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Inflammatory biomarkers predict depressive, but not anxiety symptoms during aging: The prospective Sydney Memory and Aging Study

B.T. Baune [a,*], E. Smith [b], S. Reppermund [c], T. Air [a], K. Samaras [d], O. Lux [c,g], H. Brodaty [c,e], P. Sachdev [c,f], J.N. Trollor [b,c]

[a] Discipline of Psychiatry, School of Medicine, Adelaide University, Adelaide, Australia
[b] Department of Developmental Disability Neuropsychiatry, School of Psychiatry, University of New South Wales, Sydney, Australia
[c] Brain and Aging Research program, School of Psychiatry, University of New South Wales, Sydney, Australia
[d] Clinical Diabetes and Obesity Research Group, Garvan Medical Research Institute, Sydney, Australia
[e] Dementia Collaborative Research Centre, School of Psychiatry, University of New South Wales, Sydney, Australia
[f] Neuropsychiatric Institute, Prince of Wales Hospital, Randwick, NSW, Australia
[g] South-Eastern Area Laboratory Services, Prince of Wales Hospital, Avoca Street, Randwick, NSW 2031, Australia

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Summary This study addresses the paucity of research on the prospective relationship between a range of inflammatory markers and symptoms of depression and anxiety during aging. In the Sydney Memory and Aging Study, the relationships between remitted depression, current and first onset of symptoms of depression or anxiety (Geriatric Depression Scale and Goldberg Anxiety Scale (GDS, GAS), and markers of systemic inflammation (C-reactive protein (CRP), interleukins-1β, -6, -8, -10, -12, plasminogen activator inhibitor-1 (PAI-1), serum amyloid A, tumor necrosis factor-α, and vascular adhesion molecule-1) were investigated. The sample consists of $N = 1037$ non-demented community-dwelling elderly participants aged 70—90 years assessed at baseline and after 2-years. All analyses were adjusted for gender, age, years of education, total number of medical disorders diagnosed by a doctor, cardiovascular disorders, endocrine disorders, smoking, body mass index, currently using anti-depressants, NSAIDS or statins and diabetes mellitus. The results show a significant linear relationship between increasing levels of IL-6 and depressive symptoms at baseline only, whereas IL-8 was associated with depressed symptoms at baseline and at 2 years follow-up. In addition, IL-8 was associated with first onset of mild to moderate depressive symptoms over 2 years. Logistic regression analyses showed that PAI-1 (OR = 1.37, 95% CI = 1.10—1.71, $p = 0.005$) was associated with remitted depression. Results for anxiety symptoms were negative. The findings are suggestive of IL-6

* Corresponding author at: Discipline of Psychiatry, School of Medicine, University of Adelaide, Adelaide, SA 5005, Australia. Tel.: +61 8 8222 5141; fax: +61 8 8222 2865.
E-mail address: bernhard.baune@adelaide.edu.au (B.T. Baune).

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and IL-8 being associated with current symptoms and IL-8 being associated with first onset of depressive symptoms, whereas PAI-1 could be regarded as a marker of remitted depression.

1. Introduction

Aging processes have been associated with a pro-inflammatory state in the body (Bruunsgaard et al., 2001) and the brain, mediated by increased immune responses in the periphery, disruption of the periphery-CNS immune communication, and increased and discordant CNS response (Alexopoulos and Morimoto, 2011). The complex process of age-associated inflammation is underpinned by an age-dependent up-regulation of genes regulating inflammatory processes (Lee et al., 2000; Lu et al., 2004; Lucin and Wyss-Coray, 2009) which is thought to contribute to the onset of various age-associated diseases (Bruunsgaard et al., 2001) and to pre-mature mortality (Baune et al., 2011).

While some forms of adult depression have been suggested to be caused by inflammation in the brain (Rothermundt et al., 2001; Dantzer et al., 2008a,b; Dowlati et al., 2010), the potential role of inflammation in geriatric depression appears to be complicated by age-associated factors (e.g. cardiovascular diseases, metabolic changes, morphological brain changes). These factors may contribute to both inflammation and depressive symptoms leaving the question unanswered if inflammation may be a cause or consequence or both of geriatric depression (Alexopoulos et al., 1997).

Studies in the elderly on potential effects of an age-associated pro-inflammatory state on brain function and behavior have focused on peripheral inflammatory markers, such as cytokines, based on the assumption that pro-inflammatory cytokines can contribute to the development of depressive symptoms (Dantzer et al., 2008a,b) as well as induce neurotransmitter changes in the brain as seen in depression (Anisman et al., 2008).

