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ORIGINAL ARTICLE

IL-6 and TNFα are associated with depressive symptoms among men in a community-based cohort, with a tentative trend for IL-17A: Findings from the Shika Study in Japan

Hirohito Tsuboi[1,2], Hiroyuki Sakakibara[3], Yuuki Minamida-Urata[2], Yui Takakura[2], Hiromasa Tsujiguchi[1], Akinori Hara[1], Keita Suzuki[4], Sakae Miyagi[5], Masaharu Nakamura[1], Chie Takazawa[1], Takayuki Kannon[6], Jiaye Zhao[1], Yukari Shimizu[7], Aki Shibata[1], Aya Ogawa[1], Fumihiko Suzuki[8], Yasuhiro Kambayashi[9], Atsushi Tajima[4], Hiroyuki Nakamura[1]

1 Department of Hygiene and Public Health, Faculty of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan.
2 Research Group of Psychosomatic Medicine, Faculty of Pharmacy, Pharmaceutical and Health Sciences, Kanazawa University, 1 Kakuma-machi, Kanazawa 920-1192, Japan.
3 Graduate School of Agricultural Science, Kobe University, 1-1 Rokkodai, Nada-ku, Kobe 657-8501, Japan.
4 Department of Bioinformatics and Genomics, Graduate School of Advanced Preventive Medical Sciences, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8640, Japan.
5 Innovative Clinical Research Center, Kanazawa University, 13-1 Takara-machi, Kanazawa, Japan.
6 Department of Biomedical Data Science, School of Medicine, Fujita Health University, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake 470-1192, Japan.
7 Department of Nursing, Faculty of Health Sciences, Komatsu University, 10-10 Doihara-machi, Komatsu 923-0921, Japan.
8 Department of Geriatric Dentistry, Ohu University School of Dentistry, 31-1 Misumido, Koriyama 963-8041, Japan.
9 Department of Public Health, Faculty of Veterinary Medicine, Okayama University of Science, 1-3 Ikoinooka, Imabari 794-8555, Japan.

Correspondence to: Hirohito Tsuboi
Department of Hygiene and Public Health, Faculty of Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641, Japan
TEL.: +81 76 265 2218; E-MAIL: tohtori17@gmail.com

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Abstract

OBJECTIVE: Emerging evidence suggests that low-grade systemic inflammation contributes to depressive symptoms; however, population-based longitudinal evidence, particularly from community samples, remains limited. This study examined the associations between serum cytokine levels and depressive symptoms among community-dwelling adults in Japan.

PARTICIPANTS AND METHODS: Participants were drawn from the Shika Study cohort (N = 182; 98 men, 84 women; mean age: 62.2 ± 9.34 years for men, 60.9 ± 9.49 for women). They provided blood samples in 2017 and completed the Japanese versions of the Center for Epidemiologic Studies Depression Scale (CES-D) in 2017 and its revised version (CESD-R) in 2019. Serum TNFα, IL-6,

IL-10 and IL-17A were quantified using a multiplex human immunoassay.

RESULTS: Among men, serum IL-6 levels were positively associated with CES-D scores in 2017 after adjustment for age, visceral adiposity, smoking, and alcohol consumption (standardised regression coefficient (β) = 0.25, p = 0.024). Baseline TNF-α was significantly associated with higher CES-D-R scores in 2019 (β = 0.23, p = 0.026), whereas IL-17A showed only a non-significant trend (β = 0.13, p = 0.231). No significant associations were observed among women or for IL-10.

CONCLUSION: In this exploratory community-based study, higher IL-6 levels were modestly associated with concurrent depressive symptoms in men, and baseline TNFα showed a similarly modest association with depressive symptoms two years later as measured by the CESD-R. IL-17A showed a tentative trend that requires replication. These findings suggest possible sex-specific links between peripheral inflammation and depressive symptoms, but the results should be interpreted as hypothesis generating.

Abbreviations:

CNS	- central nervous system
TNF	- tumour necrosis factor
IL	- interleukin
MDD	- major depressive disorder
INF	- interferon
CRP	- C-reactive protein
BBB	- blood-brain barrier
CES-D	- Center for Epidemiologic Studies Depression Scale
CESD-R	- Center for Epidemiologic Studies Depression Scale Revised

INTRODUCTION

While the aetiology of depression is multifactorial, increasing evidence points to immune dysregulation—particularly involving peripheral cytokines—as a critical component of its pathophysiology. Theories on serotonergic dysfunction and cortisol hypersecretion alone do not adequantly explain the nature of depression or its symptomatology. There is now substantial evidence for pathways and mechanisms through which the immune system can influence the brain and behaviour. The central nervous system (CNS) primarily affects the immune system via the neuroendocrine outflow and the autonomic nervous system, whereas the immune system, including inflammatory processes, modulates the CNS in return.

Chronic inflammation differs from normal or acute inflammation in that the body fails to suppress the immune response, resulting in continuous systemic low-grade inflammation. Links between inflammatory markers and psychological or psychiatric conditions have been reported in otherwise healthy individuals with depressive symptoms as well as in those with clinical depression. For example, low-grade systemic inflammation has been associated with both clinical depression and depressive symptoms (Rawdin *et al.* 2013) (Maes 2009). Previous studies have also demonstrated that chronic low-grade inflammation in peripheral organs can increase the brain vulnerability (Mongan *et al.* 2023) (Riazi *et al.* 2015). Several review articles have suggested that neuroinflammation and neurodegeneration in the CNS may be connected to peripheral inflammatory signalling (Abautret-Daly *et al.* 2018) (Réus *et al.* 2015).

