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Research Article

Association Between Plasma Monocyte Trafficking-Related Molecules and Future Risk of Depression in Older Adults

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Abstract

Background: The recruitment of monocytes to the brain plays an important role in the development of depression. However, the association between plasma biomarkers of monocyte trafficking and depression is unclear. This study is aimed to examine the effects of plasma monocyte chemoattractant protein 1 (MCP-1), intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1) on the risk of depression.

Methods: Data were acquired from an ongoing prospective cohort study involving randomly sampled, community-dwelling Korean older adults, which has been followed every 2 years. We included 1539 euthymic older adults (age = 68.2 [5.6] years; 51.7% were women) without a history of major psychiatric disorders and dementia and neurological diseases. Geriatric psychiatrists diagnosed incident depression through a structured interview using the Korean version of the Mini-International Neuropsychiatric Interview.

Results: Depression had developed in 134 (8.7%) participants during the follow-up period of 5.7 (0.8) years. The high-plasma MCP-1 tertile group showed twofold higher risk of depression than the low-plasma MCP-1 tertile group (hazards ratio = 2.00, 95% confidence interval = 1.27–3.13, p = .003). The association between high levels of plasma MCP-1 and future risk of depression was significant in the middle-plasma ICAM-1 and VCAM-1 tertile groups; the high-plasma MCP-1 tertile group showed about fourfold higher risk of depression than the low-plasma MCP-1 tertile group.

Conclusions: Molecules involved in monocyte trafficking may be good candidates as diagnostic biomarkers and/or therapeutic targets for late-life depression.

Keywords: Cell adhesion molecules, Late-life depression, Monocyte chemoattractant protein, Neuroinflammation, Prospective cohort study

Inflammation is an important contributor to the pathophysiology of depression (1). Recently, trafficking of monocytes from peripheral blood to the brain has been found to be a key mechanism of neuroinflammation leading to depression (2). The monocyte chemoattractant protein 1 (MCP-1), a chemokine released by the activated microglia, may play a key role in monocyte trafficking to the brain that could lead to excitotoxic neuronal injury inducing depression (3). In animal models, repeated social defeat, a psychosocial stressor causing depression, increased the number of peripheral and brain monocytes, activated microglia, and upregulated *MCP-1* gene expression in the amygdala, hippocampus, and prefrontal cortex (4,5). In humans, there were 4 case–control studies on the association between MCP-1 and depression. In a postmortem case–control study, middle-aged depressive patients who died by suicide had more activated microglia and higher *MCP-1* gene expression in the dorsal anterior cingulate cortex than euthymic controls (6). However, middle-aged patients with major depressive disorder showed comparable levels of circulating MCP-1 as euthymic controls in 2 case–control studies (7,8) and even lower plasma MCP-1 than the euthymic controls in 1 case–control study (9).

Monocyte trafficking by MCP-1 produced by activated microglia may be facilitated by the process of monocyte extravasation through the blood–brain barrier (BBB) by a dynamic interaction between endothelial cells and the microglia (10). Cell adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) are crucial mediators of the extravasation of monocytes. Under proinflammatory conditions, endothelial cells express these molecules that impair the BBB integrity and promote monocyte adherence to endothelial cells for migrating into the brain vasculature or parenchyma (3,11,12). In animal models, repeated social defeat increased *ICAM-1* and *VCAM-1* gene expression in the amygdala, paraventricular nucleus, and prefrontal cortex (13). However, it remains unknown whether plasma cell adhesion molecules may change the risk of depression independently or interactively with plasma MCP-1 in humans. One prospective cohort study (14) and 6 case–control studies involved humans (15–20). In the Sydney Memory and Aging Study involving 1037 community-dwelling older adults, plasma VCAM-1 level was not associated with the 2-year risk of depression (14). However, among the 6 case–control studies, 4 found that plasma VCAM-1 and/or ICAM-1 levels were not associated with the risks of prevalent depression in older adults (17–20), while the other 2 found that rather high levels of circulating ICAM-1 and/or VCAM-1 were associated with the risk of prevalent depression in older adults (15,16). Furthermore, none of the previous studies investigated the effects of plasma MCP-1 and cell adhesion molecules on the risk of depression simultaneously. If the microglia-driven monocyte trafficking to the brain by MCP-1 is promoted and completed by the monocyte extravasation by cell adhesion molecules produced by brain microvascular endothelial cells, the association between plasma MCP-1 and the risk of depression could be dependent on the levels of plasma cell adhesion molecules.