Several community-based epidemiological studies during aging have been carried out to address the question whether peripheral cytokines are related to depressive symptoms in older adults, primarily using cross-sectional designs (Dentino et al., 1999; Penninx et al., 2003; Tiemeier et al., 2003; Bremmer et al., 2008) with only a few prospective studies (van den Biggelaar et al., 2007; Milaneschi et al., 2009; Stewart et al., 2009). The most consistent finding has been a cross-sectional association of elevated IL-6 with depressive symptoms or depression after controlling for likely confounding variables (Dentino et al., 1999; Penninx et al., 2003; Tiemeier et al., 2003; Bremmer et al., 2008). Only recently, a prospective association of IL-1β and interleukin 1 receptor antagonist (IL1ra) with depressive symptoms in the elderly was suggested (van den Biggelaar et al., 2007; Milaneschi et al., 2009).

Since there is a paucity of studies addressing the association of depressive symptoms and inflammation in a prospective design in aging cohorts, it is unclear whether the cytokine elevations are secondary to the illness (i.e., being directly or indirectly brought on by the depression), or contributes to the provocation of the disorder. In addition, previous studies have suggested that systemic inflammation might also be associated with anxiety disorders/anxiety symptoms (Capuron and Miller, 2011; Liukkonen et al., 2011; Oxenkrug, 2011); however, an analysis of both depressive and anxiety mood states at the same time considering a range of inflammatory markers during aging processes has not been carried out yet and might add to the emerging evidence in the clinical area of anxiety.

While the above cited research indicates that selected inflammatory markers may reflect current depressive/anxiety symptoms, some first research has reported that low-grade systemic inflammation as measured by C-reactive protein and serum amyloid A was associated with remitted depression (Kling et al., 2007). Interestingly, no studies have been published to investigate whether inflammatory markers are predictive of first onset of depressive symptoms in previously non-depressed individuals during aging. Furthermore, research as to whether inflammatory markers may act as markers of current mood symptoms, remitted depression/anxiety or first onset of depressive/anxiety symptoms would be helpful to clarify the potential biological role in these mood states.

In this study, it was firstly hypothesized that peripheral inflammatory markers are associated with acute symptoms of depression, with positive and negative mood and anxiety symptoms during healthy aging (i.e., inflammation is a state marker) at baseline. Secondly, it was hypothesized that inflammatory markers are prospectively associated with symptoms of depression, anxiety and positive/negative mood over two years. Thirdly, it was hypothesized that inflammatory markers at baseline are associated with remitted depression at baseline. Finally, it was hypothesized that inflammatory markers at baseline are associated with first onset of depressive symptoms over 2-years follow-up in previously non-depressed individuals.

2. Methods

2.1. Participants and procedure

Participants were recruited from the electoral roll of the Eastern suburbs of Sydney, Australia as part of the Memory and Aging Study (MAS), an ongoing longitudinal study examining the predictors of cognitive decline in an aged, non-demented community sample (Sachdev et al., 2010). Registration on the electoral roll is compulsory in Australia. Participants were excluded from the study if any of the following was evident: dementia (according to DSM-IV criteria), developmental disabilities, psychotic symptoms, schizophrenia or bipolar disorder, multiple sclerosis, motor neuron disease, progressive malignancy and English inadequate to complete a psychometric assessment.

3. Design

In this 2-year follow-up study, 1037 participants aged between 70 and 90 years were assessed at baseline using a

detailed neuropsychological and medical assessment, brain MRI (n = 544) and blood tests (n = 943), including measurement of inflammatory biomarkers. Participants were assessed either at a study center or in their own homes. At follow-up, 889 participants (85.73% of the sample) for the 2-year follow up assessment and N = 722 blood samples were available. This indicates an attrition rate of 14.27% (n = 148). However, only 11.19% (n = 116) of the sample withdrew/passed away and the remaining 32 participants were happy to stay in the study for later follow-ups but did not want to participate in the 2-year follow-up. The reason for withdrawal for the 116 participants was (1) deceased for 43 (4.15%) and (2) refused, too unwell to participate, moved or non-contactable for 73 (7.04%). At baseline, 55% of the sample was female. The mean age and standard deviation of the sample at baseline was 78.83 $\pm$ 4.82 (range: 70–90) years, and years of education on average were 11.60 $\pm$ 3.47 (range: 3–24). The mean age of the follow-up sample was significantly younger than the participants who did not take part in the follow-up study (80.3 years vs. 78.6 years, p = 0.0001). There were no significant differences in gender, years of education, BMI, smoking status, depression, glucose level, episodes of TIA, angina or stroke, high blood pressure or high cholesterol or ApoE status (all $p > .05$) between baseline and follow-up samples. To examine the representativeness of the sample, we compared those who were invited but did not participate with those who did. The two groups did not differ on age and sex. Further, we compared the participants in the study on sociodemographic characteristics with census data for the same geographical area obtained from the Australian Bureau of Statistics. There was no difference in the sex ratio, and while the age distributions were comparable, the Sydney MAS sample had a relatively lower proportion of individuals in the 70–74 age group (26.0% vs. 32.3%, $p < 0.05$) and higher in the 75–80 age group (34.8% vs. 29.9%, $p < 0.05$). The proportions in the 80–84 (26.9% vs. 24.2%) and 85–89 (12.3% vs. 13.6%) were not different. More Sydney MAS participants lived in private homes (97.5% vs. 92.1% in the ABS data, $p < 0.05$) and were more educated than the comparable group in the census data (30.4% with tertiary and 56.4% with secondary education cf. 10.1% and 42.2% respectively for the ABS data).