Inflammatory cytokines such as tumour necrosis factor-alpha (TNFα), interleukin (IL)-6 and IL-1beta (β) are commonly used as markers of low-grade inflammation. Elevated circulating levels of these cytokines are characteristic of chronic, low-grade inflammatory states observed in conditions such as obesity, metabolic disease, and chronic pain syndromes (Uti *et al.* 2025) (Zhou *et al.* 2021). Similar peripheral cytokine elevations are also observed in depression. A meta-analysis of studies on major depressive disorder (MDD) found that two pro-inflammatory cytokines, IL-6 and TNFα, were consistently elevated, while other cytokines, such as IL-1β, IL-4, IL-2, IL-8, IL-10, and interferon-gamma (INF-γ), were not consistently raised in patients with depression (Dowlati *et al.* 2010). Other meta-analyses have also suggested associations between depression and elevated inflammatory markers, such as C-reactive protein (CRP), IL-6 and, to a lesser extent, IL-1 (Howren *et al.* 2009; Konsman *et al.* 2002).

Psychological stress may increase both psychological depression and peripheral inflammation efferently through the hypothalamic-pituitary-adrenal (HPA) axis or the sympathetic pathway. Conversely, the peripheral inflammatory signals can activate inflammatory responses in the CNS afferently via the blood-brain barrier (BBB) or the vagus nerve, potentially contributing to depression and related disorders (Sun *et al.* 2022). However, despite growing evidence implicating neuroinflammation in the pathogenesis of depressive disorders (Sun *et al.* 2022; Raison & Miller 2003), the effect of the peripheral inflammation on the CNS retain poorly understood.

In the present study, we focused the pro- and anti-inflammatory cytokines — TNFα, IL-6, IL-10 and IL-17A — to investigate their roles in chronic inflammation. TNFα is an adipokine and a cytokine that promotes insulin resistance and inflammatory pathways (Sethi & Hotamisligil 2021). It is derived from an adipose tissue and a perpetuated low-grade inflammation by establishing a vicious cycle between adipocytes and macrophages (Itoh *et al.* 2011). Thus, assessing TNFα levels is essential for evaluating metabolic and inflammatory health in the modern population. IL-6 acts as both a pro-inflammatory cytokine and an anti-inflammatory cytokine (Nara & Watanabe 2021). It is a multifunctional mediator produced by various cells — including immune cells, endothelial, fibroblasts, muscular, and adipose cells — and contribute

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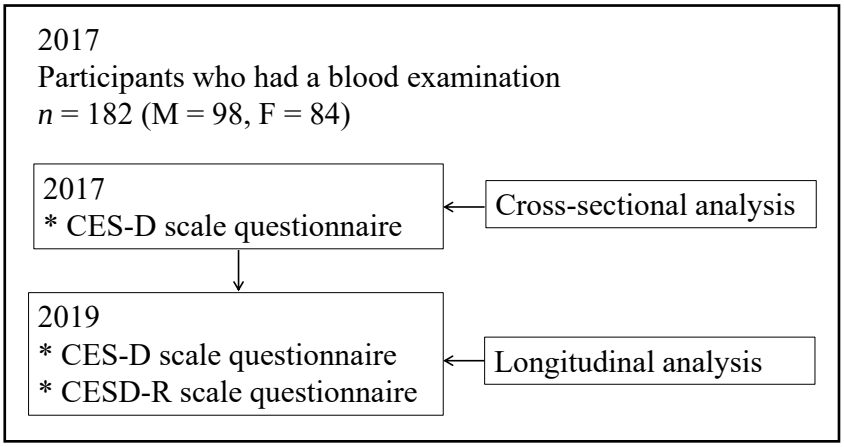

Fig. 1. Study flowchart: recruitment, data collection, and follow-up (Shika Study, 2017–2019).
Community-dwelling adults aged ≥40 in the Noto Peninsula, Japan (n = 182; 98 men, 84 women) provided fasting blood samples and completed the CES-D in 2017. Serum TNFα, IL-6, IL-10, and IL-17A were quantified by Luminex® multiplex immunoassay. In 2019, participants completed the CES-D and CESD-R. Four women were excluded from analyses (two rheumatoid arthritis; one bipolar disorder; one MDD). Effective per-cytokine n were further reduced by exclusion of undetectable and outlying values (> mean + 3 SD).

to both inflammatory and stress-induced responses (Fernández-Real & Ricart 2005). Our previous study found a positive association between depressive symptoms and peripheral IL-6 concentrations (Tsuboi *et al.* 2019). IL-17A is a pro-inflammatory cytokine mainly secreted by T-helper 17 (Th17) lymphocyte, but also by other T cells, granulocytes, monocytes, and natural killer (NK) cells (Zenobia & Hajishengallis 2015). Associations between IL-17 related allergic diseases and anxiety or depression have been frequently reported. (Hofmann *et al.* 2021). One possible explanation is that IL-17 increases BBB permeability in a dose-dependent manner (Lécuyer *et al.* 2016). We have also reported that higher serum IL-17A levels are associated with severer depressive symptoms (Tsuboi *et al.* 2018). IL-10, in contrast, is an anti-inflammatory cytokine produced by Th2 cells that exerts pleiotropic effects in immunoregulation and inflammation. It downregulates the expression of Th1 cytokines and can inhibit the NF-κB activity, which mediates inflammation, including IL-6 production and Th17 differentiation (Zhang *et al.* 2021).

Although associations between inflammatory markers and depression have been reported previously, fewer studies have examined multiple cytokines in community-dwelling populations using both cross-sectional and longitudinal analyses. The present study extends this literature by evaluating TNFα, IL-6, IL-10, and IL-17A in adults from the Shika Study cohort, with sex-stratified analyses and follow-up depressive symptom assessment. The aim was to explore whether these cytokines show distinct concurrent or prospective associations with depressive symptoms in a non-clinical population and to generate hypotheses for future, larger studies.