To better understand the association between the monocyte trafficking-related molecules and the risk of depression, the longitudinal data from older adults who underwent consecutive diagnostic interviews may be useful as aging causes a chronic proinflammatory state with activated microglia and related cytokines (21). This population-based prospective cohort study involving randomly sampled community-dwelling older adults aimed to determine whether the levels of plasma MCP-1 influence the risk of depression and whether the effect of plasma MCP-1 on the future risk of depression is influenced by plasma ICAM-1 and/or VCAM-1. We hypothesized that the high-plasma MCP-1 increases the risk of depression only when the levels of cell adhesion molecules are not low.

Method

Study Design, Setting, and Participants

We acquired data from the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD) (22). The KLOSCAD is an ongoing, nationwide, multicentered, prospective cohort study involving 6818 community-dwelling Koreans aged 60 years or older randomly sampled from among the residents of 13 districts across South Korea using the national residential roster at the end of 2009. The baseline assessment was conducted from November 2010 to October 2012, and follow-up assessments have been conducted every 2 years (the first follow-up assessment was from November 2012 to October 2014, the second from November 2014 to October 2016, and the third from November 2016 to October 2018). Among the 3024 participants who responded to all follow-up assessments, we included 1539 participants who were euthymic at the baseline assessment in the current analysis after excluding participants for the following conditions: mood disorder (n = 341), Geriatric Depression Scale score of 16 points or above (n = 331) (23), antidepressant use (n = 33), dementia (n = 53), other neurological or major psychiatric disorders (n = 37), history of major psychiatric disorder (n = 224), and absence of laboratory test results (n = 466). Supplementary Table 1 summarizes our comparison of the baseline characteristics between analytic samples and those who had no laboratory test results.

This study was approved by the Institutional Review Board of the Seoul National University Bundang Hospital (B-0912-089-010). All participants were fully informed about the study protocol and provided written informed consent.

Assessment of Depression

Geriatric psychiatrists carried out face-to-face standardized diagnostic interviews using the Korean version of the Mini-International Neuropsychiatric Interview (24) at the baseline and each follow-up assessment. Incident depression was confirmed when a participant was diagnosed with depression, major or minor depressive disorder, or subsyndromal depression in the follow-up period. Major and minor depressive disorders were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria, and subsyndromal depression was diagnosed according to operational criteria described elsewhere (25). The self-reported onset of incident depression was also assessed by diagnostic interview.

Assessments of Plasma Biomarkers

Blood samples were collected into ethylenediaminetetraacetic acid tubes after overnight fasting at the baseline assessment. All the plasma samples were centrifuged, separated into aliquots, and stored at −70°C. Plasma concentrations of MCP-1, soluble ICAM-1, and soluble VCAM-1 were measured by using commercially available quantitative sandwich enzyme immunoassay kits (Quantikine Human CCL2/MCP-1 Immunoassay, Quantikine Human ICAM-1/CD54 Non-Allele-specific Immunoassay, and Quantikine Human VCAM-1/CD106 Immunoassay; R&D Systems, Inc., Minneapolis, MN). The intraassay and interassay coefficients were 4.9% and 4.6% for MCP-1, 4.9% and 6.3% for ICAM-1, and 3.6% and 5.5% for VCAM-1, respectively.

Assessments of Covariates

Geriatric psychiatrists carried out face-to-face standardized diagnostic interviews and neurological and physical examinations using the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet Clinical Assessment Battery (26). The possible confounders, such as cardiovascular risk factors, comorbidities, and psychosocial stress, which could affect both proinflammatory changes and the risk of depression were selected as covariates (21). Trained research nurses assessed the level of social support using the Medical Outcome Study Social Support Survey (27), the level of exercise by calculating the metabolic equivalent task (28), and the burden of comorbidities using the Cumulative Illness Rating Scale (29) at the baseline assessment. Poor social support was defined as a Medical Outcome Study Social Support Survey score of less than the 25th percentile, and low exercise level was defined as engaging in exercise for less than 600 minutes/week (27,28). They also assessed the history of atherosclerotic cardiovascular disease including coronary artery diseases, stroke, transient ischemic attack, coronary or other arterial revascularization, peripheral vascular diseases, and aortic aneurysm. The blood pressure and body mass index were measured. Baseline serum concentrations of total and high-density lipoprotein (HDL) cholesterol levels were also measured, and the estimated glomerular filtration rate was calculated using the level of serum creatinine.