All assessments were conducted by trained research psychologists. The study protocol was approved by the Ethics Committees of the University of New South Wales and the South Eastern Sydney and Illawarra Area Health Service and written informed consent was obtained from each participant and informant.

3.1. Psychiatric measures

Mood status was measured at baseline (wave 1) and follow-up (wave 2) using various psychiatric measures as detailed below. There was an average of 23.39 months (SE 1.24 months) between the two assessment waves. Global cognitive function was assessed using the Mini Mental State examination (MMSE) at baseline and follow-up (Folstein et al., 1975).

3.1.1. History of depression

Participants were asked for their history and treatment of depressive episodes. A history of depression was defined as one or more depressive episodes that had required attention of a general practitioner, psychologist, or psychiatrist. Remitted depression was defined as having a history of depression but no depressive symptoms (measured by the Geriatric Depression Scale) at baseline assessment.

3.1.2. Geriatric Depression Scale

Current depressive symptoms were assessed with the 15-item short form of the Geriatric Depression Scale (GDS) (Yesavage et al., 1982; Sheik and Yesavage, 1986), a self-rating questionnaire shown to be reliable and valid for the assessment of depressive symptoms in the elderly. A higher score indicates more symptoms of depression and a cut-off of six has been established to measure clinically relevant symptoms of depression (Herrmann et al., 1996). The GDS does not include somatic and sexual items, and has been validated for use in individuals with mild impairments of cognition (Yesavage et al., 1982).

3.1.3. Goldberg Anxiety Scale

Anxiety symptoms were assessed during an interview with the Goldberg Anxiety Scale (GAS) (Goldberg et al., 1988) which consists of nine items with higher scores reflecting more anxiety symptoms. A cut-off of five has been established to measure a 50% chance of having a clinically important disturbance (Goldberg et al., 1988).

3.1.4. Missing data

There was missing data for some participants on each of the mood measures. The GDS was completed by n = 858 (3.5% missing data), and the GAS by n = 867 (2.5% missing data). There were some missing data for the self-rated GDS. Provided that 80% (12/15) or more of the questions were answered, scores were prorated (raw score/items completed x total number of items). This was done for 87 participants at baseline and for 92 participants at follow-up.

3.2. Clinical measures

Participants were asked to provide an extensive medical history. For cardiovascular, endocrine and other medical disorders the total number of disorders was summed per category and used as a continuous variable. Cardiovascular disorders included stroke, myocardial infarction, angina, atrial fibrillation, cardiac arrhythmia, cardiomyopathy, heart valve disease, aortic aneurysm and hypertension. Endocrine disorders included hypercholestrolemia, and kidney disease. Diabetes was defined as having been diagnosed with diabetes by a doctor. For analysis, all anti-depressant (AD) medications were collapsed into one group to indicate participants who were on anti-depressants at baseline (yes vs. no AD). Anti-depressant medications consisted of sertraline, citalopram, paroxetine, dothiepin, venlafaxine, amitriptyline, doxepin, escitalopram, fluoxetine, fluvoxamine, imipramine, mirtazapine, moclobemide, nortriptyline, tranylcypromine and trimipramine, and were collapsed into one group. NSAIDS consisted of celecoxib, meloxicam, diclofenac, ibuprofen, indomethacin, ketoprofen, lumiracoxib, misoprostol, naproxen, piroxicam, and sulindac, and were collapsed into one group (yes vs. no NSAIDS at baseline) for the purpose of analysis. Statins consisted of atorvastatin,

fluvastatin, pravastatin, rosuvastatin and simvastatin, and were collapsed into one group (yes vs. no Statins at baseline) for the purpose of analysis. Smoking status was defined as a person who is or was a regular smoker, and body mass index (BMI) was defined as weight in kilograms divided by height in centimeters squared.

3.3. Inflammatory markers

Blood was collected after an overnight fast, clotted, aliquoted and frozen at −80 °C. An array of inflammatory markers were analyzed for baseline measures of interleukins (IL-) -1β, -6, - 8, -10, -12p70, serum vascular cell adhesion molecule-1 (sVCAM-1), PAI-1, SAA, TNF-α and CRP.

sVCAM-1, PAI-1 and SAA levels were measured using commercially available sandwich enzyme-linked immunosorbant assay (ELISA) kits. The sVCAM-1 and PAI-1 ELISA kits were obtained from Bender Medsystems GmbH (Austria, Europe). The detectable range was 3.1—100 ng/mL for sVCAM-1, and 78—5000 pg/mL for PAI-1. SSA ELISA kit was obtained from United States Biological (USA) and had a detectable range of 9.4—600 ng/mL. High sensitivity CRP was measured by a turbidimetric method based on Near Infrared Particle Immunoassay rate methodology using the Beckman Coulter Synchron LXi analyser (Beckman Coulter, USA).