PARTICIPANTS AND METHODS

Study population

The participants were drawn from the Shika Study cohort project and had available for both 2017 and 2019. This project has been conducted in the Noto Peninsula, Ishikawa, Japan, since 2011. Its aim is to identify solutions to lifestyle diseases by investigating community-dwelling adults aged 40 years or older (Center KUaPMSR 2016). All of the participants were literate, had a good command of Japanese, and were instructed not to use proxies.

Procedures

Demographic and questionnaire data were obtained in 2017. Figure 1 shows the study procedure. A total of 182 participants (98 men, mean age ± standard deviation (SD) = 62.2 ± 9.34; 84 women, mean age ± SD = 60.9 ± 9.49) consented to participate in this study. Blood samples were collected in 2017, and depressive symptoms were assessed in both 2017 and 2019. The severity of depressive symptoms was assessed using the Japanese version of the Center for Epidemiologic Studies Depression Scale (CES-D) in 2017. At follow-up assessment in 2019, both the CES-D and CESD-R were administrated (Shima *et al.* 1985; Tsuboi *et al.* 2021). Cronbach's alpha was 0.84 (CES-D 2017), 0.86 (CES-D 2019), and 0.87 (CESD-R). The CESD-R was treated as the primary longitudinal outcome because it captures the full DSM-5 symptom range and has been validated in this cohort.

A self-administered questionnaire was distributed to participants in advance, and the completed questionnaires were collected on the day of the medical examination in 2017. On the examination day, physical measurements, including height, weight, waist circumference were obtained, and blood samples were collected. The entire process was conducted with careful attention to privacy protection. The questionnaire included items on demographic characteristics (age, sex, present health status, diseases, medication) and lifestyle characteristics (smoking status, alcohol consumption). Two years later, in 2019, the CES-D and CESD-R questionnaires were delivered and collected.

Blood collection

Fasting blood samples were collected between 0800 and 1200 hours. Blood was drawn from the antecubital

Tab. 1. Baseline characteristics of study participants by sex (Shika Study, 2017).

	Men				Women			
	N	**Mean**	**S.D.**	**Range**	***N***	**Mean**	**S.D.**	**Range**
Age (years)	98	62.2	9.34	42–81	84	60.9	9.49	42–81
BMI (kg/m^2)	98	24.0	3.04	18.1–32.7	84	22.2	3.03	16.5–31.8
Abdominal circumference (cm)	98	86.2	8.04	66.8–106.3	84	81.0	8.85	65.3–110.3
ABSI	98	0.080	0.003	0.073–0.087	84	0.083	0.004	0.074–0.091
CES-D score (2017)	98	10.2	6.26	0–34	84	10.3	6.61	1–33
CES-D score (2019)	98	9.3	6.66	0–32	84	10.0	7.38	0–33
CESD-R score (2019)	98	3.7	4.84	0–21	84	4.3	6.25	0–34
TNFα (pg/mL)	97	1.44	0.516	0.40–3.11	82	1.40	0.404	0.68–2.34
IL-6 (pg/mL)	91	0.516	0.453	0.001–2.879	83	0.739	0.699	0.020–3.941
IL-10 (pg/mL)	95	2.81	2.335	0.073–10.64	79	3.55	2.674	0.120–15.77
IL-17A (pg/mL)	96	1.86	0.998	0.098–4.486	83	2.32	1.21	0.549–5.988
	N				*N*			
Smoking habit								
Non-smoker	18				75			
Ex-smoker	56				6			
Current smoker	24				3			
Alcohol consumption								
No	26				50			
Yes	72				34			

Demographic, anthropometric, lifestyle, and serological data for men (n = 98) and women (n = 84; 80 after clinical exclusions) from the Shika Study, a community-based cohort of adults aged ≥40 in the Noto Peninsula, Japan. Continuous variables are mean ± SD; categorical variables are n (%). Serum cytokines (TNFα, IL-6, IL-10, IL-17A) were measured by Luminex® 200TM multiplex immunoassay from fasting 2017 blood samples. Effective n per cytokine (shown in parentheses) reflects exclusion of undetectable values and values exceeding mean + 3 SD. Visceral adiposity was indexed by A Body Shape Index (ABSI).

vein into heparinised and serum-separator Vacutainer tubes, after which serum was separated via centrifugation. The serum samples were transported to Kanazawa University via a commercial laboratory (SRL Kanazawa Laboratory, Kanazawa, Japan), frozen, and stored at −30°C until the assay.

Assays for inflammatory factors

Serum samples were analysed for TNFα, IL-6, IL-10, and IL-17A using a multiplex human immunoassay kit (Luminex® 200TM) with the human high sensitivity T cell panel (Merck Japan, Tokyo, Japan).

Statistical analysis

IBM SPSS Statistics 29 for the Japanese version (IBM Japan, Tokyo, Japan) was used for data analysis. Pearson's correlation coefficients were first calculated to explore bivariate associations. Linear regression analyses were subsequently conducted to adjust for confounders. The nominal level of significance was set at $p < 0.05$. Because four cytokines were each tested against three outcome measures (CES-D 2017, CES-D 2019, CESD-R 2019) across two sex strata, we did not formally adjust for multiple comparisons and instead treated all analyses as exploratory and hypothesis-generating.

RESULTS

Table 1 presents the participants' characteristics. Of the 84 women, four individuals were excluded: one was taking lithium carbonate (bipolar disorder), one was taking mirtazapine (MDD), and two had rheumatoid arthritis. Among men, no participants were excluded on clinical grounds. For both sexes, participants with undetectable cytokine levels and those whose values exceeded mean + 3 SD were excluded; effective sample sizes per cytokine are reported in Tables 1 and 2. A Body Shape Index (ABSI) was calculated to assess visceral adiposity. (Biolo *et al.* 2015).

