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Lower CSF interleukin-6 predicts future depression in a population-based sample of older women followed for 17 years

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ABSTRACT

Objective: The literature regarding cerebrospinal fluid (CSF) cytokines in geriatric depression is sparse. The aim of this study was to examine associations between CSF interleukin-6 (IL-6) and related proinflammatory cytokines and current and future depression in a population-based sample of older women who were followed for 17 years.
Methods: 83 non-demented women aged 70–84 years who participated in the Prospective Population Study of Women in Gothenburg, Sweden took part in a lumbar puncture in 1992–3. CSF- IL-6, interleukin-1β (IL-1β), interleukin- 8 (IL-8) and tumor necrosis factor-α (TNF-α) were measured. Psychiatric symptoms were rated with the Comprehensive Psychopathological Rating Scale at baseline and at three subsequent face-to-face examinations. Depression (major or minor) was diagnosed in accordance with DSM-IV/DSM-IV research criteria.
Results: At baseline, women with ongoing depression had lower levels of IL-6 ($p < 0.04$), IL-8 ($p < 0.05$) and TNF-α ($p < 0.05$) compared with those without depression. In women without depression at baseline, lower CSF IL-6 levels predicted depression at one or more follow-up examination ($p < 0.03$). Results from the generalized linear mixed logistic model using all baseline and follow-up data on depression status and Mini Mental State Examination score showed a significant relationship between IL-6 and depression ($p = 0.005$ OR 0.370 CI [0.184–0.744]).
Conclusion: Lower levels of CSF IL-6 were associated with current depression and with future depression during a follow-up of almost two decades. Our findings suggest that lower levels of CSF IL-6 may be related to depression vulnerability in later life.

1. Introduction

In recent years it has been hypothesized that changes in the immune system might play an important role in pathophysiological processes related to depression (O'Brien et al., 2004; Mossner et al., 2007; Miller et al., 2009; Schrepf et al., 2012). Proinflammatory cytokines may activate the hypothalamic–pituitary–adrenal (HPA) axis, (Leonard, 2000; O'Brien et al., 2004) modulating monoamines in the CNS and leading to depressive symptoms (Chaouloff, 2000). Cytokine receptors have been localized in the hippocampus and hypothalamus, with the highest density observed for interleukin-6 (IL-6) receptors (Hopkins and Rothwell, 1995). Clinical studies have shown that serum levels of proinflammatory cytokines are disturbed in patients with depression. A recent meta-analysis demonstrated that, while individual studies showed both positive and negative results, levels of plasma tumor necrosis factor-α (TNF-α) and plasma IL-6 were significantly higher in persons with major depression than those who were not depressed (Dowlati et al., 2010).

Despite abundant evidence of peripheral immune alterations in persons who are depressed, there are to date few published studies on cytokine levels in the cerebrospinal fluid (CSF) of depressed persons. To further clarify the roles of cytokines in depression, CSF central measurements are needed. Existing CSF studies are cross-sectional and based on relatively small clinical samples. Two studies (one of which focused on geriatric depression) showed *lower* CSF IL-6 levels in depressed patients compared to mentally healthy controls (Levine et al., 1999; Stubner et al., 1999). Another reported higher levels (Lindqvist et al., 2009), and two further studies

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showed no differences between groups (Carpenter et al., 2004; Martinez et al., 2011). Regarding other cytokines, higher CSF IL-1β (Levine et al., 1999) levels distinguished acutely depressed inpatients from healthy controls, whereas levels of TNF-α (Levine et al., 1999), IL-8, TNF-α and IL-1β levels did not differ between the groups (Lindqvist et al., 2009). Clinical studies may miss depressed persons in the population due to referral bias. The need for epidemiological approaches has been stressed (Dantzer, 2012). To our knowledge there are to date no studies examining CSF proinflammatory cytokines and depression in population-based samples. We have previously reported cross-sectional CSF findings from a population-based sample of women in support of both neurodegenerative and vascular etiology for depression in late life (Gudmundsson et al., 2007). The aim of the present study was to examine a possible association with proinflammatory cytokines in the same cohort. As most studies of peripheral plasma levels have shown that elevated cytokine levels were associated with depression, we hypothesized that we would find similar associations in CSF. As prospective studies may provide insights into pathological mechanisms that cross-sectional studies cannot, a second aim was to determine whether these cytokines were associated with *future* depression in older women followed over a period of 17 years.

