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Association between serum ferritin concentrations and depressive symptoms in Japanese municipal employees (Journal of Psychiatry Research)

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ABSTRACT

It remains unclear whether levels of body iron store are related to milder forms of depression, which are more common among apparently healthy people. We examined the association between serum ferritin concentrations and depressive symptoms among 312 men and 216 women working in two municipal offices in Japan. Depressive symptoms were assessed by using the Center for Epidemiologic Studies Depression (CES-D) scale. In men, increased prevalence of depressive symptoms (defined by using a cutoff value of ≥ 19) was significantly associated with decreased levels of serum ferritin. In age- and study-site-adjusted models, ORs (95% CIs) for depressive symptoms for men in first, second, third, and fourth quartiles of serum ferritin concentrations were 2.83 (1.01–7.94), 1.74 (0.87–3.49), 1.33 (0.71–2.47), and 1.00 (reference), respectively (p for trend = 0.02). In multivariate-adjusted model, ORs (95% CIs) in first, second, third, and fourth quartiles of serum ferritin concentrations were 2.88 (0.93–8.91), 1.91 (0.90–4.05), 1.28 (0.66–2.49), and 1.00 (reference), respectively (p for trend = 0.03). No significant association was detected in women. Our finding that men with lower levels of serum ferritin concentrations had a higher prevalence of depressive symptoms suggests that adverse psychological effects may be implicated in iron deficiency among middle-age Japanese workers.

Keywords: Depressive symptoms, Serum ferritin, Body iron store, General population, Japanese

1. Introduction

The relationship of iron to brain function, cognition, and behavior, including affective behavior, has been the subject of considerable interest during the past decades (Beard et al., 1993; Hunt and Penland, 1999). Iron deficiency anemia in infants is associated with disturbances in behavior related to alertness, responsiveness, unhappiness, fearfulness, and tension (Lozoff, 1988). More recently, alterations in iron metabolism have been suggested as potential pathological markers in patients with manifest depression (Penninx et al., 2003).

Serum ferritin plays an important role in the storage of intracellular iron and has been the subject of extensive reviews (Orino and Watanabe, 2008; Wang et al., 2010). Significantly lower serum ferritin has been reported in non-anemic women with untreated major endogenous depression than in healthy controls (Batalena et al., 1990). In contrast, increased levels of serum ferritin concentrations were positively associated with depressive symptoms in studies conducted among inpatients admitted to the treatment resistant depression ward (Maes et al., 1996) and chronic hemodialysis patients with major depression (Huang and Lee, 2007). Roles of systemic, low-grade inflammation have been frequently used to explain the relationship (Maes et al., 1996; Huang and Lee, 2007). These findings, however, were observed in patients with severe forms of major depression. Whether milder forms of depressive symptoms, which are more common among apparently healthy people, are also linked with serum ferritin levels have not been widely examined.

Four studies, to our knowledge, have explored the relationship in general population (Hunt and Penland, 1999; Baune et al., 2006; Vahdat Shariatpanaahi et al., 2007; Baune et al., 2010), and findings from these existing studies have been inconsistent. Two studies did not find significant association (Hunt and Penland, 1999; Baune et al., 2006), and two other studies concluded that depression is associated with decreased levels of serum ferritin concentrations (Vahdat Shariatpanaahi et al., 2007; Baune et al., 2010). To date, no study has been conducted in Japan where the prevalence of depressive symptoms in general population is relatively high (Kaji et al., 2010). To address the gap in the literature, we conducted this study to examine the association between serum ferritin and depressive symptoms among Japanese municipal employees. We hypothesized that levels of serum ferritin concentrations would be significantly lower in individuals with depressive symptoms after controlling for potential confounding factors.