Simple correlations between the measured variables are shown in Table 2. A significant positive correlation was observed between the 2017 CES-D scores and serum IL-6 concentrations among men (r = 0.27, $p = 0.009$, Figure 2). The 2019 CESD-R scores showed a significant positive correlation with serum TNFα concentrations (r = 0.22, $p = 0.031$, Figure 3). CESD-R

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scores also showed a positive but non-significant correlation with the serum IL-17A levels in the primary analysis after application of the pre-specified exclusion rule (r = 0.19, $p = 0.068$, Figure 4). In a sensitivity analysis that retained the excluded observation, the association was stronger and reached nominal significance (r = 0.25, $p = 0.016$, Figure 4). Accordingly, the primary IL-17A finding should be interpreted as a trend rather than a statistically significant association. No significant correlations were found between the serum concentrations of any of the other cytokines and the CES-D or CESD-R scores. Among women, no significant correlation was observed between CESD-R scores and any peripheral indicators (Table 2).

To adjust for key measured confounders, regression analyses were performed with age, visceral adiposity (ABSI), smoking, and alcohol consumption as covariates to examine associations between depressive symptoms and serum markers. As shown in Table 3, IL-6 levels were significantly and positively associated with the 2017 CES-D scores among men in a linear regression model controlling for confounders (F (5, 85) = 1.07, standardised beta (β) = 0.25, $p = 0.024$) (Table 3). TNFα levels significantly predicted the 2019 CESD-R scores after adjustment for the same confounders among men (F (5, 91) = 1.73, β = 0.23, $p = 0.026$, Table 3). IL-17A levels showed a trend towards significance in predicting the 2019 CESD-R scores after the adjustment among men (F (5, 90) = 1.37, β = 0.19, $p = 0.068$) (Table 3), and this association became statistically significant only in a sensitivity analysis that retained one pre-specified outlier (F (5, 91) = 1.87, β = 0.25, $p = 0.018$). In women, by contrast, no serum inflammatory markers showed significant association with CESD-R scores (Table 3).

DISCUSSION

In this exploratory study of community-dwelling adults aged 40 years or older, serum IL-6 levels were positively associated with depressive symptoms cross-sectionally in men, and baseline TNFα levels were positively associated with CESD-R scores at follow-up in men. Importantly, these sex specific associations for IL-6 and TNFα would require confirmation in studies that pre-specify primary cytokine–outcome pairs and incorporate appropriate control for multiple testing. IL-17A showed only a trend in the primary analysis, with stronger associations emerging only in sensitivity analyses. In contrast, no significant associations were observed in women. Overall, the findings suggest modest and sex-specific associations rather than a general inflammatory pattern of depressive symptoms.

The present findings are broadly consistent with the literature linking low-grade inflammation to depressive

Tab. 2. Pearson's correlation coefficients between serum cytokine concentrations, depressive symptom scores, and covariates, by sex (Shika Study, 2017–2019).

		Age	ABSI	CES-D (2017)	CES-D (2019)	CESD-R (2019)	TNFα	IL-6	IL-10	IL-17A
Men	Age	1.00	0.26*	0.17†	-0.08	0.01	0.01	-0.22*	-0.22*	-0.16
	ABSI		1.00	-0.03	0.04	-0.01	0.13	-0.16	-0.11	-0.01
	CES-D (2017)			1.00	0.58***	0.45***	0.13	0.27**	0.03	0.14
	CES-D (2019)				1.00	0.74***	0.12	-0.02	-0.04	-0.03
	CESD-R (2019)					1.00	0.22*	0.12	0.10	0.19†
	TNFα						1.00	0.36***	0.39***	0.53***
	IL-6							1.00	0.58***	0.65***
	IL-10								1.00	0.67***
	IL-17A									1.00
Women	Age	1.00	0.22*	0.11	0.01	0.01	-0.06	-0.18	-0.19†	-0.12
	ABSI		1.00	0.09	0.09	0.19†	-0.02	-0.15	-0.08	-0.12
	CES-D (2017)			1.00	0.65***	0.66**	-0.15	-0.16	-0.14	-0.19†
	CES-D (2019)				1.00	0.68***	-0.01	-0.07	-0.15	-0.02
	CESD-R (2019)					1.00	-0.12	-0.08	-0.22†	-0.13
	TNFα						1.00	0.34***	0.34***	0.31***
	IL-6							1.00	0.45***	0.51***
	IL-10								1.00	0.60***
	IL-17A									1.00

Shown separately for men (upper panel) and women (lower panel). Depressive symptoms: CES-D (2017; range 0–60), CES-D and CESD-R (2019; range 0–48). Cytokines (TNFα, IL-6, IL-10, IL-17A; pg/mL, log-transformed) from fasting 2017 blood samples. Covariates: age, ABSI, smoking, alcohol consumption. Effective n varies per cytokine; see Tab 1. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$, † $p < 0.10$.

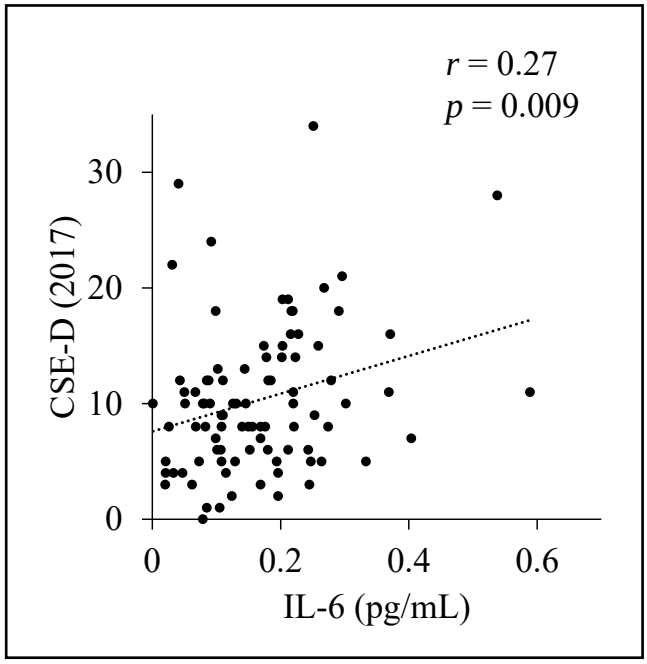

Fig. 2. Serum IL-6 concentration and concurrent depressive symptoms in men (Shika Study, 2017; n = 91).
Log-transformed serum IL-6 (pg/mL; x-axis) versus CES-D score (range 0–60; y-axis), both measured in 2017. Regression line with 95% CI shown. Pearson's r = 0.22, $p = 0.032$; adjusted standardised β = 0.25, $p = 0.024$ (covariates: age, ABSI, smoking, alcohol; Table 3). No significant association was observed in women.