2. Methods

2.1. Subjects

The study sample was derived from the Prospective Population Study of Women (PPSW), a population-based survey in Gothenburg, Sweden (Bengtsson et al., 1973). The sample was obtained from the Swedish population register, based on birth date, and included both those living in private households and in residential care. The original sample has been described in detail previously (Bengtsson et al., 1973; Gudmundsson et al., 2007). Briefly, the study began in 1968–1969 and included a representative sample of 1462 women living in Gothenburg, Sweden born on certain dates in 1908, 1914, 1918 and 1922.

In 1992–1993, 837 surviving women were invited to participate in a psychiatric examination, which for the purpose of the current study will be referred to as the baseline examination. Among 590 who agreed to take part, 85 (aged 70–84 years) consented to undergo a lumbar puncture (LP). Two of these women who were diagnosed with dementia at the time of the LP were excluded from the current analyses, leaving 83 women born in 1908 ($n = 2$), 1914 ($n = 6$), 1918 ($n = 33$) and 1922 ($n = 42$). The mean age of the participants at baseline in 1992–1993 was 72.5 years (SD 3.1).

Follow-up psychiatric examinations were conducted in 2000, 2005 and 2009. In 2000, 61 out of 70 surviving women accepted participation (response rate 87%). In 2005, 41 out of 49 surviving women agreed to be examined (response rate 84%). In 2009, 19 of the 25 surviving women took part (response rate 76%).

After complete description of the study, written informed consent was obtained from all participants at each examination wave. For women with dementia at follow-up, close informants gave proxy consent. The study was approved by the Ethics committee for medical research at the university of Gothenburg.

As previously reported (Gudmundsson et al., 2007), there were no differences at baseline between the women who participated in the lumbar puncture ($n = 85$) and those who participated in the psychiatric exam only ($n = 505$) with regard to age, psychiatric illnesses, including symptoms of depression, smoking status, alcohol intake, physical activity, systolic and diastolic blood pressures, body mass index, blood levels of cholesterol, high density lipoprotein, and triglycerides, age of menopause, history of angina pectoris, myocardial infarction and diabetes, and use of a variety of medications including lipid-lowering agents, antihypertensive agents and hormone replacement therapy. Further, no differences could be shown regarding Mini Mental State Examination (MMSE) scores (Folstein, Folstein et al., 1975) ($p = 0.438$), and ratings of the personality traits neuroticism ($p = 0.666$) and extroversion ($p = 0.941$) as measured by the Eysenck Personality Inventory.

2.2. Procedures

The clinical examination was conducted at a geriatric outpatient department or in the participant's home and included comprehensive social, functional, physical, neuropsychiatric and neuropsychological examinations, as well as a close informant interview (Palsson et al., 2001). Information about medication use was collected and classified according to the Anatomical Therapeutic Chemical Classification codes (ATC) (Oslo, 1997).

2.3. Psychiatric examination and diagnostics

The baseline psychiatric examination was semi-structured and performed by psychiatrists in 1992–1993. Follow-up exams were carried out by trained psychiatric nurses. The Comprehensive Psychological Rating Scale (CPRS) (Asberg et al., 1978) was used to rate psychiatric symptoms at baseline and each following exam. Major depression was diagnosed in accordance with DSM-IV and minor depression was diagnosed according to DSM- IV research criteria (either a sad or depressed mood or loss of interest or pleasure in nearly all activities). In total at least 2 but less than 5 additional symptoms (American Psychiatric Association, 1994). Depression symptom burden was measured with the Montgomery-Åsberg Depression Rating scale (MADRS), which is derived from the CPRS (10 items, maximum score 60) (Montgomery and Asberg, 1979).

The neuropsychiatric exam has been described in detail (Skoog et al., 1993). Briefly, the exam included the MMSE and tests of short- and long term memory as well as tests of aphasia, apraxia, agnosia and abstract thinking. The diagnosis of dementia was made on the basis of the neuropsychological examination and the interview with the close informant, with each considered separately, using DSM-III-R criteria (Association 1987). Each symptom had to have attained a level at which it caused the subject substantial difficulty in social functioning and the duration of dementia had to be at least six months. A final diagnosis was made on the basis of the combined information (Skoog et al., 1993). Dementia was an exclusion criterion at baseline.

