



Short communication

The association between inflammatory markers and general psychological distress symptoms

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ABSTRACT

Objective: This study explored the association between low-grade inflammation measured using multiple common inflammatory markers and general psychological distress symptoms.

Method: A total of 68,463 Korean adults were included. White blood cell counts with differential count, fibrinogen, C-reactive protein (CRP), ferritin and rheumatoid factor were measured. General psychological distress symptoms were assessed using 18 questions of psychosocial well-being index short form (PWI-SF).

Results: Among the eight inflammatory markers measured, WBC count, segmented neutrophil count, monocyte and CRP level were significantly and independently associated with broad psychological symptoms. In contrast, fibrinogen and ferritin showed a weak association with limited number of items. No significant association was detected with lymphocyte and RF.

Conclusion: General psychological distress symptoms were associated with multiple inflammatory markers in Korean adults. The association patterns differed by the types of inflammatory markers. Additional investigation into the relationship between general inflammatory markers and diverse psychological distress symptoms is warranted.

1. Introduction

Substantial evidence supports the association between low-grade inflammation and psychological symptoms [1–3]. However, it is naive to generalize the associations. Few studies evaluated multiple inflammatory markers [4], and most studies primarily focused on individual markers including C-reactive protein (CRP) [5] and ferritin [3]. Limited evidence exists for the role of markers in the overall immune system such as white blood cell counts (WBCs) [1] and immune markers associated with chronic inflammatory disease. Furthermore, most previous studies focused on depression or specific psychological symptoms related to depression. Additional studies are needed to identify the role of low-grade inflammation in a wide range of psychological symptoms. We previously reported the association between CRP [6] and general psychological distress symptoms in Korean adults.

To expand our understanding, we investigated if the general psychological distress symptoms were associated with other inflammatory markers.

2. Materials and methods

The study population comprised 68,463 participants who underwent comprehensive health examination at the Samsung Medical Center in Seoul, South Korea, between January 1, 2010 and December 31, 2016 (Table 1). Participants were voluntarily enrolled in the health check-up program at the Center for Health Promotion, Samsung Medical Center. We excluded any subject who reported cough, sputum, febrile sense and chill to exclude any subject who had infectious disease. The levels of eight inflammatory markers measured using standardized procedures (white blood cell count [WBC count, median,

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Table 1
Demographic characteristics and levels of inflammatory markers of participants.

	Participants (n = 68,463)
Characteristic	
Age (years)	51.53 ± 11.83
Gender (% male)	35,906 (52.45)
Body mass index (kg/m ²)	23.41 ± 3.14
Smoking (%)	
Never smoker	38,167 (58.85)
Former smoker	15,687 (24.19)
Current smoker	10,996 (16.96)
Alcohol drinking (% yes)	44,023 (65.25)
Hypertension (%)	14,831 (21.66)
Diabetes mellitus (%)	5601 (8.18)
Dyslipidemia (%)	13,847 (20.23)
Cerebral infarction (%)	799 (1.17)
Cardiac infarction (%)	802 (1.17)
Thyroid disorder (%)	4473 (6.53)
Cancer (%)	4509 (6.59)
Total score of Psychosocial Wellbeing Index-short form (PWI-SF)	16 (11–22)
Levels of inflammatory markers	
White blood cell count (×10 ⁹ /L)	5.33 (4.50–6.30)
Segmented neutrophil (×10 ⁹ /L)	2.88 (2.28–3.61)
Lymphocyte (×10 ⁹ /L)	1.86 (1.54–2.23)
Monocyte (×10 ⁹ /L)	0.35 (0.28–0.43)
Fibrinogen (mg/dL)	288 (257–323)
C-reactive protein (mg/dL)	0.04 (0.03–0.08)
Ferritin (ng/mL)	94.5 (49.2–165.1)
Rheumatoid factor (IU/mL)	7.5 (6.4–9.4)

Data are presented n (%), mean ± standard deviation or median (25th–75th percentiles).