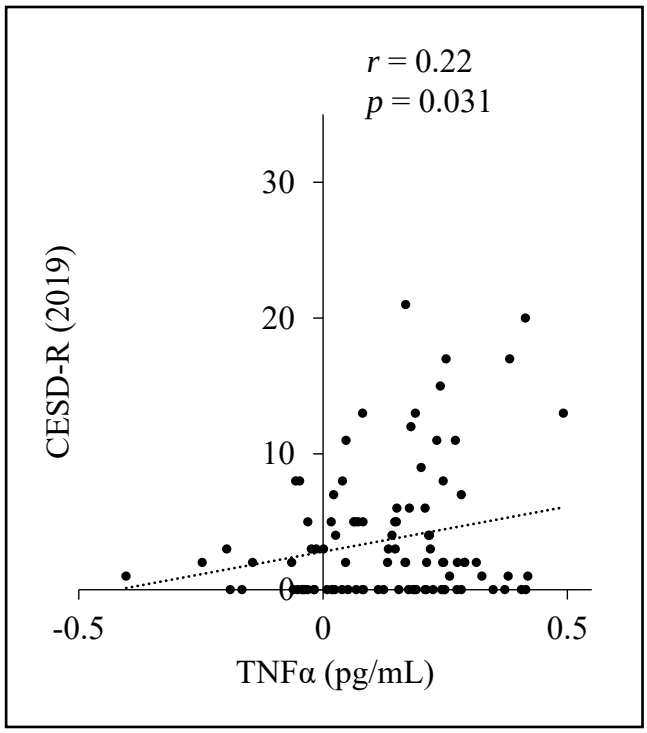

Fig. 3. Baseline serum TNFα concentration and depressive symptoms two years later in men (Shika Study, 2017–2019; n = 97).
Log-transformed serum TNFα (pg/mL; x-axis) from 2017 versus CESD-R score (range 0–48; y-axis) from 2019 (primary longitudinal outcome). Regression line with 95% CI shown. Pearson's r = 0.23, $p = 0.030$; adjusted β = 0.23, $p = 0.026$ (Table 3). TNFα was not significantly associated with the concurrently administered CES-D 2019 (β = 0.13, $p = 0.231$), likely reflecting instrument differences. No significant association was observed in women.

symptoms; however, the observed effect sizes were modest and differed by biomarker, sex, and depressive symptom measure, suggesting that any inflammatory contribution to depressive symptoms in community samples is unlikely to be large. In line with prior meta-analyses (Dowlati *et al.* 2010), IL-6 and TNFα showed the clearest associations, whereas IL-17A and IL-10 did not show robust effects in this sample. Proposed neuro-immune mechanisms, including activation of the HPA axis and signalling across the vulnerable BBB caused by inflammatory cytokines, may help explain why chronic low-grade inflammation is related to mood regulation, although the present data cannot distinguish between these pathways. Future studies with larger samples and repeated cytokine and symptom measurements will be needed to clarify which specific inflammatory pathways are most relevant in community populations (Maes 1999).

IL-6

IL-6 has been reported to play an important role in the development and pathophysiology of depression, with many studies suggesting involvement in stress response, symptom severity, and even structural brain changes. Elevated levels of IL-6 have been observed in patients with MDD compared with healthy controls. Meta-analyses have also reported higher cerebrospinal fluid and serum IL-6 concentrations in patients with MDD, with reductions after antidepressant treatment, supporting a link between inflammation and depressive symptoms (Hodes *et al.* 2016) (Lombardi *et al.* 2023). Another Meta-analysis concluded that levels of several pro-inflammatory cytokines, including IL-6, are significantly increased in depressed patients, suggesting that chronic low-grade inflammation is often present in MDD (Dowlati *et al.* 2010). Inflammatory processes may precede and contribute to the development of depression in some individuals, suggesting that elevated IL-6 might not only as a consequence but a marker of increased risk for future depressive symptoms or episodes in some contexts, although the present observational data cannot establish causality. (Valkanova *et al.* 2013).

The mechanisms by which elevated IL-6 may contribute to depressive symptoms are complex and multifaceted, and primarily involve interactions between the brain and the immune system. IL-6 can activate the HPA axis, leading to increased cortisol production (Del Giudice & Gangestad 2018). Chronic overactivity of the HPA axis may then impair feedback mechanisms, resulting in HPA axis dysregulation, which is a common neuroendocrine finding in MDD (Del Giudice & Gangestad 2018). In addition, the tryptophan-kynurenine pathway, via the enzyme indoleamine 2,3-dioxygenase (IDO), may also be involved. Activation of IDO diverts tryptophan away from serotonin synthesis toward kynurenine metabolites, some