Statistical Analysis

We compared the baseline characteristics according to the level of MCP-1 using Pearson's chi-square tests and analysis of variance. As the plasma concentrations of ICAM-1 and VCAM-1 were positively skewed, the mean concentrations of those cell adhesion molecules were compared after log transformation.

To examine the effect of plasma MCP-1 level on the risk of incident depression, we performed Cox proportional hazard analyses after adjusting for age, sex, social support, alcohol consumption, smoking, exercise, body mass index, systolic blood pressure, cholesterol levels (total, HDL), estimated glomerular filtration rate, history of atherosclerotic cardiovascular disease, and comorbidities. In addition, we performed Cox proportional hazard analyses adjusting for plasma ICAM-1 and VCAM-1. To examine the association between plasma MCP-1 and the risk of incident depression by the levels of plasma ICAM-1 and VCAM-1, we performed Cox proportional hazard analyses computing plasma MCP-1 (low tertile and middle-to-high tertile), plasma ICAM-1 or VCAM-1 (low tertile, middle tertile, and high tertile), and their interaction as independent variables. Then, we stratified the subjects into tertile groups using plasma ICAM-1 and VCAM-1 levels, and we examined the effect of plasma MCP-1 level on the risk of incident depression in each group using Cox proportional hazard analyses after adjusting for age, sex, social support, alcohol consumption, smoking, exercise, body mass index, systolic blood pressure, cholesterols (total, HDL), estimated glomerular filtration rate, history of atherosclerotic cardiovascular disease, and comorbidities. The survival time based on subject-specific interview date was used for each Cox proportional hazard analysis.

SPSS Statistics 19.0 software (IBM Corporation) was used for all statistical analyses.

Results

As summarized in Table 1, the high MCP-1 group showed higher systolic blood pressure (p = .010) but lower high-density lipoprotein cholesterol (p = .038) and estimated glomerular filtration rate (p = .011) than the low MCP-1 group. The high MCP-1 group showed higher plasma VCAM-1 levels than the low MCP-1 group (p = .006) but comparable plasma ICAM-1 levels to the low MCP-1 group (p = .003). The relationships between the levels of plasma MCP-1 level and plasma cell adhesion molecules were shown in Supplementary Figure 1.

During the follow-up period (mean = 5.7 years, standard deviation = 0.8 years), depression developed in 134 out of 1539 participants (8.7%). Incident depression was observed in 10.5% of the high MCP-1 group, 9.2% of the middle MCP-1 group, and 6.4% of the low MCP-1 group. In the Cox proportional hazard analysis after adjusting for age, sex, social support, alcohol consumption, smoking, exercise, body mass index, systolic blood pressure, cholesterol levels (total, HDL), estimated glomerular filtration rate, history of atherosclerotic cardiovascular disease, and comorbidities, the high MCP-1 group showed about twofold higher risk of incident depression than the low MCP-1 group (hazard ratio [HR] = 2.07, 95% confidence interval [CI] = 1.32–3.25, p = .001), which remained significant when plasma ICAM-1 and VCAM-1 levels were additionally adjusted (HR = 2.00, 95% CI = 1.27–3.13, p = .003; Table 2).