$5.33 \times 10^9/L$], segmented neutrophil count [$2.88 \times 10^9/L$], lymphocyte count [$1.86 \times 10^9/L$], monocyte count [$0.35 \times 10^9/L$], fibrinogen [288 mg/dL], CRP [0.40 mg/L], ferritin [94.5 ng/mL] and rheumatoid factor [RF, 7.5 IU/mL]) were log-transformed after removing the outliers exceeding ± 4 SDs from the mean value.

General psychological distress symptoms were assessed using the psychosocial well-being index short form (PWI-SF) [7]. The PWI-SF is a self-administered screening instrument with 18 items on a 4-point Likert scale based on Goldberg's general health questionnaire [8] to identify common psychiatry health problems. The PWI-SF showed adequate reliability and validity in the epidemiological studies [7]. Instead of the 4-point Likert scale, we adopted alternative binary method known as the 'GHQ scoring' ('Not at all', and 'No more than usual' as score 0, and 'Rather more than usual' and 'Much more than usual' as score 1) according to previous studies [6,9]. This study was approved by the Institutional Review Board of the Samsung Medical Center. Written informed consent was obtained.

We investigated the relationship of eight inflammatory markers with each of the 18 symptoms, and with a total score (0–54). A multivariable logistic regression analysis of each item and a generalized linear regression analysis with overdispersed Poisson distribution for the total score were conducted. The covariates included age, sex, body mass index, smoking status, alcohol consumption, hypertension, diabetes, dyslipidemia, cerebral infarction, cardiac infarction, thyroid disorder, cancer, and the year blood test was conducted. The statistical significance of the 18 items was corrected with the Holm-Bonferroni method [10].

3. Results (Table 2)

Among the eight inflammatory markers, WBC count was significantly associated with 14 items. Among WBC, segmented neutrophils and monocytes exhibited significant associations with 17 and 14 items, respectively. In contrast, lymphocytes displayed no

association. CRP level was positively associated with 6 items, and ferritin level was positively associated with 2 items. The fibrinogen level was negatively associated with only one item. No significant association was detected between RF and general psychological distress symptoms. In additional analyses with total score, WBC count, segmented neutrophil and monocyte count, and the CRP level exhibited statistically significant positive associations, whereas the fibrinogen level displayed a negative association.

4. Discussion

We focused on 1) low-grade inflammation based on changes in reliable and easily measurable inflammatory markers, and 2) mild psychological distress experienced in the general population. A small effect size of low-grade inflammation is difficult to detect [11]; we have large sample enough to detect the specific effect size with sufficient statistical power. We adjusted for potential covariates including age, sex, body mass index, smoking status, alcohol consumption and medical conditions.

Even mild low-grade inflammation can initiate pro-inflammatory response, which may have impact at the organism and population levels [12]. Recent studies demonstrated the effect of low-grade inflammation on general well-being including longevity, aging and age-related diseases [13].

As the association between inflammatory markers and psychological symptoms in previous studies varied depending on the types of inflammatory markers [14] and psychological symptoms evaluated [15], the pattern of association differed according to the markers. Considering that each inflammatory marker has different biological characteristics, the association might reveal biological underpinnings. Although WBC and differential counts are the most reliable markers for systemic inflammation, they received little attention in studies investigating depression. WBC, segmented neutrophil counts and monocytes in our study were consistently associated with broader spectrum of general psychological distress symptoms even compared to CRP. No sex effect was detected, which was suggested in previous study [1].

In contrast, fibrinogen and ferritin exhibited correlation with a limited numbers of symptoms with opposite direction of association compared to prior reports [2,3]. It is difficult to compare the results directly. Further study is needed to confirm the association. Lymphocyte and RF did not show significant association with any item of the general psychological distress symptoms.

The study findings need to be interpreted in the context of the study design. History of medical illnesses was evaluated using self-report. Although we excluded subjects who reported any clinical sign of infection as well as excluding outliers before the analyses, this may not be enough to exclude all subjects with systematic infectious illnesses. We also could not infer any causal relationship because this was cross-sectional study. Future study with prospective research design is needed.

In conclusion, general psychological distress symptoms were associated with multiple inflammatory markers in Korean adults. A follow-up study to determine the specific mechanisms is needed.

