional, or sexual abuse, separation, and neglect (Baumeister et al., 2016). A recent meta-analysis investigated the effects of trauma and concluded the association between traumatic events and pro-inflammatory state and dysregulated immune system in later years, which could be a mediating factor projecting the vulnerability to allostatic load, resulting in various psychiatric and physical disorders (Baumeister et al., 2016, Nikkheslat et al., 2020; Suvarna et al., 2020).

Cardiovascular risk factors

Diet and obesity are also regarded as influential factors regarding depression and inflammation (Gregor & Hotamisligil, 2011; Schachter et al., 2018). Depressed individuals have a tendency for health comprising behaviors such as “emotional eating” which is

associated with poorer, usually high-fat food choices and weight gain (Konttinen, 2020). This translates in the studies indicating a positive association between cytokines and gain of fat mass (Ouchi et al., 2011) as well as higher body mass index in the depressed population (Leas & McCabe, 2007). This could also be related to the dysregulation of the HPA axis and a possible AL in depression (Suvarna et al., 2020). In addition, obesity is also a risk factor for developing various illnesses including diabetes and hypertension, as well as depression, which suggests a complex link between depression, diet, and inflammatory responses (Graham et al., 2021).

Age

Age is also associated with susceptibility to inflammation. It is linked to an increased state of inflammation, referring to the notion of "inflammaging" (Michaud et al., 2013) and related to age-linked diseases such as cancer, neurodegenerative disorders, insulin resistance, and cardiovascular diseases (Singh & Newman, 2011). Literature suggests that aging leads to prolonged immune responses, impaired peripheral-CNS communication, resulting in possible changes in the neural systems (Alexopoulos & Morimoto, 2011). Consequently, this increases frequent comorbidity and poses a greater risk and poor outcomes of various illnesses such as a prior mentioned case of Sars-CoV-2 (Grolli et al., 2021). Around 192 million older adults are affected by either mental or neurological disorders, with depression and anxiety being the most prevalent ones which potentially adds to the risk of dysregulation of the immune system and inflammatory responses (Grolli et al., 2021). Therefore, taking into account the vicious cycle of inflammation and depression, depressed older individuals should be regarded as a vulnerable group for greater impact of inflammation, however, there is still a lack of literature regarding the topic. Consequently, the current study will focus on this particular age group of individuals older than 70 years due to the importance of adding to the literature. Moreover, in order to expand the knowledge, in reference to the aforementioned literature and meta-analysis suggesting elevated levels of interleukin-6 found in depressed older individuals (Ng et al., 2018) additional hypothesis that higher depression scores will result in increased levels of IL-6 will be explored.

Psychosocial factors such as exercising, smoking, cardiovascular factors, and alcohol use have thus also been found to play a role in depression and were associated with possible links to inflammation (Nahon et al., 2012; Berk et al., 2013). Following the literature, additional factors of body mass index, smoking status, use of alcohol, and use of cardiovascular

medication will be corrected for in understanding any observed relationships between depression and inflammation.

Methods

Participants

The Swedish Adoption/Twin Study of Aging (Finkel & Pedersen, 2004) is a longitudinal study which was developed to explore the health both physical and psychological in the gerontological sample of middle- and late-aged twin adults that were reared apart or reared together (*N* =3838) (Pedersen et al., 1991). The SATSA study began in 1984, spanned over the period of 30 years, and consisted of nine questionnaire-based waves that were sent almost every three years (Pedersen et al., 1991). In addition, in-person-testing which included health examination and structured interviews was administered and included 861 individuals. Due to data availability, the current study utilized information from the second waves of both mail-out questionnaires and in-person testing (Q2; 1987-1989, *n*= 1637). Participants included in the present study had available data on the depression symptoms measured prior to the inflammation, CRP and IL-6 levels, age, sex, body mass index, smoking status, alcohol use, and cardiovascular medication use, (*n*= 179).

The recruitment of the OCTO-Twin study, as well as SATSA, was done through the Swedish Twin registry. The longitudinal OCTO-Twin study focused on the late-aged adults (80 years and older) and even though the assessment procedures were almost identical as in SATSA, the data in the OCTO-Twin study was collected through home visits only and consisted of 5 waves (McClearn et al, 1997). In total, there were more than 600 participants, however, due to the inclusion criteria mentioned earlier, complete data for the current study was available for 295 individuals.