2. Materials and methods

2.1. Study subjects and procedures

The study procedure has been described in greater details elsewhere (Murakami et al., 2008; Nanri et al., 2010). In brief, the survey was conducted in July and November 2006 among employees working in two municipal offices in northeastern Kyushu, Japan. All full-time employees ($n=601$) were invited to participate in this study, except for those on long sick or maternity leave. Out of those invited, 323 men and 224 women participated, yielding a response rate of 91.0%. We excluded 16 subjects with missing information on depression, serum ferritin, body mass index, alcohol drinking, and smoking status. We further excluded three subjects with a history of diseases that may affect serum ferritin levels (one with anemia and two with chronic liver disorder). Finally, 312 men and 216 women remained in the present study.

Participants were asked to fill in the survey questionnaires well before the day of health checkup. The questionnaires were then checked by research staff for completeness, and where necessary, clarifications were made by asking the subjects during the examination. We measured demographic characteristics, lifestyle, anthropometric, and biochemical markers according to the same survey protocol at both study sites. The Ethics Committee of the National Center for Global Health and Medicine approved the study protocol, and a written informed consent was obtained from each participant.

2.2. Depressive symptoms

Depressive symptoms were assessed by using a Japanese version (Shima et al., 1985) of the Center for Epidemiologic Studies Depression scale (CES-D) (Radloff, 1977). This scale consists of 20 questions addressing six symptoms of depression, including depressed mood, guilt or worthlessness, helplessness or hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance experienced during the preceding week. Each question is scored on a scale of 0 to 3 according to the frequency of the symptoms, and the total CES-D score ranges from 0 to 60. The criterion validity of the CES-D scale has been well established in Western (Radloff, 1977) and Japanese (Shima et al., 1985) subjects. We defined depressive symptoms as present when a subject had a CES-D score of ≥ 16 . Other cutoff values for the definition were also used: ≥ 19 that has been recommended for use among Japanese workers and ≥ 23 indicative of severe depressive state (Wada et al., 2007).

2.3. Serum ferritin concentration

After an overnight fast, 7 mL of venous blood was drawn from each participant into a vacuum tube and then conveyed in a cooler box to a laboratory. The blood was centrifuged for 15 min, and the separated serum was divided into a maximum of six tubes (0.5 mL each) at -20°C or -80°C until the analyses were performed. We measured serum ferritin concentrations by using chemiluminescence immunoassay on the Bayer ADVIA Centaur at an external laboratory (Mitsubishi Chemical Medience Corp, Tokyo, Japan).

2.4. Other variables

Marital status, social status as defined by job position, and status of current smoking and alcohol drinking were self-reported in a lifestyle questionnaire. Occupational physical activity was divided into sedentary or active work according to job title; clerical jobs were classified as sedentary work, whereas other types of work including childcare work, school lunch cooking, and technical jobs were classified as active work (Ohta et al., 2007). Non-job physical activity was computed as the average metabolic equivalent-hours per week (Ainsworth et al., 1993) on the basis of self-reported usual frequency and duration of six different activities (walking, low-, moderate-, and high-intensity activities, gardening, and commuting to work). Body height was measured to the nearest 0.1 cm with the subject standing without shoes. Body weight in light indoor clothes was measured to the nearest 0.1 kg. Body mass index (BMI) was calculated as body weight (kg) divided by the square of body height (meters).

2.5. Statistical analyses

Differences in proportions and means of covariates between subjects with and without depressive symptoms and according to the quartiles of serum ferritin concentrations were assessed by using χ^2 test and t test or one-way analysis of variance (ANOVA), respectively. The association between depressive symptoms and serum ferritin concentrations was examined separately among men and women. In women, because serum ferritin concentrations considerably increases after menopause (Whitfield et al., 2003), we further analyzed the data separately for those aged <50 years and ≥ 50 years, with reference to data regarding the mean age of menopause in Japanese women (48.3 years old) (Amagai et al., 2006).