When we analyzed subsyndromal and syndromal depression (major and minor depressive disorders) separately, incident syndromal depression was reported in 2.3% of the high MCP-1 group, 1.6% of the middle MCP-1 group, and 1.2% of the low MCP-1 group. In the Cox proportional hazard analysis after adjusting for age, sex, social support, alcohol consumption, smoking, exercise, body mass index, systolic blood pressure, cholesterol levels (total, HDL), estimated glomerular filtration rate, history of atherosclerotic cardiovascular disease, and comorbidities, the high MCP-1 group showed about threefold higher risk of incident syndromal depression than the low MCP-1 group (HR = 3.17, 95% CI = 1.08–9.24, p = .035), which remained significant when plasma ICAM-1 and VCAM-1 levels were additionally adjusted for (HR = 3.14, 95% CI = 1.07–9.28, p = .038; Table 2). Incident subsyndromal depression was reported in 8.2% of the high MCP-1 group, 7.6% of the middle MCP-1 group, and 5.3% of the low MCP-1 group. In the adjusted Cox proportional hazard analysis, the high MCP-1 group showed about twofold higher risk of incident subsyndromal depression than the low MCP-1 group (HR = 1.89, 95% CI = 1.15–3.10, p = .012), which remained significant when plasma ICAM-1 and VCAM-1 levels were additionally adjusted for (HR = 1.81, 95% CI = 1.10–2.98, p = .019; Table 2). The interaction between the middle-to-high tertile of plasma MCP-1 level and the middle tertile of plasma ICAM-1 level was

Table 1. Baseline Characteristics by the Level of Plasma MCP-1*

	Low MCP-1[a] (*n* = 513)	Middle MCP-1[b] (*n* = 513)	High MCP-1[c] (*n* = 513)	Statistics**	
				p	*post hoc*
Age, years, mean (*SD*)	67.8 (5.3)	68.4 (5.6)	68.4 (5.7)	.120	—
Women, *n* (%)	259 (50.5)	270 (52.6)	267 (52.0)	.777	—
Poor social support, *n* (%)†	74 (14.5)	75 (14.6)	85 (16.6)	.582	—
Current drinking, *n* (%)‡	70 (14.1)	69 (13.5)	71 (13.9)	.956	—
Current smoking, *n* (%)	56 (10.9)	47 (9.2)	55 (10.7)	.598	—
Low exercise, *n* (%)§	229 (45.1)	199 (39.1)	209 (41.0)	.141	—
Systolic BP, mmHg, mean (*SD*)	124.9 (14.6)	126.0 (14.4)	127.6 (14.5)	.013	a < c
BMI, kg/m², mean (*SD*)	24.0 (3.1)	24.1 (3.0)	24.4 (3.4)	.071	—
Total cholesterol, mg/dL, mean (*SD*)	188.1 (34.0)	189.3 (35.0)	190.9 (35.3)	.436	—
HDL cholesterol, mg/dL, mean (*SD*)	50.4 (12.7)	49.7 (12.6)	48.5 (11.2)	.040	a > c
eGFR, mL/min, mean (*SD*)	70.3 (10.9)	69.1 (12.8)	68.2 (11.1)	.014	a > c
CIRS total scores, mean (*SD*)	4.0 (2.7)	4.1 (2.7)	4.1 (2.6)	.843	—
History of ASCVD, *n* (%)	66 (12.9)	62 (12.1)	47 (9.2)	.144	—
ICAM-1, ng/mL, mean (*SD*)	304.0 (65.5)	299.0 (63.3)	312.6 (71.2)	.004¶	b < c
VCAM-1, ng/mL, mean (*SD*)	695.3 (191.7)	707.7 (193.7)	735.3 (218.3)	.007¶	a < c

Note: SD = standard deviation; BP = blood pressure; BMI = body mass index; HDL = high-density lipoprotein; eGFR = estimated glomerular filtration rate; CIRS = Cumulative Illness Rating Scale; ASCVD = atherosclerotic cardiovascular diseases; MCP-1 = monocyte chemoattractant protein 1; ICAM-1 = intercellular adhesion molecule 1; VCAM-1 = vascular cell adhesion molecule 1.

*Low tertile, <152.99 pg/mL; middle tertile, 152.99–216.67 pg/mL; high tertile, ≥216.67 pg/mL.

**Comparisons between groups using Chi-squared test for categorical variables and analysis of variance for continuous variables.

†Medical Outcomes Study Social Support Survey scores under 25 percentiles.

‡Drinking above 7 standard units per week within the past 1 year.

§Under 600 metabolic equivalent task minutes per week.

¶Log-transformed mean values were compared between groups.