Taking into account the recruitment and assessment similarities of both SATSA and OCTO-Twin studies, the current research combined the datasets into a single sample which yielded 474 participants. The descriptive statistics are presented in Table 1.

Table 1

Descriptive statistics

	%	N	Mean	SD
Age at the time of inflammation measurement		474	79.69	7.54
Sex				

Female	63.3%	300		
Male	36.7%	174		
BMI		474	24.82	3.88
Smoking status				
Non smoker	66.7%	316		
Ex-smoker	23.0%	109		
Current smoker	10.3%	49		
Alcohol use				
No	29.1%	138		
Yes	70.9%	336		
Use of CVD medication				
No	76.6%	363		
Yes	23.4%	111		
Status of depression				
Not depressed	84%	398		
Depressed	16%	76		
C-reactive protein		474	3.88	7.01
Interleukin-6		474	3.10	2.62

CVD cardiovascular, *BMI* body mass index

Measures

Depressive symptoms were measured using the Center for Epidemiological Studies-Depression (CES-D) scale (Radloff, 1977). The 20-item measure includes questions regarding depressed mood, feelings of guilt, worthlessness, helplessness, and hopelessness, as well as psychomotor and sleep difficulties, loss of appetite (Radloff, 1977). The participants had to indicate how they felt and experienced every symptom during the past week on a 3-point scale, with 0 = rarely or none of the time (less than 1 day), 1 = some or a little of the time (1/2 days), 2 = occasionally or a moderate amount of time (3/4 days), 3 = most or all of the time (5/7 days). The reliability and validity of the CES-D scale have been extensively tested and studies concluded high internal consistency of the four-factor model: depressed affect, lack of well-being, somatic and retarded activity, interpersonal difficulties (Cosco et al., 2017).

According to the CES-D, the total possible score is 60, with the obtained score of 16 or higher indicating depression (Radloff, 1977). In order to test the aforementioned hypothesis, *CES-D* measured prior to the inflammation measurement was recoded into a binary variable of the *status of depression*. If the CES-D score (obtained prior to the measurement of inflammation) was equal to or higher than 16, a new value of 1 was assigned. Scores lower than 16 were assigned a value of 0, indicating no depression.

Inflammatory markers

C-reactive protein and Interleukin-6 measures that the current study focuses on were taken during the in-person-testing in 1989 (later than the currently used CES-D measurement) and was administered by registered nurses at a close location to homes of participants due to the fact that many older participants preferred not to travel far (Pedersen et al., 1991). Individuals were given the instructions to fast at least 6 hours prior to the testing. The majority of blood samples (67%) were drawn in the morning (Pedersen et al., 1991). The normal concentration of *C-reactive protein* in human serum is less than 3mg/L with elevated levels up to 10mg/L indicating a mild inflammation, more than 10mg/L marking acute bacterial or viral infections, or major trauma (Nehring et al., 2021). The suggested normal range of *Interleukin-6* serum level is up to 2ng/L (Akbaraly et al., 2013).

C-reactive protein and Interleukin-6 levels were both not normally distributed. Consequently, before conducting the analyses both of these variables were log-transformed, values of 0 were scaled by adding 1 (Matthews et al., 2010).

Age, alcohol use (0 = no use, 1 = use of alcohol), use of cardiovascular medication (0 = no use of CVD medication, 1 = use of CVD medication), smoking status (0 = non-smoker, 1 = ex-smoker, 2 = current smoker), BMI (kg/ $((cm/100)^2)$ were assessed in the mail-out questionnaire.

Data analysis

Prior to conducting the analysis, the data was explored and one influential case, with the CRP level of 208 which indicates a severe infection such as sepsis (Koozi et al., 2020), was removed.

Longitudinal associations between C-reactive protein and depression status, as well as Interleukin-6 and depression status, were evaluated using multiple linear regression analyses. Two sets of models were utilized. In the first set of models, the dependent variable was CRP with the status of depression as the independent variable. In the second set of models, the dependent variable was IL-6 with the status of depression as the independent variable. The same covariates that were determined *a priori* from the literature were corrected for in both sets of the models. First adjusted models corrected for age and sex, and then fully adjusted models also included covariates for alcohol use, CVD medication use, smoking status, and BMI. In addition, the same analyses with depressive symptoms measured on a scale rather

than as a dichotomous variable were run. All the statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 23.0.