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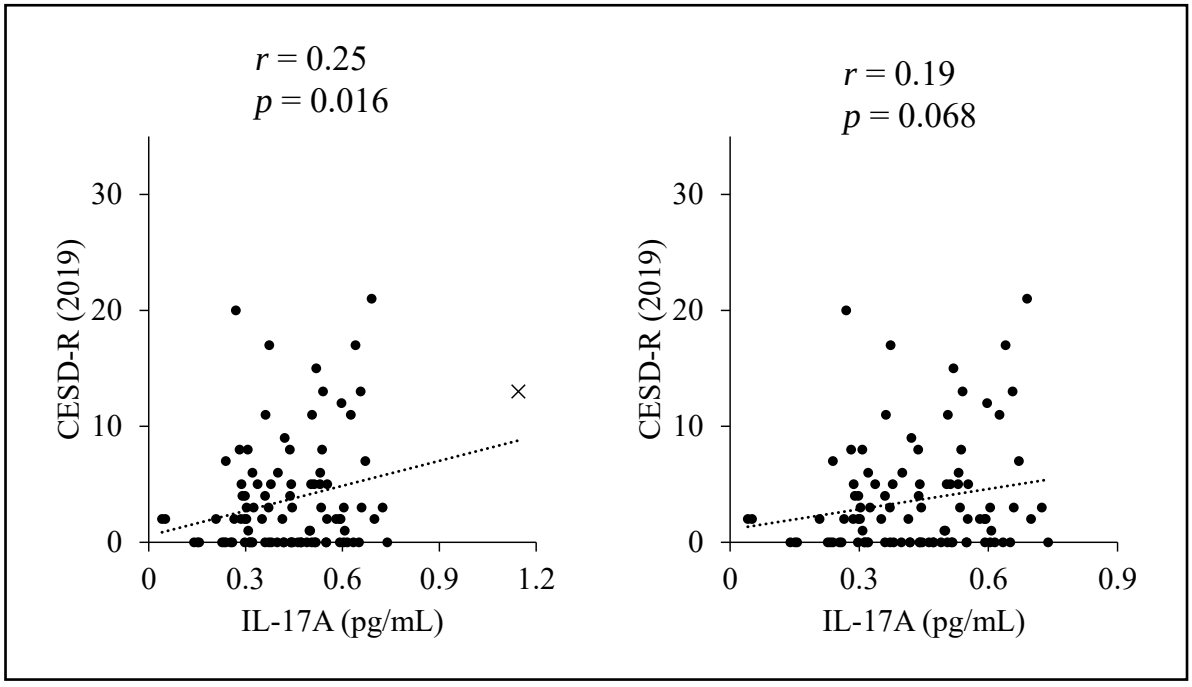

Fig. 4. Baseline serum IL-17A concentration and depressive symptoms two years later in men — primary analysis and sensitivity analysis (Shika Study, 2017–2019).
Log-transformed serum IL-17A (pg/mL; x-axis) from 2017 versus CESD-R score (range 0–48; y-axis) from 2019. Regression line with 95% CI shown in each panel. Left (primary; n = 91): Pre-specified outlier (>mean + 3 SD) excluded. r = 0.19, *p* = 0.068; adjusted β = 0.19, *p* = 0.068 — a sub-threshold trend. **Right (sensitivity; n = 92):** Outlier retained. r = 0.25, *p* = 0.016; adjusted β = 0.25, *p* = 0.018. The left panel represents the pre-specified result. No significant association was observed in women.

of which are neurotoxic such as quinolinic acid, and may impair neuronal function (Dantzer *et al.* 2008). One limitation of these explanations is the difference between the composition of CNS fluids and peripheral serum, particularly because the BBB separates the brain from circulating blood and cytokines are relatively large molecules that do not freely cross the BBB. However, some studies have identified several ways in which inflammatory signals may be transmitted from the periphery to the brain. Increased levels of circulation inflammatory factors may increase BBB permeability, allowing cytokines to cross, particularly via the choroid plexus and circumventricular organs (Capuron & Miller 2011). In addition, cytokine signals may be transmitted through afferent vagus nerve fibres, triggering the release of second messengers in the brain, such as prostaglandins and nitric oxide (Capuron & Miller 2011). Alternatively, cytokines may cross the BBB through active transport (Capuron & Miller 2011).

In the present study, which involved community-dwelling adults aged 40 years or older in a rural area of Japan, a significant positive correlation was found between serum IL-6 levels and depressive symptoms assessed using the CES-D scale (Figure 2). A similar relationship was observed in our previous study of female nursing workers (Tsuboi *et al.* 2019), although sex differences exist.

TNFα

Among men, higher baseline TNFα was associated with higher CESD-R scores in 2019, whereas no significant association was observed for CES-D. Because both CES-D and CESD-R were administered in 2019.

TNFα is a pro-inflammatory cytokine secreted by many types of cells and tissues, and it has recently attracted attention in relation to obesity and inflammation (Popko *et al.* 2010) (Suganami & Ogawa 2010). In relation to depression, it has been established that TNFα, as well as IL-1 and IL-6, can induce not only symptoms of physical illness but also MDD in physically ill patients with no previous history of mental disorder (Dantzer *et al.* 2008). In addition, animal studies have indicated that TNFα inhibition improves depression-like behaviour (Şahin *et al.* 2015) (Krügel *et al.* 2013). The effects of TNFα on depression may be mediated by activation of the HPA axis and the subsequent reduction in serotonin (5-HT) metabolism as well as the vulnerability of the BBB to the inflammatory effects of TNFα. Several findings suggest that indicate TNFα influences both 5-HT metabolism and the HPA axis. It has been suggested that TNFα activates the HPA axis during inflammatory reactions (Dunn 2000). Another study suggested that TNFα and the HPA system mutually influence one another in depressed patients without inflammatory diseases (Himmerich *et al.* 2006). Furthermore, TNFα

Tab. 3. Adjusted standardised regression coefficients (β) for associations between serum cytokines and depressive symptom scores, by sex (Shika Study, 2017–2019).