The cytokines IL-1β, IL-6, IL-8, IL-10, IL-12p70 and TNF-α concentrations were measured using cytometric bead array (CBA, BD Biosciences, San Diego, USA). Six bead populations with distinct fluorescence intensities were coated with capture antibodies specific for the corresponding proteins. These bead populations were mixed together to form the BD CBA, which resolved in the FL3 channel of a flow cytometer (BD FACSCalibur). The capture beads, PE-conjugated detection antibodies, and recombinant standards were incubated together to form sandwich complexes. Following acquisition of sample data using the flow cytometer, the results were generated in graphical and tabular format using the BD CBA Analysis Software. The intra-assay coefficients of variation were 4—7% for IL-1β, 5—8% for IL-6, 2—5% for IL-8, 5—6% for IL-10, 3—6% for IL-12p70 and 6—10% for TNF-α. The inter-assay coefficients of variation were 8—13% for IL-1β, 8—10% for IL-6, 4—7% for IL-8, 8—11% for IL-10, 6—9% for IL-12p70 and 8—15% for TNF-α.

3.4. Statistical analysis

Analyses were conducted using Stata version 10.1 (StataCorp, 2009). All data were examined for normality of distribution. The inflammatory markers were normalized using Blom's formula due to their positively skewed distribution (Blom, 1958). GDS scores at baseline and follow-up were normalized with log transformations, and expressed as geometric means in descriptive analyses. The GAS at both baseline and follow-up were extremely skewed and were unable to be transformed.

In order to analyze the relationships between the mood scales and sociodemographic and clinical variables, one-way ANOVAs and the Kruskal—Wallis test was used to examine the relationships between the GAS, GDS and the categorical variables. Spearman's correlations were calculated to determine the correlation between total number of medical disorders, years of education, BMI, MMSE and measures of mood variables (Table 1).

Analysis 1: Association between baseline biomarkers and baseline mood
Using linear regression analysis, we examined single inflammatory biomarker levels at baseline as independent variables in relation to the GDS total scores at baseline as dependent variable. Spearman's correlation analyses were performed on the GAS due to the skewed nature of the data. We also performed logistic regression analyses to assess the associations between the inflammatory markers at baseline and GDS and GAS caseness.

Analysis 2: Association between baseline markers and mood at follow-up
We followed the same analytic strategy as in Analysis 1; however follow-up measures of mood disorders were used as the dependent variables in all analyses.

Analysis 3: Association between biomarkers and remitted depression
Using logistic regression, we assessed the relationships between individual biomarkers and remitted depression both at baseline.

Analysis 4: Association between biomarkers and first onset of depression
Logistic regression was used to address the question whether the baseline inflammatory markers IL-6, IL-8, PAI-1 and CRP were associated with the first onset of depressive symptoms at follow-up.

3.5. Antidepressants, statins and NSAIDs as confounders

99 participants (9.55%) of the sample were on antidepressants (AD) at baseline. No significant differences in age and education between participants using vs. not using ADs were observed; however, females were more likely to be on ADs than males ($chi^2 = 6.93$, $p = 0.008$). Participants using ADs had significantly higher levels of VCAM-1 ($t = -2.22$, df = 914, $p = 0.026$) and IL-10 ($t = -2.56$, df = 914, $p = 0.011$) at baseline than those who were not using anti-depressants. The remaining inflammatory markers showed no significant differences between use and no use of ADs. For use of NSAIDS, no differences in levels of inflammatory markers between those with vs. without NSAIDs ($N = 167$ (16.1%)) were found. Finally, participants using statins ($N = 520$ (50.1%)) were found to have significantly higher VCAM-1 ($t = -2.34$, df = 914, $p = 0.019$), IL-6 ($t = -2.56$, df = 914, $p = 0.011$), and IL-10 ($t = -2.56$, df = 914, $p = 0.011$) levels, and lower CRP levels ($t = -2.56$, df = 914, $p = 0.011$) compared to those without statin use. Due to their potential role as confounders, ADs, statins and NSAIDs were included in subsequent analyses as co-variates.

3.6. Adjustment for confounders

Gender, age, years of education, total number of medical disorders diagnosed by a doctor, cardiovascular disorders, endocrine disorders, smoking, BMI, currently using antidepressants, currently using NSAIDS, currently using statins, MMSE and diabetes mellitus were included as covariates in all linear and logistic regressions.

Table 1 Relationships between demographic and clinical variables and baseline measures of mood.