Author contributions

Dr. H Choi had full access to all of the data in the study, and assumes responsibility for the data integrity and the accuracy of data analysis.

Study concept and design: JH Baek, W Myung and H Choi

Acquisition of data: H Choi

Statistical analysis: HW Lee and W Myung

Interpretation of data: All authors

Drafting of the manuscript: JH Baek, HW Lee and W Myung

Study supervision: H Choi

Table 2
The association between eight inflammatory markers and general psychological distress symptoms (GPDS).

Items	Presence of symptom, no. (%)	White blood cell count	Segmented neutrophil	Lymphocyte	Monocyte	Fibrinogen	CRP	Ferritin	RF
		n = 68,291	n = 68,290	n = 68,289	n = 67,849	n = 67,965	n = 54,689	n = 66,617	
Odds ratio (95% CI) ^a									
1. (No) feeling of well-being and health	26,333 (38.5)	1.062 (1.044–1.081)**	1.076 (1.058–1.094)**	0.998 (0.981–1.015)	1.036 (1.018–1.054)**	1.015 (0.997–1.033)	1.057 (1.039–1.076)**	1.035 (1.012–1.059)*	0.993 (0.976–1.010)
2. (Not) feeling refreshed after sleep	18,170 (26.5)	1.056 (1.037–1.077)**	1.049 (1.030–1.069)**	1.023 (1.005–1.042)	1.071 (1.050–1.092)**	0.983 (0.965–1.002)	1.048 (1.028–1.068)**	1.032 (1.007–1.058)	0.993 (0.975–1.012)
3. Fatigue and loss of appetite	2056 (3)	1.129 (1.074–1.187)**	1.126 (1.073–1.182)**	1.018 (0.970–1.068)	1.107 (1.052–1.165)**	0.943 (0.898–0.991)	1.052 (1.002–1.106)	1.011 (0.951–1.075)	0.983 (0.937–1.031)
4. Loss of sleep because of worry	5160 (7.5)	1.065 (1.031–1.099)**	1.058 (1.025–1.091)**	1.026 (0.995–1.059)	1.076 (1.041–1.111)**	0.979 (0.949–1.011)	1.049 (1.016–1.082)*	1.089 (1.044–1.135)**	0.982 (0.953–1.013)
5. (Not) able to concentrate	24,497 (35.8)	1.042 (1.024–1.061)**	1.045 (1.028–1.063)**	1.005 (0.988–1.022)	1.035 (1.017–1.054)**	0.982 (0.965–1.000)	1.021 (1.004–1.039)	1.033 (1.010–1.057)	0.995 (0.979–1.012)
6. (Not) feeling energetic	38,539 (56.3)	1.060 (1.043–1.079)**	1.066 (1.049–1.084)**	1.009 (0.993–1.026)	1.046 (1.028–1.064)**	1.013 (0.996–1.031)	1.050 (1.033–1.068)**	1.014 (0.992–1.037)	0.993 (0.977–1.009)
7. Restless at night	3020 (4.4)	1.087 (1.043–1.133)**	1.071 (1.029–1.115)**	1.037 (0.996–1.079)	1.112 (1.066–1.159)**	0.956 (0.918–0.996)	0.995 (0.955–1.037)	1.059 (1.004–1.116)	1.016 (0.977–1.057)
8. (Not) self-managing as well as most people would	22,913 (33.5)	1.096 (1.076–1.116)**	1.104 (1.085–1.124)**	1.020 (1.002–1.038)	1.051 (1.032–1.071)**	1.012 (0.993–1.030)	1.073 (1.054–1.092)**	1.008 (0.985–1.031)	0.990 (0.973–1.007)
9. (Not) everything is going well	18,969 (27.7)	1.024 (1.005–1.043)	1.040 (1.021–1.059)**	0.984 (0.966–1.002)	1.011 (0.992–1.030)	0.980 (0.962–0.999)	1.016 (0.997–1.035)	0.988 (0.964–1.012)	0.995 (0.977–1.013)
10. (Not) satisfied with performance of tasks	16,816 (24.6)	1.013 (0.993–1.033)	1.026 (1.007–1.046)*	0.985 (0.966–1.004)	0.999 (0.979–1.019)	0.979 (0.960–0.998)	1.012 (0.992–1.032)	1.003 (0.978–1.028)	0.999 (0.980–1.018)