Table 2. Association Between the Level of Plasma Monocyte Chemoattractant Protein-1 (MCP-1) and the Risk of Incident Depression*

	Low MCP-1*	Middle MCP-1*	High MCP-1*
Depression†			
Incident cases	33/513	47/513	54/513
Unadjusted model‡	Reference	1.53 (0.97–2.42)	**1.88 (1.21–2.93)**
Adjusted model 1§	Reference	1.56 (0.98–2.46)	**2.07 (1.32–3.25)**
Adjusted model 2¶	Reference	1.52 (0.96–2.40)	**2.00 (1.27–3.13)**
Subsyndromal depression††			
Incident cases	27/513	39/513	42/513
Unadjusted model‡	Reference	1.52 (0.92–2.50)	**1.72 (1.05–2.82)**
Adjusted model 1§	Reference	1.53 (0.92–2.52)	**1.89 (1.15–3.10)**
Adjusted model 2¶	Reference	1.50 (0.91–2.48)	**1.81 (1.10–2.98)**
Syndromal depression§§			
Incident cases	6/513	8/513	12/513
Unadjusted model‡	Reference	1.60 (0.52–4.92)	2.71 (0.95–7.70)
Adjusted model 1§	Reference	1.83 (0.58–5.75)	**3.17 (1.08–9.24)**
Adjusted model 2¶	Reference	1.72 (0.54–5.48)	**3.14 (1.07–9.28)**

*MCP-1 of below 152.99 pg/mL in the low tertile group, MCP-1 between 152.99 and 216.67 pg/mL in the middle tertile group, MCP-1 of 216.67 pg/mL or higher in the high tertile group; bold values for $p < .05$.

†Major depressive disorder, minor depressive disorder, or subsyndromal depression.

‡Hazard ratio with 95% confidence intervals in the parenthesis estimated by Cox proportional hazard analysis.

§Adjusted for age, sex, social support, alcohol consumption, smoking, exercise, body mass index, systolic blood pressure, cholesterol (total, HDL), estimated glomerular filtration rate, history of atherosclerotic cardiovascular disease, and comorbidities

¶Adjusted for the same covariates with model 1 and the levels of intercellular adhesion molecule 1 and vascular cell adhesion molecule 1.

††Diagnosed by the operational diagnostic criteria as follows: (a) the occurrence of 2 or more symptoms of depression within the same 2-week period listed in criterion A for a major depressive episode in the DSM-IV; (b) the presence of at least a depressed mood or anhedonia; (c) each depressive symptom should be present for more than half a day or more than 7 days during the 2-week period; (d) participants must not fulfill the criteria for the diagnosis of major or minor depressive disorders; (e) the symptoms must not be due to the direct physiological effects of a substance or a general medical condition; (f) the symptoms must not be attributable to bereavement, dementia, or schizophrenia and other psychotic disorders; and (g) there should not be a history of the occurrence of a manic or hypomanic episode.

§§Major depressive disorder or minor depressive disorder.

Table 3. Association Between the Level of Plasma MCP-1 and the Risk of Incident Depression Stratified by the Levels of Cell Adhesion Molecules*

	Low MCP-1	Middle-to-high MCP-1		
		All	Middle MCP-1	High MCP-1
ICAM-1				
Low tertile				
Incident cases	13/178	26/334	12/176	14/158
Adjusted HR (95% CI)†	Reference	1.13 (0.57–2.25)	0.84 (0.37–1.91)	1.57 (0.71–3.44)
p	—	.729	.668	.265
Middle tertile				
Incident cases	7/165	41/348	20/183	21/165
Adjusted HR (95% CI)†	Reference	**3.24 (1.44–7.28)**	**2.73 (1.14–6.51)**	**3.96 (1.66–9.44)**
p	—	**.004**	**.024**	**.002**
High tertile				
Incident cases	13/170	34/343	15/154	19/189
Adjusted HR (95% CI)†	Reference	1.58 (0.79–3.16)	1.36 (0.61–3.05)	1.80 (0.84–3.86)
p	—	.199	.455	.133
VCAM-1				
Low tertile				
Incident cases	12/189	21/324	11/170	10/154
Adjusted HR (95% CI)†	Reference	1.45 (0.68–3.11)	1.31 (0.55–3.12)	1.64 (0.67–4.03)
p	—	.342	.536	.282
Middle tertile				
Incident cases	7/163	39/340	17/183	22/157
Adjusted HR (95% CI)†	Reference	**2.80 (1.24–6.37)**	1.98 (0.80–4.92)	**3.97 (1.66–9.51)**
p	—	**.014**	.140	**.002**
High tertile				
Incident cases	14/161	41/352	19/160	22/192
Adjusted HR (95% CI)†	Reference	1.44 (0.77–2.70)	1.45 (0.71–2.94)	1.43 (0.71–2.87)
p	—	.259	.309	.316