Sociodemographic and clinical variables	Baseline GDS		Baseline GAS	
	Mean[d] (se)	*p*-Value	Mean (se)	*p*-Value
Age				
<75 (*n* = 268)	2.378 (0.038)	0.0000[a]	0.977 (0.102)	0.6241[c]
75–79 (*n* = 358)	2.793 (0.030)		1.023 (0.089)	
≥80 (*n* = 411)	3.043 (0.029)		0.936 (0.080)	
Gender				
Male (*n* = 465)	2.878 (0.027)	0.0612[a]	0.928 (0.073)	0.6974[c]
Female (*n* = 572)	2.688 (0.024)		1.016 (0.072)	
Smoked regularly				
No (*n* = 476)	2.618 (0.027)	0.0030[a]	0.932 (0.073)	0.6866[c]
Yes (*n* = 559)	2.917 (0.025)		1.018 (0.073)	
Education (*n* = 1037)	−0.1004	0.0012[b]	0.0043	0.8915[b]
Clinical factors				
Endocrine disorders				
No (*n* = 358)	2.697 (0.030)	0.2314[a]	0.777 (0.074)	0.0053[c]
Yes (*n* = 673)	2.823 (0.023)		1.087 (0.068)	
CVD				
No (*n* = 265)	2.412 (0.035)	0.0000[a]	0.902 (0.093)	0.7413[c]
Yes (*n* = 767)	2.906 (0.021)		0.997 (0.061)	
Diabetes mellitus				
No (*n* = 906)	2.743 (0.020)	0.2586[a]	0.986 (0.056)	0.7965[c]
Yes (*n* = 126)	2.921 (0.049)		0.928 (0.136)	
Baseline anti-depressants				
No (*n* = 930)	2.763 (0.019)	0.5883[a]	0.995 (0.055)	0.2725[c]
Yes (*n* = 109)	2.854 (0.056)		0.824 (0.147)	
Baseline NSAIDs				
No (*n* = 864)	2.803 (0.020)	0.1748[a]	1.020 (0.058)	0.0830[c]
Yes (*n* = 175)	2.624 (0.048)		0.764 (0.106)	
Baseline statins				
No (*n* = 517)	2.754 (0.025)	0.7104[a]	0.886 (0.066)	0.3511[c]
Yes (*n* = 520)	2.791 (0.026)		1.066 (0.079)	
Total no. diags (*n* = 1037)	0.2398[b]	0.0000	0.1383	0.0000[b]
BMI (*n* = 1010)	0.0529[b]	0.0937	−0.0212	0.5028[b]
MMSE	−0.0456[b]	0.1531	−0.0190[b]	0.5523

[a] *p*-Values obtained from one-way ANOVAs.
[b] Spearman's correlation coefficient.
[c] *p*-Values obtained by Kruskal Wallis.

4. Results

4.1. Clinical characteristics of the sample

In the entire sample, *N* = 160 (16.0%) participants reported a previous depressive episode. Although no significant age and gender difference between those with and without history depression were reported, females were more likely to have had a previous depressive episode ($chi^2 = 4.41$, $p = 0.036$). Of these 160 participants, 139 subjects had no clinically significant symptoms of depression at baseline (remitted depression) and the remaining 21 subjects (12.9%) scored above the GDS cut-off for clinically relevant depressive symptoms. 11 of these subjects reported that they were currently using antidepressants. In total, 73 participants (7.07%) were found to be clinically significantly depressed at baseline and similar figures (*N* = 72; 8.39%) at follow-up (GDS caseness). 42 (4.9%) people developed a new depression at follow-up, according to the GDS caseness. Comparable figures were also observed for clinically relevant anxiety symptoms present in 71 participants (6.85%) at baseline and in 74 (8.54%) at follow-up (GAS caseness).

Table 1 presents results on the potential influence of demographic and clinical variables on mood at baseline. Age, education, medical disorders, behaviors such as smoking showed associations with the mood variables at baseline. Table 2 displays the means and standard deviations of raw biomarker serum concentrations showing a number of correlations between inflammatory biomarkers (see legend Table 2).

Analysis 1: Association between biomarkers and mood at baseline

At baseline, increased levels of IL-8 and IL-6 were significantly related to higher levels of depressive symptoms (GDS) (Table 3). No significant associations between any of

Table 2 Means and standard deviations for biomarker concentrations ($n = 916$).