11. (Not) able to start new work	19,008 (27.8)	1.024 (1.005–1.044)	1.041 (1.022–1.060)**	0.981 (0.963–0.999)	1.011 (0.992–1.031)	0.994 (0.976–1.013)	1.023 (1.004–1.042)	0.971 (0.949–0.995)	0.989 (0.971–1.007)
12. (Not) able to enjoy daily life	9107 (13.3)	1.088 (1.062–1.116)**	1.095 (1.068–1.121)**	1.008 (0.984–1.032)	1.053 (1.027–1.080)**	0.973 (0.950–0.998)	1.038 (1.013–1.064)*	1.003 (0.971–1.035)	0.991 (0.968–1.015)
13. Restless and ill-tempered	3542 (5.2)	1.062 (1.022–1.103)*	1.039 (1.001–1.078)	1.043 (1.005–1.082)	1.084 (1.042–1.127)**	1.013 (0.975–1.051)	1.025 (0.987–1.064)	1.004 (0.955–1.054)	0.980 (0.944–1.017)
14. (Not) able to face problems	8115 (11.9)	1.038 (1.012–1.066)*	1.040 (1.014–1.067)**	1.005 (0.980–1.031)	1.027 (1.000–1.055)	0.998 (0.972–1.024)	1.009 (0.983–1.036)	0.968 (0.938–1.000)	0.986 (0.962–1.011)
15. Depressed and unhappy	2982 (4.4)	1.033 (0.992–1.077)	1.037 (0.996–1.079)*	0.981 (0.942–1.021)	1.104 (1.058–1.152)**	0.928 (0.891–0.967)	1.004 (0.963–1.046)	1.032 (0.979–1.087)	0.997 (0.958–1.038)
16. Loss of self-confidence	3577 (5.2)	1.084 (1.043–1.126)**	1.083 (1.044–1.124)**	1.020 (0.983–1.058)	1.091 (1.049–1.134)**	0.985 (0.948–1.022)	1.043 (1.004–1.083)	0.996 (0.949–1.044)	1.023 (0.986–1.060)
17. (Not) feeling happiness	15,788 (23.1)	1.052 (1.032–1.073)**	1.062 (1.042–1.083)**	1.000 (0.908–1.019)	1.033 (1.012–1.054)**	0.980 (0.961–1.000)	1.021 (1.001–1.042)	1.017 (0.991–1.043)	1.005 (0.986–1.024)
18. (Not) feeling that life is worth living	8919 (13)	1.047 (1.021–1.074)**	1.050 (1.025–1.076)**	1.004 (0.980–1.029)	1.045 (1.019–1.072)**	0.961 (0.937–0.985)*	1.018 (0.993–1.043)	0.974 (0.944–1.005)	1.006 (0.982–1.030)
Relative risk (95% CI) ^b		1.015 (1.011–1.019)**	1.018 (1.014–1.022)**	1.000 (0.996–1.004)	1.009 (1.005–1.013)**	0.995 (0.991–0.999)*	1.008 (1.005–1.012)**	1.003 (0.998–1.008)	0.999 (0.995–1.003)
Total score									

Statistical significance for items was calculated after Holm-Bonferroni corrections for 18 items.

***, **, * denote statistical significance at the 0.001, 0.01, and 0.05 levels after Holm-Bonferroni corrections for 18 items, respectively.

The models were adjusted for age, sex, smoking status, alcohol consumption, hypertension, diabetes, dyslipidemia, cerebral infarction, cardiac infarction, thyroid disorder, cancer, and year. The year was included because any yearly event may have affected general psychological distress symptoms.

^a Odds ratios and 95% CI per 1-standard deviation (SD) increase in log-transformed inflammatory markers.

^b Relative ratios and 95% CI per 1-SD increase in log-transformed inflammatory markers.

Conflict of interest disclosure

None reported.

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