Multivariate logistic regression analyses were then used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) of depressive symptoms for the quartiles of serum ferritin concentrations, taking the highest quartile category as a reference. In the

first model, we adjusted for age and study site. In the final models, we further adjusted for marital status, social status, occupational physical activity, non-job physical activity, BMI, current smoking, current alcohol drinking, and serum folate. Trend of the association was assessed by using multiple linear regression analyses with the ordinal numbers 0 to 3 assigned to the quartile categories of serum ferritin concentrations. In addition, we conducted multivariate linear regression analyses in which both serum ferritin concentrations and CES-D score were log-transformed and included as continuous variables. Two-sided p -values of less than 0.05 were regarded as statistically significant. All data analyses were performed with SPSS version 17.0 (SPSS Inc, Chicago, IL, USA).

3. Results

In total, 36.5% of men and 36.1% of women had a CES-D scale score of ≥ 16 . The prevalence of those with a CES-D score of ≥ 19 and ≥ 23 was 26.0% and 14.4% for men and 26.4% and 14.4% for women, respectively. As shown in Table 1, men with depressive symptoms were significantly more likely to be unmarried and in lower social status. Women with depressive symptoms were significantly more likely to be engaged in sedentary work compared to those without depressive symptoms.

Mean values of serum ferritin concentrations were significantly higher in men (Mean = $163.9\text{ }\mu\text{g/L}$, S.D. = 141.9) than in women (Mean = $49.7\text{ }\mu\text{g/L}$, S.D. = 59.9) ($p < 0.001$). In women, those aged 50 years or older had significantly higher levels of serum ferritin concentrations (Mean = $38.6\text{ }\mu\text{g/L}$, S.D. = 50.7) compared to those aged younger than 50 years (Mean = $77.6\text{ }\mu\text{g/L}$, S.D. = 71.8) ($p < 0.001$). The comparisons of characteristics of subjects according to the quartiles of serum ferritin concentrations stratified by gender are shown in Table 2.

Table 3 presents the ORs (95% CIs) of depressive symptoms according to quartile categories of serum ferritin concentrations in age- and study-site-adjusted and multivariate-adjusted models stratified by gender. In men, the association between serum ferritin concentrations and prevalence of depressive symptoms remained statistically significant when the cutoff for CES-D of ≥ 19 was used even after adjustment for potential confounding variables, with multivariate adjusted ORs (95% CIs) in the first, second, third, and fourth quartiles of serum ferritin concentrations of 2.88 (0.93–8.91), 1.91 (0.90–4.05), 1.28 (0.66–2.49), and 1.00 (reference), respectively (p for trend = 0.03). However, we could not detect such association when the cutoff for CES-D of ≥ 16 and ≥ 23 were used with a p for trend in the multivariate-adjusted model of 0.21 and 0.91, respectively.

In women, no significant association was found between serum ferritin concentrations and prevalence of depressive symptoms defined by the three different cutoff values of CES-D, and U-shape relationships were observed (Table 3). Consistently, no significant difference was obtained even after exclusion of women aged 50 years and older in both the age- and study-site-adjusted and the multivariate-adjusted models. When the presence of depressive symptoms was defined as having CES-D score of ≥ 16 , the multivariate-adjusted ORs (95% CIs) for depressive symptoms in first, second, third, and fourth quartiles of serum ferritin concentration were 0.79 (0.17–3.68), 0.82 (0.17–4.02), 0.62 (0.12–3.24), and 1.00 (reference), respectively (p for trend = 0.73). Similarly, no significant association was found when the cutoff for CES-D of ≥ 19 and ≥ 23 were used.

In multiple linear regression analyses including both serum ferritin and CES-D score as continuous variables, there was no significant association between them in both men ($\beta = -0.13$, $p = 0.09$) and women ($\beta = -0.05$, $p = 0.40$).

4. Discussion

This study examined the relationship between levels of serum ferritin concentrations and depressive symptoms in well-functioning people in Japan. To the best of our knowledge, this study is among a few studies to date that attempts to explore the link between serum

Table 1
Characteristics of the study subjects with and without depressive symptoms stratified by gender.