2.4. CSF analyses

Lumbar punctures were carried out in 1992–1993 only. CSF-samples (12 ml) were taken through the L3/L4 interspace and gently mixed to avoid gradient effects. The samples were immediately centrifuged at 2000*g* for 10 min to eliminate cells and other insoluble materials, aliquoted in 1 ml portions, snap frozen at −80 °C, stored at that temperature and brought in an unbroken freeze chain to the laboratory for analyses. CSF levels of IL-1β, IL-6, IL-8, and TNF-α were analyzed by certified laboratory technicians using the Human Pro-inflammatory II 4-Plex Assay Ultra-Sensitive Kit (Meso Scale Discovery, Gaithersburg, MD, USA). Intra-assay coefficients of variation were below 10% for all analytes. The limit of detection was 0.61 pg/ml. Cytokine concentrations below the detection limit were set to 0.6 pg/ml.

2.5. Statistical analysis

Differences in cytokine levels were tested with the non-parametric Mann–Whitney-U test. Binary logistic regressions were

used to explore how cytokine levels were related to cross-sectional associations with depression, adjusting for age, Body- Mass- Index (BMI) and smoking as possible confounders. Age and dementia were included in multivariate models in the longitudinal analyses. MADRS score was used as a continuous variable to test for associations between cytokine levels and depression severity. Generalized linear mixed logistic models (GLMM) were used to fit a repeated measures logistic regression to the data on depression from each study period with the baseline cytokine values. Statistical tests were carried out using SPSS for Windows (version17, SPSS Chicago, IL.). A two-tailed level of significance, $p < 0.05$ was used in all tests.

3. Results

3.1. Baseline findings

Baseline depression status including mean MADRS scores is shown in Table 1. One fifth of the women fulfilled criteria for depression (major depression, $n = 8$, minor depression, $n = 11$). There was no age difference between participants with and without ongoing depression ($p = 0.899$).

Table 1
Baseline characteristics in a population-based sample of non-demented older women who participated in a lumbar puncture ($N = 83$). The prospective population study of women.

	N (%)	MADRS score mean (SD)
Age in years (SD)	72.5 ± 3.1	
No depression	64 (77.1)	4.0 (4.0)
Any depression	19 (22.9)	17.6 (9.1)
Major	8 (9.6)	25.8 (6.5)
Minor	11 (13.3)	11.6 (5.3)
Antidepressant use	4 (4.8)	18.5 (13.1)
Cytokine levels in CSF (pg/ml)	Median	Range
IL-1β[a]	0.6	<0.61–7.05
IL-6	1.67	0.63–20.30
IL-8	35.7	17.5–78.7
TNF-α[1]	0.6	<0.61–2.73

[a] Regarding IL-1β (75 measurements) and TNF-α (71 measurements) were below the detection limit.

Table 1 shows median values and ranges for the CNS cytokines studied. Levels of IL-1β and TNF-α were below the detection limit for many of the women. All women in the depression group had CSF TNF-α levels below the detection limit as did 75% in the non-depressed group. When TNF-α concentrations below the detection limit were set to 0.6 pg/ml, a significant difference was noted between women with and without depression. However, the association did not remain after adjustment for age.

In the cross-sectional analysis (Table 2), no association could be shown between CSF IL-1β and baseline current depression. However, baseline current depression *was* associated with lower CSF-levels of IL-6 and IL-8 (Table 2). These associations were also tested with binary logistic regressions adjusted for age. As Body-Mass- Index and smoking status are confounders for CSF- IL-6 levels (O'Connor, 2009), we added these variables to the regression model and the association remained ($p = 0.036$, OR 0.572 CI [0.339–0.963]). Due to skewness in the distribution of IL-6, regression models were examined both with CSF values and quartiles. CSF-IL-6 values were associated with depression at baseline ($p = 0.042$, OR 0.389, CI [0.157–0.965]). In CSF IL-6 quartiles were significantly associated with depression at baseline as well ($p = 0.048$, OR 0.601, CI [0.363–0.995]). Lower quartiles of CSF IL-8 were associated with depression ($p = 0.047$, OR 0.605 CI [0.369–0.994].