Note: HR = hazard ratio; CI = confidence interval; MCP-1 = monocyte chemoattractant protein 1; ICAM-1 = intercellular adhesion molecule 1; VCAM-1 = vascular cell adhesion molecule 1.

*Low MCP-1, <152.99 pg/mL; middle MCP-1, 152.99–216.67 pg/mL; high MCP-1, ≥216.67 pg/mL; low ICAM-1, <273.48 ng/mL; middle ICAM-1, 273.48–324.33 ng/mL; high ICAM-1, ≥324.33 ng/mL; low VCAM-1, <609.95 ng/mL; middle VCAM-1, 609.95–761.6 ng/mL; high VCAM-1, ≥761.6 ng/mL; bold values for $p < .05$.

†Cox proportional hazard analyses adjusted for age, sex, social support, alcohol consumption, smoking, exercise, body mass index, systolic blood pressure, cholesterol (total, HDL), estimated glomerular filtration rate, history of atherosclerotic cardiovascular disease, and comorbidities.

statistically significant (HR = 2.94, 95% CI = 1.03–8.41, $p = .045$) but that between the middle-to-high tertile of plasma MCP-1 level and the high tertile of plasma ICAM-1 level was not (HR = 1.58, 95% CI = 0.61–4.10, $p = .349$). The interactions between the middle-to-high tertile of plasma MCP-1 and the middle or high tertiles of plasma VCAM-1 level were not statistically significant (HR = 2.03, 95% CI = 0.68–6.06, $p = .203$ for the middle tertile of plasma VCAM-1 level; HR = 1.12, 95% CI = 0.43–2.93, $p = .823$ for the high tertile of plasma VCAM-1 level).

Then, we stratified the participants into tertile groups using plasma ICAM-1 and VCAM-1 levels (Table 3). The middle-to-high MCP-1 group showed about threefold higher risk of incident depression than the low MCP-1 group in the participants whose plasma ICAM-1 levels were in the middle tertile. When we analyzed the middle and high MCP-1 tertile groups separately, the high MCP-1 group showed about fourfold higher risk of incident depression than the low MCP-1 group in the participants whose plasma ICAM-1 were in the middle tertile. Although the interactions between the middle-to-high tertile of plasma MCP-1 and the middle or high tertiles of plasma VCAM-1 level were not statistically significant, the high MCP-1 group showed about fourfold higher risk of incident depression than the low MCP-1 group in the participants whose plasma VCAM-1 were in the middle tertile. Among the participants whose plasma ICAM-1 levels were in the middle tertile, the middle MCP-1 group also showed about threefold higher risk of incident depression than the low MCP-1 group. However, among the participants whose plasma ICAM-1 and VCAM-1 levels were in the low or high tertiles, the high MCP-1 group showed a comparable risk of incident depression as the low MCP-1 group.

Discussion

To the best of our knowledge, this is the first prospective study on the association between the biomarkers of monocyte trafficking and the future risk of depression. In this study, older adults with higher plasma MCP-1 showed a high future risk of depression only when their plasma ICAM-1 and VCAM-1 levels were moderate.