	Men (<i>n</i> = 312)		<i>p</i> ^c	Women (<i>n</i> = 216)		<i>p</i> ^c
	Subjects with depressive symptoms ^a	Subjects without depressive symptoms ^b		Subjects with depressive symptoms ^a	Subjects without depressive symptoms ^b	
Number of subjects	114 (36.5)	198 (63.5)		78 (36.1)	138 (63.9)	
Study site ^d			0.25			0.11
A	32 (28.1)	68 (34.3)		17 (21.8)	44 (31.9)	
B	82 (71.9)	130 (65.7)		61 (78.2)	94 (68.1)	
Marital status			0.02			0.94
Married	77 (67.5)	157 (79.3)		49 (62.8)	86 (62.3)	
Unmarried	37 (32.5)	41 (20.7)		29 (37.2)	52 (37.7)	
Occupational physical activities			0.87			0.04
Sedentary work	102 (89.5)	176 (88.9)		59 (75.6)	85 (61.6)	
Active work	12 (10.5)	22 (11.1)		19 (24.4)	53 (38.4)	
Social status (defined by job position)			0.02			0.40
High	15 (13.2)	44 (22.2)		0 (0.0)	2 (1.5)	
Middle	45 (39.5)	52 (26.3)		27 (34.6)	49 (35.5)	
Low	54 (47.4)	102 (51.5)		51 (65.4)	87 (63.0)	
Non-job physical activity			0.14			0.98
0 MET-h/week	47 (41.2)	64 (32.3)		40 (51.3)	71 (51.4)	
0–<5 MET-h/week	31 (27.2)	50 (25.3)		23 (29.5)	42 (30.5)	
≥5 MET-h/week	36 (31.6)	84 (42.4)		15 (19.3)	25 (18.1)	
Current smoking			0.65			0.16
No	62 (54.4)	113 (57.1)		78 (100.0)	133 (96.4)	
Yes	52 (45.6)	85 (42.9)		0 (0.0)	5 (3.6)	
Current alcohol drinking			0.09			0.35
No	59 (51.8)	83 (41.9)		61 (78.2)	100 (72.5)	
Yes	55 (48.2)	115 (58.1)		17 (21.8)	38 (27.5)	
Age (years)	44.2 ± 10.4	44.6 ± 11.1	0.79	41.6 ± 10.1	40.6 ± 10.7	0.79
Body mass index (kg/m ²)	23.2 ± 3.4	23.8 ± 3.2	0.15	21.1 ± 3.2	21.0 ± 3.1	0.76

Values are means ± S.D. for continuous variables and numbers of subjects (proportion) for categorical variables.

^a Subjects with a Center for Epidemiology Studies Depression Scale (CES-D) score of <16.

^b Subjects with a CES-D score of ≥ 16.

^c Independent *t*-test was used for continuous variables; chi-square test was used for categorical variables.

^d Study site A: survey conducted in July 2006; B: survey conducted in November 2006.

ferritin and depression. Men with lower levels of serum ferritin concentrations had a higher risk of exhibiting depressive symptoms. However, the association was statistically significant only when depressive symptoms were defined by using a cutoff value for CES-D of ≥ 19. No statistically significant association was detected in women.

A limited number of observational studies have examined the association of serum ferritin concentrations and depression in clinical and non-clinical subjects with inconclusive findings. In patients, depression is associated with normal or increased levels of serum ferritin concentrations in studies conducted mostly in Western countries (Brock, 1994; Maes et al., 1996). In a study in Taiwan, chronic hemodialysis patients with major depressive symptoms had significantly higher levels of serum ferritin concentrations than

patients without major depressive symptoms (Huang and Lee, 2007). Chronic inflammatory process has been addressed to explain this association. Major depression is accompanied by biochemical and immune changes suggesting the presence of either an acute or a chronic inflammatory process (Maes, 1995; Maes et al., 1996). Important determinants of an inflammatory process are the release of cytokines and alterations of iron metabolism characterized by decreased serum iron and transferrin levels with normal or increased serum ferritin levels (Huang and Lee, 2007).