None of the participants were on treatment with systemic steroids or antirheumatics at baseline. Ongoing antidepressant treatment was reported in four women and three of these fulfilled criteria for depression at the time of the baseline examination. After excluding the latter group, the association with CSF IL-6 remained ($p = 0.034$). There were no correlations between any CSF cytokine levels and MADRS scores at baseline (data not shown).

3.2. Future depression

Of the total sample ($n = 83$), 19 women fulfilled criteria for major or minor depression at one or more follow-up examinations. Ten of these had depression at baseline in 1992–1993 leaving nine

Table 2
CSF cytokine levels in relation to depression (major or minor) in a population sample of older women followed over 17 years.

	No depression ($n = 64$) Mean (SD)	Depression ($n = 19$) Mean (SD)	p (MWU)[1]
Cytokine levels by depression status at baseline ($N = 83$)			
IL-1β[5]	0.8 (0.8)	0.6 (0.03)	0.421 (570)
IL-6	2.5 (3.0)	1.4 (0.6)	0.023 (399)
IL-8	40.2 (12.0)	34.1 (10.9)	0.029 (406)
TNF-α[5]	0.7 (0.4)	0.6 (0)	0.017 (456)
Cytokine levels by depression status at any follow-up excluding depression at baseline ($N = 50$)			
	No depression at any follow-up ($n = 41$) Mean (SD)	Depression at any follow-up ($n = 9$) Mean (SD)	p (MWU)[2]
L-1β	0.8 (1.0)	0.6 (0.1)	0.862 (177)
IL-6	2.9 (3.6)	1.4 (0.7)	0.030 (99)
IL-8	40.2 (11.6)	33.4 (4.8)	0.168 (129)
TNF-α	0.8 (0.5)	0.7 (0.3)	0.882 (179)
Cytokine levels by depression status at any examination[3] ($N = 83$)			
	No depression at any examination ($n = 55$) Mean (SD)	Depression at any examination (n = 28) Mean (SD)	p (MWU)[4]
IL-1β	0.8 (0.9)	0.6 (0.05)	0.535 (737)
IL-6	2.6 (3.2)	1.4 (0.6)	0.002 (456)
IL-8	41.3 (12.4)	33.9 (9.3)	0.008 (493)
TNF-α	0.7 (0.4)	0.6 (0.2)	0.050 (630)

[1] Mann Whitney U-test between women with and without depression at baseline.
[2] Mann Whitney U-test between women with and without depression at any follow-up for the subgroup of women without depression at baseline.
[3] Women were examined in 1992, 2000, 2005 and 2009.
[4] Mann Whitney U-test between women with depression at any examination vs those with no depression at any examination.
[5] Regarding IL-1β (75 measurements) and TNF-α (71 measurements) were below the detection limit.

of the 64 women in the subgroup with no depression at baseline fulfilling the criteria for depression at one or more of the follow-up examinations. Seven women without depression at baseline were diagnosed with depression in 2000 (one woman with major depression and six with minor depression), and there were two new cases of major depression in 2009. There was no age difference between women who developed depression at any follow-up examination (mean age at baseline 71.9 years SD 2.1) and those who did not (mean age 72.7 years SD 3.1, $p = 0.394$).

For women with no depression at baseline ($n = 64$), lower CSF IL-6 levels predicted depression at any follow-up examination ($p = 0.046$, OR 0.558 CI [0.315–0.990]). It could be argued that some of the symptoms included in the depression algorithms (fatigue or loss of energy, loss of appetite) could be caused by an underlying somatic condition that could affect cytokine levels. Omitting these items, however, did not change the cases classified as having at least a minor depression at any follow-up exam. Hence, the association between baseline CSF-IL-6 level and future depression was unaffected. No significant correlations were found between baseline CSF cytokine levels and MADRS scores at the follow-up examinations (results not shown).

Twenty-four women developed dementia at some point during the follow-up period. No significant differences could be shown regarding baseline levels of CSF IL-6 ($p = 0.892$), IL-8 ($p = 0.218$) and TNF-α ($p = 0.261$) between those who did and did not develop dementia.

A final set of binary logistic regression models tested the association of CSF cytokine levels on an outcome of depression at any of the four study waves, adjusting for age, smoking status and Body-Mass- Index. A total of 28 women fulfilled criteria for major or minor depression at any examination. Lower baseline levels of IL-6 ($p = 0.008$ OR 0.292 CI [0.117–0.729]) and IL-8 ($p = 0.008$ OR 0.292 CI [0.117–0.729]) were related to depression (Table 2). CSF- TNF-α was not associated with depression in the regression model ($p = 0.161$ OR 0.143 CI [0.009–2.172]).