		Men				Women			
	Cytokine	**TNFα**	**IL-6**	**IL-17**	**IL-10**	**TNFα**	**IL-6**	**IL-17**	**IL-10**
CES-D (2017)	F value	1.08 (5,91)	1.75 (5,85)	0.95 (5,90)	0.69 (5,90)	1.00 (5,76)	1.07 (5,76)	1.13 (5,77)	0.76 (5,76)
	Serum cytokine levels	0.14	0.25*	0.12	-0.01	-0.16	-0.17	-0.17	-0.1
	Age	-0.18†	-0.13	-0.16	-0.18†	0.02	0.01	0.03	0.02
	ABSI	-0.03	0.03	-0.01	0.00	0.11	0.09	0.09	0.10
	Smoking habit	0.07	0.04	0.07	0.07	-0.08	-0.11	-0.10	-0.08
	Alcohol consumption	0.09	0.05	0.08	0.07	-0.15	-0.15	-0.10	-0.1
CES-D (2019)	F value	0.64 (5,91)	0.35 (5,85)	0.38 (5,90)	0.41 (5,90)	0.77 (5,76)	0.91 (5,76)	0.78 (5,77)	1.01 (5,76)
	Serum cytokine levels	0.13	-0.05	-0.05	-0.06	-0.01	-0.10	0.00	-0.13
	Age	-0.11	-0.13	-0.12	-0.13	-0.08	-0.10	-0.08	-0.11
	ABSI	0.03	0.05	0.06	0.05	0.16	0.15	0.16	0.16
	Smoking habit	0.09	0.09	0.08	0.09	-0.07	-0.08	-0.07	-0.04
	Alcohol consumption	0.04	0.03	0.02	0.02	-0.14	-0.16	-0.14	-0.13
CESD-R (2019)	F value	1.73 (5,91)	0.86 (5,85)	1.37 (5,90)	0.82 (5,90)	1.70 (5,76)	1.56 (5,76)	1.56 (5,77)	2.10 (5,76)
	Serum cytokine levels	0.23*	0.12	0.19†	0.09	-0.13	-0.09	-0.08	-0.20†
	Age	-0.02	0.00	0.01	0.00	-0.06	-0.06	-0.04	-0.08
	ABSI	-0.05	0.00	-0.02	-0.01	0.26*	0.25*	0.25*	0.25*
	Smoking habit	0.19†	0.17	0.18†	0.18	-0.11	-0.12	-0.12	-0.08
	Alcohol consumption	-0.03	-0.07	-0.04	-0.06	-0.13	-0.12	-0.09	-0.09

Each cell derives from a separate linear regression model with the named log-transformed cytokine as predictor and age, ABSI, smoking, and alcohol consumption as covariates (5 predictors; F-statistics and df shown). Outcomes: CES-D 2017 (cross-sectional), CES-D 2019, and CESD-R 2019 (longitudinal; CESD-R designated primary outcome for its DSM-5 alignment and cohort validation). Men: n ≈ 85–97; women: n ≈ 72–80 after exclusion of four participants (two rheumatoid arthritis, one bipolar disorder, one MDD). Final row of men's panel shows sensitivity analysis retaining the pre-specified IL-17A outlier. * $p < 0.05$, † $p < 0.10$.

has been shown to markedly decrease 5-HT transporter function (Foley *et al.* 2007).

The discrepancy in the present study may reflect differences in scale content and construct coverage rather than a robust biomarker effect across depressive symptom measures. The TNFα finding is therefore potentially informative but should be interpreted cautiously until replicated in studies using consistent longitudinal outcomes.

IL-17A

IL-17A is a pro-inflammatory cytokine and the first member of the IL-17 family to be identified. The overproduction of IL-17A promotes hyperinflammation and tissue damage in a variety of diseases (Xu *et al.* 2022). The role of IL-17 in the pathogenesis and progression of depression is a relatively new area of research that has recently gained attention. Patients with MDD have been reported to exhibit increased levels of circulating cytokines, such as IL-1β, IL-6 and TNFα, which play important roles in Th17 differentiation and effector function (Syed *et al.* 2018) (Slyepchenko *et al.* 2016). IL-17 stimulates the production of various inflammatory mediators, such as intercellular adhesion molecule 1 (ICAM-1), prostaglandin E2 (PGE2), matrix metalloproteinases (MMPs) and antimicrobial peptides, all of which are involved in tissue damage (Zhu & Qian 2012). The induction and release of such mediators also appears to amplify IL-17 production via a positive feedback loop, thereby propagating the inflammatory damage (Benedetti & Miossec 2014). Furthermore, patients with MDD who responded to antidepressants treatment showed reduced plasma IL-17 levels (Syed *et al.* 2018).

Although little is currently known how IL-17A infiltrates the brain and how it acts, whether directly or indirectly via signalling cascades across the BBB, recent reports suggest a relationship between peripheral IL-17 levels and depression. For example, patients with first-episode depressive disorder showed higher serum IL-17 levels (Mao *et al.* 2022). Serum IL-17 concentrations were significantly higher in patients with MDD than in the control subjects (Davami *et al.* 2016). Preclinical studies in animal models have shown that stress induced IL-17 promotes depression-like behaviours (Kim *et al.* 2021) (Tallerova *et al.* 2011). Although there some have reported that elevated IL-17 levels are not implicated in MDD, this may be due to differences in

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the source of IL-17 under different depression-inducing conditions (Kim *et al.* 2021). The origin of IL-17 is not precisely understood; it can be produced by many types of cells and be induced through a variety of pathways that may contribute to depression (Rivet-Noor *et al.* 2022).

In the present study, IL-17A showed a non-significant positive trend with CESD-R scores in men in the primary analysis, with stronger results only in sensitivity analysis (Figure 4). This pattern may indicate a possible signal, but it remains hypothesis-generating and should not be interpreted as firm longitudinal evidence. Replication in larger cohorts with pre-specified outlier handling and consistent outcome measures will be important.

IL-10

In the present study, the serum concentration of IL-10 tended to be inversely associated with CESD-R scores in women in the unadjusted model ($r = -0.22$, $p < 0.1$, Table 2). This trend attenuated after adjustment for confounders (Table 3). Lifestyle factors may influence the association between IL-10 and depressive symptoms.