In non-clinical subjects, depression, as measured by the Minnesota Multiphasic Personality Inventory (MMPI), was not related to serum iron, hemoglobin, and ferritin levels among premenopausal women in the United States (Hunt and Peland, 1999). Similarly, the MEMO Study

Table 2
Characteristics of subjects according to the quartiles of serum ferritin concentration stratified by gender.

	Men (<i>n</i> = 312)					Women (<i>n</i> = 216)				
	Q1	Q2	Q3	Q4	<i>p</i> for trend ^a	Q1	Q2	Q3	Q4	<i>p</i> for trend ^a
Number of subjects	78	79	77	78		54	54	54	54	
Study site A ^b	21.1	14.9	33.3	42.2	<0.001	29.2	32.3	14.8	20.0	0.25
Married	78.9	76.1	78.1	71.1	0.32	62.8	58.5	66.7	80.0	0.47
Sedentary work	78.9	89.6	87.6	91.7	0.18	69.0	63.1	63.0	70.0	0.61
Low social status	52.6	44.8	50.5	52.1	0.52	63.7	75.4	51.9	50.0	0.02
NPA ≥ 5 MET-h/week	36.8	47.8	36.2	35.5	0.24	19.5	7.7	33.3	40.0	0.07
Current smoking	36.8	35.8	44.8	48.8	0.03	1.8	3.1	3.7	0.0	0.78
Current drinking	42.1	44.8	56.2	60.3	0.02	26.5	21.5	29.6	30.0	0.87
Age (years)	50.8 ± 11.5	44.3 ± 11.1	43.9 ± 10.3	44.0 ± 10.8	0.11	39.7 ± 9.4	38.9 ± 10.1	46.2 ± 11.8	53.4 ± 7.5	<0.001
BMI (kg/m ²)	23.2 ± 3.0	23.1 ± 3.0	23.0 ± 2.9	24.4 ± 3.6	0.006	20.7 ± 3.2	20.9 ± 3.0	22.2 ± 2.8	22.8 ± 3.6	0.008

Abbreviations: Q, quartile; BMI, body mass index; NPA, non-job physical activity; MET-h, metabolic equivalent-hour. Values are means for continuous variables and proportion (%) for categorical variables.

^a *p* for trend values were based on linear regression analyses with ordinal numbers 0 to 3 assigned to quartile categories of serum ferritin.

^b Study site A: survey conducted in July 2006.

Table 3

Odds ratios and 95% confident intervals for depressive symptoms according to quartile of serum ferritin concentration stratified by gender.