Results from the GLMM using all baseline and follow-up data on depression status and MMSE score showed a significant relationship between IL-6 and depression ($p = 0.005$ OR 0.370 CI [0.184–0.744]. GLMMs were not significant for IL-8, TNF-α and IL-1b ($p = 0.102$) ($p = 0.110$), ($p = 0.089$). All GLMMs were rerun after exclusion of women with depression at baseline. Both IL-6 (IL-6, $p = 0.047$ OR 0.426 CI [0.184–0.988]) and IL-8 (IL-8, $p = 0.003$ OR 0.905 CI [0.847–0.967]) were significantly associated with depression at any follow-up examination. MMSE score was not a significant factor.

4. Discussion

To our knowledge, this is the first prospective population-based study to demonstrate an association between CSF IL-6 and later depression during a follow-up time of nearly two decades. Contrary to our hypothesis, *lower* levels of CSF IL-6 were associated with both current and future depression in this population-based sample of older women.

One reason for the unexpected results might be that we are dealing with an older population. Our cross-sectional finding parallels reports from two clinical studies involving geriatric/middle-aged inpatients (Levine et al., 1999; Stubner et al., 1999). There is evidence that inflammation within the brain increases with age (Norden and Godbout, 2013) and it is possible that age affects the association between CSF cytokines and depression. The effect of gender also needs to be clarified. The current study involved women only and single-gender CSF studies are lacking for comparison. It is clear, however that hormonal changes throughout the female life have impact on inflammation levels (O'Connor, 2009). In a recent clinical study examining plasma IL-6, levels were elevated in men during current depression, but not in women (Vogelzangs et al., 2012).

We could show no relationship between CSF IL-6 levels and MADRS score. While this might reflect low study power, another interpretation could be that lower CSF IL-6 might constitute a marker of increased depression *vulnerability* in older women in the general population, rather than a marker of depression severity. It must be remembered that this is a population-based study and previous community-derived studies suggest that low symptom load may reduce the influence of depression on peripheral cytokine concentrations (Whooley et al., 2007; Howren et al., 2009). It is not clear if this applies to CSF cytokines as well. There is one clinical study showing a strong *positive* correlation with depression score (Lindqvist et al., 2009). That study focused on younger persons (mean age 39 years) who were hospitalized in connection with a suicide attempt. CSF studies on that patient group may be confounded by factors related to the method used for suicide attempt, such as high intake of drugs and/or alcohol, or ischemia during unconsciousness, which may activate an acute-phase response with cytokine release, which is not related to depression.

While an association between CSF IL-1β levels and depression has been reported in a clinical sample with acute depression (mean age 56 years) (Levine et al., 1999), we could not show such a relationship. One reason for this might be that CSF IL-1β levels were below the detection limit for many participants. However, we used a conservative estimate for concentrations below the detectable limit.

Our finding regarding lower levels of CSF TNF-α in those with depression is in contrast to one previous report of higher CSF TNF-α levels (Martinez et al., 2011). The large proportion of women with levels under the detection limit in our population-based study makes it difficult to draw conclusions. As participants were recruited from the population, few had the depression symptom burden of the magnitude that would be seen in clinical settings.

It is important to stress that the mean age of the participants in our study was higher than in previous CSF studies. Results from this survival sample are not directly comparable to younger cohorts. Aging-related neurodegeneration may influence results. CSF biomarkers may be altered already 5–10 years before dementia onset (Buchhave et al., 2012). Depression can be an early sign in Alzheimer's disease (AD), preceding cognitive symptoms by many years (Rapp et al., 2011). Further, inflammation and IL-6 is involved in the neurodegenerative cascade leading to AD (Blum-Degen et al., 1995; Tarkowski et al., 2003). In the current study we could not show an association between baseline CSF cytokine levels and future dementia. Further, results of the GLMM showed that cognitive performance was not a confounder in the observed association between IL-6 and depression.