Results

In the crude model depressive symptoms were not significantly associated with prognostic CRP levels (β=.017, p=.691, R^2=.000). However, the fully adjusted model had significant covariates of BMI and smoking status and the model itself was significant (p=.001, R^2=.050, Table 2).

For the IL-6, the crude model showed that depression was not significantly associated with higher levels of interleukin-6, (β=.020, p=.444, R^2=.001, Table 3). Significant covariates in the adjusted models were age, BMI, and smoking status. In addition, both of the adjusted models were significant (Table 3).

Analyses using depressive symptoms measured on a scale rather than a dichotomous variable did not yield different results.

Table 2

Multivariate linear regression set of models of the association predicting C-reactive protein (dependent variable) from depression status (independent variable)

	C-reactive protein			
	Model 1	Model 2	Model 3	
Variable	B	B	B	95%CI
Constant	.512	.275	-.193	[-.601, .215]
Status of Depression	.017	.023	.002	[-.081, .085]
Sex		.034	.008	[-.061, .077]
Age		.003	.004	[.000, .008]
BMI			.017**	[.009, .025]
Smoking status			.052**	[.002, .103]
Alcohol use			-.051	[-.119, .017]
Use of CVD medication			-.014	[-.085, .058]
R^2	.000	.006	0.50**	

BMI body mass index, *CVD* cardiovascular, *CI* confidence interval; Predictor/independent variable - status of depression; Covariates – sex, age, BMI;
** $p < .05$

Table 3

Multivariate linear regression set of models of the association predicting Interleukin-6 (dependent variable) from depression status (independent variable)

	Interleukin-6			
	Model 1	Model 2	Model 3	
Variable	B	B	B	95%CI
Constant	.551	.000	-.161	[-.408, .087]
Status of Depression	.020	.033	.024	[-.026, .074]
Sex		.033	.008	[-.034, .050]
Age		.007*	.007**	[.004, .009]
BMI			.007**	[.002, .011]
Smoking status			.043**	[.013, .074]
Alcohol use			-.015	[-.056, .027]
Use of CVD medication			.007	[-.037, .050]
R^2	.001	.062*	.087**	

BMI body mass index, CVD cardiovascular, CI confidence interval; Predictor/independent variable - status of depression; Covariates – sex, age, BMI
*p<.000, **p<.000

Discussion

The purpose of this study was to investigate to what extent heightened inflammatory responses can be explained by depression. The hypotheses stating that more severe depressive symptoms will result in higher CRP and IL-6 levels were rejected. The results suggest that depression does not predict prognostic inflammatory markers in the population of older adults, however, other factors such as age, BMI, and smoking do.

The current finding indicating that depression does not predict the later CRP levels is not in line with the literature described earlier and specifically with conclusions presented by Matthews and his colleagues (2010) which the current paper aimed to replicate in a different sample. Several explanations for this could be applied. In the Matthews and his colleagues' study (2010), the sample consisted of women only, assessed at the time around menopause, with ages ranging from 42 to 52. Changes in inflammatory responses are evident during the hormonal fluctuations in women (Mattina et al., 2019), which might have affected the observed results and drawn conclusions. Another explanation for the rejection of the investigated hypothesis could be that levels of pro-inflammatory cytokines in depression may be associated with specific symptoms as well as responsiveness to the treatment. More specifically, CRP elevation could be linked to treatment-resistant depression as well as

vegetative and somatic but not cognitive symptoms of depression (Chamberlain et al., 2019). These different factors were not investigated in the current study which raises a question: are different characteristics of depression the core of adding to the inflammation and not the depression itself? In addition, no information regarding the history of antidepressant treatment was available. This could have led to different results than expected because cytokines are especially prominent in not only treatment-resistant but also never-treated depression (Syed et al., 2018). Therefore, taking into account that around 20% of individuals who are >60 years old do use antidepressants (Winerman, 2017), the explanation that the observed levels of CRP and its association with depression in the studied population was affected by the use of medication cannot be ruled out.