	Q1 (lowest)	Q2	Q3	Q4 (highest)	p for trend ^a
Men (n = 312)					
Median serum ferritin (µg/L)	50.7	106.0	168.0	281.0	
CES-D (15/16)					
With/without depressive symptoms (n)	36/42	26/53	28/49	24/54	
Age- and study-site-adjusted OR (95% CI)	2.17 (0.80–5.87)	1.33 (0.71–2.49)	0.96 (0.55–1.67)	1.00 (reference)	0.14
Multivariate-adjusted OR (95% CI) ^b	1.92 (0.66–5.62)	1.37 (0.69–2.71)	0.92 (0.51–1.66)	1.00 (reference)	0.21
CES-D (18/19)					
With/without depressive symptoms (n)	28/50	18/61	21/56	14/64	
Age- and study-site-adjusted OR (95% CI)	2.83 (1.01–7.94)	1.74 (0.87–3.49)	1.33 (0.71–2.47)	1.00 (reference)	0.02
Multivariate-adjusted OR (95% CI) ^b	2.88 (0.93–8.91)	1.91 (0.90–4.05)	1.28 (0.66–2.49)	1.00 (reference)	0.03
CES-D (15-/23) ^c					
With/without depressive symptoms (n)	12/42	10/53	12/49	11/54	
Age- and study-site-adjusted OR (95% CI)	0.70 (0.15–3.35)	1.08 (0.47–2.49)	0.76 (0.36–1.64)	1.00 (reference)	0.86
Multivariate-adjusted OR (95% CI) ^b	0.54 (0.10–2.88)	1.30 (0.53–3.21)	0.33 (0.33–1.68)	1.00 (reference)	0.91
Female (n = 216)					
Median serum ferritin (µg/L)	6.3	21.4	40.8	117.0	
CES-D (15/16)					
With/without depressive symptoms (n)	22/32	17/37	17/37	22/32	
Age- and study-site-adjusted OR (95% CI)	1.05 (0.26–4.22)	1.11 (0.26–4.67)	0.80 (0.17–3.65)	1.00 (reference)	0.74
Multivariate-adjusted OR (95% CI) ^b	0.79 (0.17–3.68)	0.82 (0.17–4.02)	0.62 (0.12–3.24)	1.00 (reference)	0.73
CES-D (18/19)					
With/without depressive symptoms (n)	16/38	13/41	7/47	17/37	
Age- and study-site-adjusted OR (95% CI)	1.63 (0.31–8.67)	1.77 (0.32–9.85)	1.41 (0.23–8.51)	1.00 (reference)	0.67
Multivariate-adjusted OR (95% CI) ^b	1.26 (0.22–7.28)	1.26 (0.20–7.75)	1.30 (1.20–8.53)	1.00 (reference)	0.72
CES-D (15-/23) ^c					
With/without depressive symptoms (n)	8/32	7/37	7/37	9/31	
Age- and study-site-adjusted OR (95% CI)	0.81 (0.40–1.65)	1.15 (0.59–2.26)	0.85 (0.42–1.73)	1.00 (reference)	0.78
Multivariate-adjusted OR (95% CI) ^b	0.89 (0.40–2.02)	1.24 (0.59–2.59)	0.94 (0.45–1.98)	1.00 (reference)	0.95

Abbreviations: Q, quartile; CES-D, Center for Epidemiologic Studies Depression scale; OR, odds ratio; CI, confidence interval.

^a p for trend values were based on linear regression analyses with the ordinal numbers 0 to 3 assigned to quartile categories of serum ferritin.^b Adjusted for age (years, continuous), marital status (married or unmarried), study site (A, survey conducted in July 2006 or B, survey conducted in November 2006), occupational physical activity (sedentary or active), social status (high, middle, or low), body mass index (kg/m², continuous), non-job physical activity (0, 0–<5, or ≥5 metabolic equivalent-hours per week), current smoking (no or yes), current drinking (no or yes), and serum folate (ng/mL, continuous).^c Subjects with a CES-D score of 16–22 were excluded.

(Memory and Morbidity in Augsburg Elderly) conducted among elderly people aged 65 years and older also concluded that there was a lack of association between serum ferritin concentrations and depressive mood (Baune et al., 2006). More recently, the German Health Interview and Examination Survey found significant association between major depression and decreased levels of serum ferritin concentrations in general population aged 18 to 65 years (Baune et al., 2010). Similarly, significant inversed association was also observed in the relationship between serum ferritin concentrations and depressive symptoms among female medical university students in Tehran, Iran (Vahdat Shariatpanaahi et al., 2007).

In the present study, the levels of serum ferritin concentrations were lower in men with a higher prevalence of depressive symptoms; the association, however, was statistically significant only when the presence of depressive symptoms was defined by using the cutoff of ≥ 19 on the CES-D scale. Although the cutoff for CES-D of ≥ 16 has been widely recommended, the cutoff of ≥ 19 has been recommended and validated for use among Japanese workers with the sensitivity and specificity of 92.7% and 91.8%, respectively (Wada et al., 2007). Such a higher cutoff is reasonable given that Japanese tend to express their positive emotion in a modest manner, leading to a high score on depression scales (Iwata et al., 1998).

In addition, it is worth noting that a gender difference was observed in regard to the association between decreased levels of serum ferritin concentrations and depressive symptoms among participants in this study. The inconsistency may be partly attributed to the significant difference in the levels of serum ferritin concentrations which was significantly lower in women than in men. Moreover, because the number of subjects, especially women, was not sufficiently large, this finding may be simply due to chance. Future

community-based studies should confirm the existence of a gender difference in the link between some specific biomarkers and depressive symptoms before potential explanations are hypothesized.