Biomarker	Mean	SD	Range
sVCAM-1 (ng/mL)	1093.98	722.62	207.9—14704.2
PAI-1 (pg/mL)	81.37	29.50	22.1—218.7
SAA (ng/mL)	57.51	181.33	1.7—3236.3
TNF-α (ng/mL)	2.79	11.72	0—345.4
CRP (mg/L)	3.03	5.45	0.2—78
IL-1β (pg/mL)	3.23	6.39	0—179.2
IL-6 (pg/mL)	6.56	8.33	4.2—164.3
IL-8 (pg/mL)	20.11	13.38	0—36.9
IL-10 (pg/mL)	2.64	1.98	0—41.1
IL-12p70 (pg/mL)	3.10	2.52	0—162.9

Significant Spearman's rho correlations between sVCAM-1 and PAI-1 (rho = −0.08, $p = 0.01$), CRP (rho = 0.16, $p = 0.000$), IL-6 (rho = 0.15, $p = 0.000$), IL-8 (rho = 0.10, $p = 0.004$), IL-10 (rho = 0.16, $p = 0.000$); PAI-1 and CRP (rho = 0.18, $p = 0.000$); SAA and CRP (rho = 0.46, $p = 0.000$), IL-6 (rho = 0.20, $p = 0.000$); TNF-α and IL-1β (rho = 0.47, $p = 0.000$), IL-6 (rho = 0.17, $p = 0.000$), IL-10 (rho = 0.41, $p = 0.000$), IL12p70 (rho = 0.46, $p = 0.000$); CRP and IL-6 (rho = 0.31, $p = 0.000$), IL-8 (rho = 0.09, $p = 0.007$), IL-10 (rho = 0.08, $p = 0.02$); IL-1β and IL-6 (rho = 0.30, $p = 0.000$), IL-8 (rho = 0.20, $p = 0.000$), IL-10 (rho = 0.36, $p = 0.000$), IL-12p70 (rho = 0.45, $p = 0.000$); IL-6 and IL-8 (rho = 0.33, $p = 0.000$), IL-10 (rho = 0.34, $p = 0.000$), IL-12p70 (rho = 0.36, $p = 0.000$); IL-8 and IL-10 (rho = 0.21, $p = 0.000$), IL-12p70 (rho = 0.21, $p = 0.000$); IL-10 and IL-12p70 (rho = 0.52, $p = 0.000$).

the individual inflammatory markers and baseline GAS scores were found.

Consistent with this result, IL-8 — among all other inflammatory markers — was significantly associated with GDS caseness at baseline (OR = 1.36, 95% CI = 1.021—1.802, $p = 0.035$) and IL-6 approached significance (OR = 1.28, 95% CI = 0.960—1.694, $p = 0.093$). No other inflammatory markers were significant in this analysis fully adjusted for confounding variables. There were no significant associations between the individual inflammatory marker and baseline GAS caseness.

Analysis 2: Association between baseline biomarkers and follow-up mood

Increasing baseline IL-8 levels predicted significantly higher levels of depressive symptoms (GDS) at follow-up, while IL-12p70 showed a significant inverse relationship (Table 4). No significant relationships were found between other baseline inflammatory markers and GDS scores at follow-up, although a trend for higher levels of IL-6 to be associated with increased GDS scores ($p = 0.094$) was observed. No significant relationships were observed between the individual inflammatory markers and follow-up GAS scores (data not shown).

Analysis 3: Association between biomarkers and remitted depression

Remitted depression at baseline ($N = 139$; previously diagnosed depression without symptoms at baseline) was associated with the baseline inflammatory marker PAI-1 (OR = 1.37, 95% CI = 1.10—1.71, $p = 0.005$) in a logistic regression analysis.

Analysis 4: Association between biomarkers and first onset depression

Among participants who had not reported a previous depression or were not classified as GDS case at baseline, IL-8 at baseline predicted higher depressive symptoms at two-year follow-up (beta = 0.051, se = 0.022, $p = 0.021$), however, not reaching significance for new GDS caseness at follow-up (OR = 0.94, 95% CI 0.67—1.32, $p = 0.719$). Estimates were obtained in fully adjusted models.

Table 3 Relationships between inflammatory markers and GDS total score at baseline.[b]

Baseline inflammatory marker	Baseline log GDS total	
	B coefficient (se)	*p*-Value
sVCAM-1[a]	0.008 (0.019)	0.661
PAI-1[a]	−0.005 (0.019)	0.804
SAA[a]	0.015 (0.020)	0.433
TNF-α[a]	0.001 (0.020)	0.973
Crp[a]	−0.007 (0.021)	0.727
IL-1β[a]	0.007 (0.020)	0.739
IL-6[a]	0.041 (0.019)	0.035
IL-8[a]	0.042 (0.019)	0.025
IL-10[a]	−0.002 (0.020)	0.908
IL-12p70[a]	−0.034 (0.019)	0.083

[a] *p*-Values obtained by individual linear regressions adjusted for age, gender, years of education, total number of medical disorders, cardiovascular disease, endocrine disorders, diabetes mellitus, BMI, MMSE, ever smoked regularly, currently using antidepressants, currently using NSAIDs, and currently using statins.

[b] GAS not displayed due to analytical strategies using non-parametric tests.