With regard to the results concerning IL-6, the hypothesis that depression will predict the levels of this inflammatory marker was also rejected. IL-6 regulates the activity of the HPA-axis which in turn stimulates ACTH and cortisol, also CRP release increases following the secretion of IL-6 (Ng et al., 2018). It has been speculated in the literature that even though the elevation of cytokines as well as dysregulation of the HPA axis is often observed in depressed as well as in elderly individuals, the vulnerability of this axis to various illnesses might be more evident in younger adults as compared to older ones (Andersson et al., 2015). This could be illustrated by the meta-analytic observation which suggests that with age, even though rates of both depression and inflammation rise significantly, the association between IL-6 and depression decreases as the mean age increases (Howren et al., 2009). This adds to the results found in the current study because after adjusting for age, the model predicting IL-6 from depression became significant, suggesting that age is a better predictor of inflammation in the elderly despite whether they do exhibit any depressive symptoms or not (Cohen et al., 1997). One of the possible explanations for the effect of age on inflammatory response could be the age-related impacts on dendritic cells that begin to secrete elevated levels of pro-inflammatory cytokines and decreased levels of anti-inflammatory ones (Agrawal et al., 2017). The impact of dendritic cells could also add to the insufficient input for the regulation of the HPA axis (Azuma et al., 2017) which as described earlier is a core mechanism regulating the immune responses.

Furthermore, the current study revealed that BMI and smoking status are strong predictors of inflammatory response expressed by CRP and IL-6 levels. A study done by Amaral and colleagues (2015) suggests that this is due to the fact that genetic influences on the CRP and IL-6 expression during an inflammatory state are regulated through codependent pathways as

obesity, while in turn, obesity increases smoking behavior (Carreras-Torres et al., 2018). Additionally, depression is thought to be a priming factor for smoking (Mathew et al., 2017). However, these covariates did not explain the variation in the relationship between depression and inflammation relationship in the current research. This is in line with inconclusive conclusions presented in the literature. Some studies report that CRP and depression are associated more when adjusting for smoking and BMI while in other findings the association disappears after controlling for these variables (Häfner et al., 2008). This implies that the relationship between these lifestyle factors is still unclear and further research is required in order to be able to draw conclusions.

Important to mention is that the assessment of depression might have significantly affected the results which is the major limitation of the current study. Even though the CES-D scale is often used as an assessment tool with high internal and external validity, it has been suggested that in the elderly (75 years or older) this particular scale becomes susceptible to biases due to the inclusion of somatic symptoms that in this specific population might be influenced by comorbidities or certain medications (Grayson et al., 2000). Moreover, the CES-D scale is a self-report measure that asks how an individual felt during the last week while the diagnostic guidelines for depression indicate that the symptoms should be present for at least 2 weeks (American Psychological Association, 2019). Therefore, this may be an underlying explanation for inconclusive results with other longitudinal studies which analyzed individuals with a present clinical diagnosis of depression which was significantly associated with inflammation markers (Pitharouli et al., 2021). In addition, the serum measurement of peripheral inflammatory markers as used in the Swedish Twin Registry Studies does not necessarily reflect the processes in the brain. IL-6 levels in the CSF have been found to be uncorrelated with IL-6 levels in the periphery (Roohi et al., 2021), implying that a different measurement of inflammatory markers might have led to diverse results.

However, despite these limitations, this study investigated longitudinal data which expanded the current knowledge regarding the question to what extent heightened inflammatory responses expressed by CRP and IL-6 can be explained by depression in the elderly population. The discussed results yielded no prognostic effects of depressive symptoms, however, highlighted the importance of age and lifestyle factors such as smoking and BMI on the inflammation observed in the elderly. Causal conclusions are extremely challenging to draw due to unknown confounding variables, however, keeping in mind the rise of disabilities following depression as well as the crisis of Sars-CoV-2 which imposes great

risks for older individuals, future research should continue exploring the topic of whether there is a relation of depressive symptoms and inflammation in the elderly, as well as the possible bi-directional link of depression and inflammation. Literature concerning depression and its effects in the elderly is very limited, therefore future studies should continue exploring this population and look into a) the possible longitudinal differences between clinical and community-based samples with regard to levels of CRP and IL-6 and their dependence on depressive symptoms, b) the potential longitudinal effects of antidepressants on the pro-inflammatory responses with relation to other comorbidities, c) whether the number of depressive episodes as well different types of depression have a different effect on CRP and IL-6 as well as inflammation in general.

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