All population-based studies to date that examined the relationships between depression and serum ferritin have been cross-sectional. Consequently, it is impossible to draw a conclusion regarding the causal pathway. However, it could be speculated that the observed link between depression and serum ferritin concentrations is due to a reciprocal process (Penninx et al., 2003). This might indicate the possible roles of iron in brain function and the establishment of depressive mood (Vahdat Shariatpanaahi et al., 2007). Iron plays an important role in the oxygenation of brain parenchyma and the synthesis of many neurotransmitters and enzymes of the nervous system (Beard et al., 2005). Iron acts on the molecular level and its impacts on depression are multifactorial with positive and negative effects. For a negative effect, a sufficient amount of iron is particularly important for the synthesis of dopamine, a neurotransmitter that plays a significant role in mood disorders (Paul et al., 2002).

Our study has several limitations. First, the cross-sectional design does not allow causal inference. For example, lower serum ferritin concentrations may follow the onset of depression due to loss of appetite among depressive subjects. However, this is not plausible because, in this study, total energy intake was not significantly different in subjects with and without depressive symptoms. Second, our study sample was restricted to a relatively healthy subset of workers, in which prevalence of depressive symptoms may be lower compared to other subgroups in general population. Consequently, our findings may not be generalized to the more frail older population. Third, we used CES-D scale to measure depressive symptoms and did not include a psychiatric depression assessment. It is likely that the link between depression and

biomarkers is stronger in psychiatric patients who suffer from more severe and chronic depressive symptoms. Finally, although adjustment for a variety of potential confounding factors was done, residual confounding could not be ruled out.

Our findings that depressive symptoms, as assessed by CES-D (with a cutoff of ≥ 19), are associated with decreased levels of serum ferritin concentrations in apparently healthy men suggest that adverse mental health effects may be implicated in iron deficiency in Japanese workers.