Table 4 The prospective relationships between inflammatory markers and GDS total score at follow-up.[b]

Baseline inflammatory marker	Follow-up log GDS total	
	B coefficient (se)	*p*-Value
sVCAM-1[a]	0.010 (0.021)	0.650
PAI-1[a]	0.006 (0.021)	0.755
SAA[a]	0.015 (0.022)	0.495
TNF-α[a]	−0.002 (0.023)	0.915
Crp[a]	0.017 (0.024)	0.471
IL-1β[a]	0.005 (0.022)	0.803
IL-6[a]	0.037 (0.022)	0.093
IL-8[a]	0.043 (0.021)	0.038
IL-10[a]	−0.008 (0.022)	0.696
IL-12p70[a]	−0.056 (0.022)	0.010

[a] *p*-Values obtained by individual linear regressions adjusted for age, gender, years of education, total number of medical disorders, cardiovascular disease, endocrine disorders, diabetes mellitus, BMI, MMSE, ever smoked regularly, currently using anti-depressants, currently using NSAIDs, and currently using statins.

[b] GAS not displayed due to analytical strategies using non-parametric tests.

5. Discussion

This study was performed to investigate whether inflammatory markers were prospectively associated with symptoms of depression and anxiety, and specifically to address the question whether inflammatory markers of current, remitted or novel onset of various mood symptoms during normal aging in a large community sample using a prospective design of community dwellings and accounting for a range of potential confounders.

5.1. Inflammatory proteins as biomarkers of depressive symptoms

Overall, our findings indicate that the inflammatory markers IL-6, IL-8, IL-12p70 and PAI-1 showed specific associations (a) with depressive symptoms cross-sectionally and prospectively, (b) with first onset of depressive symptoms and (c) with remitted depression, but not with anxiety symptoms.

Specifically, the results implicate IL-6 as a marker of current depressive symptoms at baseline even after including a number of potential confounders for inflammation. These findings are in line with a recent review article which consistently showed IL-6 to be linked with depression in the middle-aged (Mikova et al., 2001; Dowlati et al., 2010). In the elderly, IL-6 has also been shown to be associated with depression (Tiemeier et al., 2003; Dimopoulos et al., 2008). The association of IL-6 with acute symptoms of depression is supported by previous studies in depression and by the observation that IL-6 tends to stay at moderately increased levels in depression even after successful antidepressant treatment (Kubera et al., 2000). IL-6 at baseline was found to not predict depressive or anxiety symptoms at follow-up. Thus, this cytokines may be a marker of current symptoms of the illness, but does not play an etiological role in depression (Anisman et al., 1999; Maes et al., 1999).

Our study was the first to show that IL-8 at baseline is a marker of caseness of depression at baseline and of depressive symptoms both at baseline and follow-up in the elderly. Another novel finding is that the chemokine IL-8 predicted first onset of mild to moderate depressive symptoms in incident cases over 2 years, suggestive of IL-8 being a marker of first onset of depressive symptoms in the elderly. Moreover, IL-8 was particularly associated with higher levels of severity of depressive symptoms both at baseline and follow-up.

Although IL-8 has been shown to be elevated in individuals with bipolar disorder (O'Brien et al., 2006), the role in depression in middle-aged individuals is not consistent (Dowlati et al., 2010). Congruently, IL-8 has been shown to be associated with low cognitive performance (Baune et al., 2008), suggesting IL-8 may affect the central nervous system (CNS) in more than one way.

IL-8 is an 8 kDa protein and a member of a family of soluble molecules called chemokines, which are a subclass of the cytokine superfamily (Mukaida et al., 1998). The cytokine IL-8, which represents the prototypical chemokine, has not been examined in relation to depressive or anxiety symptoms previously. IL-8 has a number of pro-inflammatory effects including promotion of neutrophil adhesion, chemotaxis and lysosomal discharge (Huber et al., 1991; Baggiolini, 1998; Remick, 2005) and is able to cross the blood–brain-barrier (BBB) (Narita et al., 2005). IL-8 may be produced early in the inflammatory response and may persist for days and even weeks, in contrast to most other inflammatory cytokines which are produced and cleared within a few hours (Remick, 2005). Our findings support the notion that IL-8 might be specific for more long-term changes in neurodegenerative and neuropsychological alterations in the brain.

With improved understanding of reciprocal communication between the central nervous system and the peripheral immune system, potential mechanisms for an inflammation-associated pathway influencing depressive and anxiety symptoms have emerged (Wilson et al., 2002). Given the central role of cytokines in neuroimmmunoendocrine processes, it is assumed that these molecules influence emotion processing via diverse mechanisms. Peripheral cytokines penetrate the blood–brain barrier directly via active transport mechanisms or indirectly via vagal nerve stimulation (Wilson et al., 2002). In addition to their roles in neurodegenerative processes, apoptosis and excitotoxicity, cytokines are capable of influencing neurotransmitter (Dunn et al., 1999) and neuroendocrine responses (McCann et al., 2000) subserving cognition and are able to directly modulate neuronal and glial cell function (Griffin et al., 1998). IL-8 has been observed as the most prominent factor expressed by adult human microglia stimulated with Ah1-42 (Walker et al., 2001), and IL-8 is highly expressed in the brains of patients with Alzheimer's disease (Galimberti et al., 2003). Microglia can contribute to brain damage by producing glutamate, which is toxic for neurons and oligodendrocytes (Pitt et al., 2000). Microglia also has an important regulatory function through the induction of apoptosis in autoreactive T lymphocytes. Inflammation is implicated in the pathogenesis of many neurological disorders (Chavarriaa and Alcocer-Varela, 2004).