In a postmortem study, depressive patients who died by suicide showed higher *MCP-1* gene expression, higher number of activated microglia, and higher recruitment of monocytes in the dorsal anterior cingulate cortex than euthymic controls (6). Along with other proinflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α, MCP-1 released from activated microglia

is taken up by activated endothelium, transcytosed in caveolae, and released into peripheral blood (30,31). Circulating MCP-1 binds to chemokine receptor-2 (CCR2) of peripheral monocytes. The monocytes then migrate to the BBB following a chemokine gradient and transmigrate via the BBB by the mediation of cell adhesion molecules (10,30). The monocytes recruited into the brain secrete proinflammatory cytokines such as IL-1β, TNF-α, and interferon-γ, which may induce excitotoxic injury to neurons and decreased serotonergic tone (3,32,33). MCP-1 also binds to the CCR2 of brain microvascular endothelial cells and compromises the integrity of the BBB (34). MCP-1 bound to endothelial cells promotes the phosphorylation of myosin light chain and ezrin/radixin/moesin proteins in the endothelial cells. Phosphorylated myosin light chain and ezrin/radixin/moesin proteins may facilitate the recruitment of monocytes into the brain via the BBB by pulling tight junction proteins away from the cell-to-cell border (34).

In contrast to this study, the previous case–control studies could not find the association of circulating MCP-1 levels with the risk of depression (7–9). This discrepancy may be attributable to the methodological differences between this study and previous studies. First, the study participants in previous studies (39.4–53.7 years) were much younger than those of this study (68.2 ± 5.6 years). The levels of circulating MCP-1 increase with advancing age (35), and the impact of MCP-1 overexpression on the neuroinflammation appears in older age only (36). Therefore, the impact of increased plasma levels of MCP-1 on the risk of depression may be significant only in older adults. Second, all the previous studies were cross-sectional. If plasma levels of MCP-1 increase in the early stage of depression and decrease to normal or even subnormal level in the late stage of depression, the association of this protein with the risk of depression may be different according to the study design. Further studies are warranted to identify the long-term trajectories of plasma levels of MCP-1 associated with depression.

In this study, the effect of high plasma levels of MCP-1 was not significant when the levels of plasma cell adhesion molecules were too low or too high. In addition to microglial activation, a dynamic interaction between monocytes and endothelial cells plays a key role in the process of monocyte trafficking into the brain (10). Peripheral monocytes attracted by circulating MCP-1 could be recruited to the brain by transmigration through endothelial cells of the BBB. The ICAM-1 and VCAM-1 on the surface of endothelial cells of the BBB facilitate the capture, rolling, and adhesion of peripheral monocytes (37). Therefore, when plasma levels of ICAM-1 and/or VCAM-1 are low, the risk of depression may not increase even when plasma levels of MCP-1 are high owing to the low efficiency of monocyte trafficking. However, in this study, high plasma levels of MCP-1 did not increase the risk of depression even when plasma levels of ICAM-1 and/or VCAM-1 were high. It is not clear why this phenomenon is happening at the moment and further research is needed. Furthermore, the moderation effects of VCAM-1 on the association between MCP-1 and depression should be cautiously interpreted, because the results from our interaction analyses were not statistically significant.

Results from this study indicate that pharmacotherapy for decreasing monocyte trafficking may be beneficial for older adults with depression. Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, also known as statins, are known to have antidepressant effects (38). The statins inhibit the release of proinflammatory cytokines from monocytes and reduce CCR2 expression of monocytes and MCP-1-mediated monocyte recruitment (39,40). In middle-aged adults with coronary heart diseases or with risk factors for coronary heart diseases, statins reduce the levels of circulating MCP-1 as well as of cell adhesion molecules (41). Our findings suggest that the antidepressant effects of statins may be, at least in part, attributable to the inhibition of monocyte trafficking by statins. Clinical trials on the antidepressant effect of statins may be needed particularly in the older depressive adults with high plasma levels of MCP-1.

We should note several limitations of this study. First, the participants of this study were aged 60 years or older. Therefore, the results of this study may not be generalized to depressive disorders in younger adults. Second, the numbers of sample size and incidence cases of depression were small. Third, the levels of plasma MCP-1, ICAM-1, and VCAM-1 were not evaluated in the follow-up assessments. The effect of their trajectories on the risk of depression should be investigated in future research. Finally, other molecules such as IL-1β, P-selectin, E-selectin, integrins, and matrix metalloproteinases that are also involved in monocyte trafficking and microglial activation (10,42) were not evaluated in this study.

To conclude, this is the first population-based prospective study to demonstrate that plasma MCP-1 is associated with future risk of depression in older adults. Further studies are warranted to identify whether monocyte trafficking could be a potential therapeutic target for late-life depression.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

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