Findings regarding the associations between serum IL-10 levels and depression have been inconsistent. A case–control study involving patients with MDD and individuals without depression showed that the patients with MDD had higher plasma IL-10 levels (Syed *et al.* 2018). However, in the same study, patients receiving antidepressant treatment showed elevated plasma IL-10 concentrations (Syed *et al.* 2018). In a mouse model of depression, microglial but not peripheral blood, IL-10 levels were reduced in learned helplessness mice; administration of IL-10 improved procognitive outcomes in learned helplessness mice or in mice with cognitive impairments (Worthen *et al.* 2020). These contradictory findings may be explained by the pleiotropic effects of IL-10. IL-10 is an anti-inflammatory cytokine produced by Treg cells and plays an important role in limiting inflammation. However, IL-10 can activate Th2 cells and B cells (Laouini *et al.* 2003), while inhibiting macrophages and Th1 cells and suppressing Th17 cell-mediated inflammation; thus, IL-10 may act as both an immunostimulatory and immunosuppressive cytokine.

Pathways to the central nervous system

When considering peripheral inflammatory markers and brain responses to depression, the pathway by which cytokines cross the BBB should be considered, as noted in the IL-6 section. There are two main pathways by which peripheral immune signals are transmitted to the brain: BBB-dependent and BBB-independent pathways (Quan 2008). BBB-independent pathways use the vagus nerve to bypasses the BBB, whereas BBB-dependent pathways include BBB vulnerability itself, humoral pathways, cellular pathways such ad active transport, activation of NF-κB signalling, and adhesion molecules (Capuron & Miller 2011). Although it was recently discovered that microglia play a role in BBB permeability during systemic inflammation (Haruwaka *et al.* 2019), the precise factor affecting BBB function remains unclear. Some inflammatory signals may evoke CNS inflammation, which can in turn induce depression. One study of found that increased IL-6 levels were correlated with dysconnectivity of a brain functional network (Aruldass *et al.* 2021). However, further research is required to clarify these pathways.

Effects of disease and medication

It is essential to consider the effects of diseases and medication on immune function. In the 2017 survey, two women were diagnosed with rheumatoid arthritis (RA). RA is an IL-6-related disease and may also affect the production of other cytokines. One woman was taking lithium carbonate 200 mg/day, amoxan 25 mg/day, and pramipexole 0.5 mg/day, suggesting that the prescription was for bipolar disorder and restless leg syndrome. Another woman was taking mirtazapine 15 mg/day and had been diagnosed with MDD. Even when these four excluded individuals were retained in the analysis, the levels of significance reported in Table 3 remained unchanged, confirming that the exclusions did not materially affect the results.

Applications in treatment and novel therapeutics

Given that low-grade inflammation may partly drives depressive symptoms, anti-inflammatory agents or non-pharmacological interventions in daily life may be beneficial. Non-pharmacological interventions — including physical exercise, probiotics, and omega-3 fatty acids — have shown promise in reducing inflammatory burden and associated depressive symptoms (Suneson *et al.* 2021). Our results are consistent with the broader literature that has motivated trials of anti-inflammatory treatments as potential adjuncts for depression or depressive states, including monoclonal antibody-based therapies, although the present study alone does not support specific treatment recommendations. A meta-analysis of anti-inflammatory treatment reported that anti-TNF antibodies, such as infliximab, non-steroidal anti-inflammatory drugs (NSAIDs) and omega-3 fatty acids improved depressive symptoms (Simon *et al.* 2023), although this remains an emerging field.

Limitations

Several limitations should be noted. First, the sample size was modest, particularly after sex stratification and cytokine-specific exclusions, which limits statistical power. Second, the analyses involved multiple cytokines, outcomes, and sex strata, and we did not correct for multiple testing; therefore, some statistically significant associations may represent chance findings, and all results should be regarded as exploratory. Third,

the use of non-equivalent instruments across time points complicates longitudinal interpretation, especially because the TNFα association was observed for CESD-R 2019 but not for CES-D 2019. Fourth, residual confounding cannot be excluded because potentially important factors such as comorbidity, physical activity, diet, sleep, and broader medication use were not fully assessed or modelled. As a result, the observed associations cannot be interpreted as causal. Finally, the biological basis of the observed sex-specific pattern remains uncertain.

Conclusion

In conclusion, higher serum IL-6 levels were associated with concurrent depressive symptoms in men, and higher baseline TNFα was associated with higher CESD-R scores two years later. IL-17A showed a tentative trend that requires confirmation. These findings support the need for further research on sex-specific associations between peripheral inflammation and depressive symptoms in community populations, particularly using larger samples and consistent longitudinal outcome measures.

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DISCLOSURE

The authors declare that there are no conflicts of interest.

ETHICAL CONSIDERATIONS

The study protocol was approved by the Ethics Committee at Kanazawa University (on 18 December 2013, receipt number 1491). Written informed consent was obtained from all participants.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Hirohito Tsuboi: Conceptualization, Methodology, Software, Validation, Formal analysis, Writing - Original Draft, Visualization, Funding acquisition. Hiroyuki Sakakibara: Investigation. Yuuki Minamida-Urata: Investigation. Yui Takakura: Investigation. Hiromasa Tsujiguchi: Investigation Akinori Hara: Investigation. Keita Suzuki: Investigation. Sakae Miyagi: Investigation. Masaharu Nakamura: Investigation. Chie Takazawa: Investigation. Takayuki Kannon: Data Curation. Yukari Shimizu: Investigation. Aki Shibata: Investigation. Aya Ogawa: Investigation. Fumihiko Suzuki: Investigation. Yasuhiro Kambayashi: Investigation. Atsushi Tajima: Investigation. Hiroyuki Nakamura: Resources, Writing - Review & Editing, Supervision, Project administration.

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