Interestingly, IL-12p70 was found to be inversely and prospectively associated with depression severity in our sample. This could be explained by taking into account the role IL-12p70 has in the immunity. Specifically, IL-12p70 has been shown to exacerbate interferon gamma (Puddu et al., 1997), and in turn interferon gamma has repeatedly been shown to improve immunity (Schroder et al., 2004). Because depression has been associated with decreased immunity (Herbert and Cohen, 1993), IL-12p70 may be ameliorating the immune system of the depressed patient consequently alleviating symptoms of depression. More research is needed on the mechanistic role of IL-12p70 and depression.

PAI-1 was found to be associated with remitted depression in this study, but not with acute symptoms of depression or anxiety. Indeed, previous studies in younger people have linked depression to this marker (Ford and Erlinger, 2004; Lahlou-Laforet et al., 2006; Tsai et al., 2008). While PAI-1 has been found to be elevated in those with severe anxiety disorders (Geiser et al., 2008), such an association with anxiety was not found in this sample.

PAI-1 has been located in some parts of the brain, suggesting it crosses the brood blain barrier (Hino et al., 2001) as does the tissue-type plasminogen activator (tPA) (Benchenane et al., 2005), which is inhibited by PAI-1. In fact, research has suggested that PAI-1 could have neuroprotective effects in neurons in that PAI-1 may prevent the disintegration of neuronal networks by maintaining or promoting neuroprotective signaling through the MAPK/ERK pathway

(Soeda et al., 2008). Because stress and subsequent depression have been shown to affect the central nervous system by increasing the susceptibility to apoptosis (McKernan et al., 2009), it can be hypothesized that the PAI-1 is involved in repair mechanisms in depression and/or prevents from stress-associated cell damage. Accordingly, PAI-1 was found to be increased in remitted depression in our study.

We could not verify our hypotheses on the relationship between inflammation and anxiety as no significant association between inflammation and anxiety symptoms were observed. Interestingly, another study did find reduced levels of IL-8 in individuals with post-traumatic stress disorder (Song et al., 2007). Thus, it can be hypothesized that anxiety symptoms must be acutely severe before changes in inflammation can be detected. However, this requires further exploration in specifically designed studies.

Our study has several strengths including the ability to study inflammation and emotional processes in a large prospective sample allowing the investigation of inflammation as a marker of emotional processes such as depression and anxiety. Although the study included relatively healthy aging conditions, we were able to consider a variety of confounding factors relevant to inflammation during aging. Through the inclusion of a larger range of inflammatory markers, we were able to research pro-inflammatory, anti-inflammatory and measures of vascular processes relevant to aging and neurodgeneration. If we were to employ a strict method accounting for multiple testing such as Bonferroni correction for multiple comparisons, the results would likely become negative; however, applying such a rigorous method might be regarded as too strict given the exploratory character of the study using a variety of inflammatory markers rather than an hypothesis driven selection of specific markers. Our study has not used a structured interview to determine the diagnosis of depression and anxiety and clinical diagnoses of depression reported by patients were made by health professionals (psychiatrists, psychologists and GPs), which is a methodological limitation that should be addressed in future studies. Since the self-report measures used to assess the symptoms of depression and anxiety have been validated in the aging population (see Section 2 for details), the mood assessment was based on a standard accepted in the literature. If the use of antidepressants, statins and NSAID would be significantly different across depression (never/current/remitted depression), it might have influenced the results on inflammatory markers since these medications have anti-inflammatory effects. However, 22% of the participants with current depression and a similar proportion of those with remitted depression (26%) were on antidepressants, while those 'never' depressed were not on ADs. The proportions of participants on statins and NSAIDs were similar for 'current depression' (15% and 53% respectively), with 'remitted depression' (17% and 44% respectively) and in the group of 'never depressed' (16% and 51% respectively). Due to the similar distribution of statin and NSAID use across the depression groups, it can be concluded that these medications had no particular influence on the reported significant relationship between groups of depression and inflammatory markers.

In conclusion, the results of this study suggest that cytokines are etiological factors in the development of depressive symptoms and may also be associated with remitted stages of depression in addition to their well-known role as markers of the current disease activity of depression. Thereby, our results suggest that inflammatory markers show specificity for depressive symptoms at various disease stages during aging. These findings and particular the new finding on the role of IL-8 are worthwhile for future replication studies.

Role of the funding source

All authors declare that the funding source had no impact on the study design, the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

Conflict of interest

All authors declare no conflict of interest.

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