Our study involves CSF cytokines and we can make no conclusions regarding peripheral cytokines. No correlation was seen between serum levels and CSF levels in the above-cited study that focused on suicide attempters (Lindqvist et al., 2009). Another study found a positive correlation between CSF IL-1β levels in depressed patients and serum TNF-α, whereas no other correlations could be seen (Levine et al., 1999). In Interferon –alpha treated hepatitis patients CSF levels of IL-6 exhibited significant elevations in CSF IL-6, despite no increase in plasma IL-6 (Raison et al., 2009). CSF cytokine levels in relation to serum levels have also been investigated in AD. Patients with AD had higher TNF-α level in the cerebrospinal fluid than in serum and no correlation was found between TNF-α and albumin CSF/serum ratios (Tarkowski et al., 1999).

There are a few prospective studies examining a possible association between peripheral proinflammatory cytokines and future depression; findings are mixed (Kiecolt-Glaser et al., 2003; Gimeno

et al., 2009; Stewart et al., 2009; Duivis et al., 2011; Baune et al., 2012). The pathways by which peripheral cytokine signals reach the brain are not fully understood. Cytokines are relatively large molecules that do not freely pass through the blood–brain-barrier (Banks et al., 1994; Maier and Watkins, 1998; Dunn, 2006). However, several hypotheses have been put forth to explain the relationship between peripheral and central immune regulations (Kronfol and Remick, 2000; Dunn, 2006; Raison et al., 2009), one stating that cytokines can be secreted de novo in the brain by microglia, astrocytes and under some circumstances by neurons (Beumer et al., 2012). Microglia is pivotal in immune surveillance and also facilitate the coordinated responses between the immune system and the brain (Norden and Godbout, 2013). Under normal conditions, microglia interpret and propagate inflammatory signals. Models of the aging brain show increased proinflammatory cytokines in the brain and increased expression of inflammatory receptors (Dilger and Johnson, 2008; Norden and Godbout, 2013), a condition refered to as "priming". The role of microglial priming in the development of depression in later life remains to be clarified (Banks et al., 1994; Beumer et al., 2012; Norden and Godbout, 2013).

4.1. Strengths and weaknesses of the study

Among the strengths of this study are the population-based sample, the comprehensive examinations and the prospective design with repeated follow-ups over nearly 20 years. The women were well-characterized, enabling us to take into consideration possible confounders including antidepressant treatment, BMI and smoking (O'Connor, 2009).

Some methodological considerations need to be addressed. First, samples were stored at −80 °C for a very long time before analysis and the long-term stability of the analytes is unknown. However, all samples were treated in the same manner. The temperature chain was unbroken for the analyzed aliquots and the interleukin concentrations were similar to those previously reported in a clinical study that used the same technique (Lindqvist et al., 2009). Despite this, changes in cytokine-levels after long-term storage might have occurred, but this would have diminished the chances to find statistically significant differences between women with and without depression. All this minimizes the risk that sample storage would have influenced the results. Secondly, depression was broadly defined in this study. The small number of women with major depression constitutes a major weakness. While the number of participants with CSF data is relatively large compared to previous studies, the number of cases with major depression was limited due to the population-based study design. This necessitated the merging of major and minor depression cases for the analyses. We note, however that the mean CSF IL-6 levels in depressed participants in the current study were similar to those shown in clinical studies (Stubner et al., 1999; Carpenter et al., 2004). Thirdly, affective psychopathology was assessed at four time points only. Some of the women may have had depressive episodes prior to baseline, and others may have had periods of major or minor depression between examination waves. Fourthly, CSF IL-1β levels and TNF-α levels were below the detection limit for many participants, which are also related to our use of a population-based sample. Fifthly, lumbar punctures were performed at baseline only, and we could thus not test for change in CSF cytokines over time. Sixthly, while we were unable to show differences between women with and without lumbar puncture regarding a number of health-related factors, including cognitive functioning and personality traits, women who took part in this examination may have been healthier, which might limit generalizability to the underlying population. However, this type of selection bias would be expected to decrease the likelihood of significant findings. Finally, this is a population study focusing on women aged 70–84 years at baseline and results cannot be extrapolated to clinical samples or to younger/male populations.

In conclusion, lower levels of CSF IL-6 were associated with both current and future depression in this population-based sample of older women, suggesting that lower CSF IL-6 is related to increased depression vulnerability in this age group. Findings indicate a role for proinflammatory cytokines in late-life depression, but possible pathogenic mechanisms require further clarification.

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