References

- Ainsworth, B.E., Haskell, W.L., Leon, A.S., Jacobs Jr., D.R., Montoye, H.J., Sallis, J.F., Paffenbarger Jr., R.S., 1993. Compendium of physical activities: classification of energy costs of human physical activities. *Medicine and Science in Sports and Exercise* 25, 71–80.
- Amagai, Y., Ishikawa, S., Gotoh, T., Kayaba, K., Nakamura, Y., Kajii, E., 2006. Age at menopause and mortality in Japan: the Jichi Medical School Cohort Study. *Journal of Epidemiology* 16, 161–166.
- Batalena, L., Placidi, G.F., Martin, E., Falcone, M., Pellegrini, L., Dell'Osso, L., Pacchiarotti, A., Pinchera, A., 1990. Nocturnal serum thyrotropin (TSH) surge and the TSH-releasing hormone: dissociated behavior in untreated depressives. *The Journal of Clinical Endocrinology and Metabolism* 71, 650–655.
- Baune, B.T., Eckardstein, A.V., Berger, K., 2006. Lack of association between iron metabolism and depressive mood in an elderly general population. *International Psychogeriatrics* 18, 337–444.
- Baune, B.T., Neuhauser, H., Ellert, U., Berger, K., 2010. The roles of inflammatory workers ferritin, transferrin and fibrinogen in the relationship between major depression and cardiovascular disorders – The German Health Interview and Examination Survey. *Acta Psychiatrica Scandinavica* 121, 135–142.
- Beard, J.D., Connor, J.R., Jones, B.C., 1993. Iron in the brain. *Nutrition Reviews* 51, 157–170.
- Beard, J.L., Hendricks, M.K., Perez, E.M., Murray-Kolb, L.E., Berg, A., Vernon-Feagans, L., Irlam, J., Isaacs, W., Sive, A., Tomlinson, M., 2005. Maternal iron deficiency anemia affects postpartum emotions and cognition. *The Journal of Nutrition* 135, 267–272.
- Brock, J.H., 1994. Iron in infection, immunity, inflammation and neoplasia. In: Brock, J.H., Halliday, J.W., Pippard, M.J., Powell, L.W. (Eds.), *Iron Metabolism in Health and Disease*. WB Saunders, London, pp. 37–67.
- Huang, T.-L., Lee, C.-T., 2007. Low serum albumin and high ferritin levels in chronic hemodialysis patients with major depression. *Psychiatry Research* 152, 177–180.
- Hunt, J.R., Penland, J.G., 1999. Iron status and depression in premenopausal women: an MMPI study. *Minnesota Multiphasic Personality Inventory. Behavioral Medicine* 25, 62–68.
- Iwata, N., Umesue, M., Egashira, K., Hiro, H., Mizoue, T., Mishima, N., Nagata, S., 1998. Can positive affect items be used to assess depressive disorders in the Japanese population? *Psychological Medicine* 28, 153–158.
- Kaji, T., Mishima, K., Kitamura, S., Enomoto, M., Nagase, Y., Li, L., Kaneita, Y., Ohida, T., Nishikawa, T., 2010. Relationship between late-life depression and life stressors: large-scale cross-sectional study of a representative sample of the Japanese general population. *Psychiatry and Clinical Neurosciences* 63, 426–434.
- Lozoff, B., 1988. Behavioral alterations in iron deficiency. *Advance in Pediatrics* 35, 331–359.
- Maes, M., 1995. Evidence for an immune response in major depression: a review and hypothesis. *Progress in Neuropsychopharmacology Biological Psychiatry* 19, 11–38.
- Maes, M., Van de Vyvere, J., Vandoolaeghe, E., Bril, T., Demedts, P., Wauters, A., Neels, H., 1996. Alterations in iron metabolism and the erythron in major depression: further evidence for chronic inflammatory process. *Journal of Affective Disorders* 40, 23–33.
- Murakami, K., Mizoue, T., Sasaki, S., Ohta, M., Sato, M., Matsushita, Y., Mishima, N., 2008. Dietary intake of folate, other B vitamins, and ω -3 polyunsaturated fatty acids in relation to depressive symptoms in Japanese adults. *Nutrition* 24, 140–147.
- Nanri, A., Mizoue, T., Matsushita, Y., Sasaki, S., Ohta, M., Sato, M., Mishima, N., 2010. Serum folate and homocysteine and depressive symptoms among Japanese men and women. *European Journal of Clinical Nutrition* 64, 289–296.
- Ohta, M., Mizoue, T., Mishima, N., Ikeda, M., 2007. Effect of the physical activities in leisure time and commuting to work on mental health. *Journal of Occupational Health* 49, 46–52.
- Orino, K., Watanabe, K., 2008. Molecular, physiological and clinical aspects of the iron storage protein ferritin. *The Veterinary Journal* 178, 191–210.
- Paul, I., Tumer, R.E., Ross, D., 2002. *Update Nutrition* 8th edn. John Pow Company, USA.
- Penninx, B.W., Kritchewsky, S.B., Yaffe, K., Newman, A.B., Simonsick, E.M., Rubin, S., Ferrucci, L., Harris, T., Pahor, M., 2003. Inflammatory markers and depressed mood in older persons: results from the Health, Aging and Body Composition Study. *Biological Psychiatry* 54, 566–572.
- Radloff, L.S., 1977. The CES-D scale: a self-report depression scale for research in the general population. *Applied Psychological Measurement* 1, 385–401.
- Shima, S., Shikano, T., Kitamura, T., Asai, M., 1985. New self-rated scale for depression (in Japanese). *Japanese Journal of Clinical Psychiatry* 27, 717–723.
- Vahdat Shariatpanaahi, M., Vahdat Shariatpanaahi, Z., Moshtaaghi, M., Shahbaazi, S.H., Abadi, A., 2007. The relationship between depression and serum ferritin level. *European Journal of Clinical Nutrition* 61, 532–535.
- Wada, K., Tanaka, K., Theriault, G., Satoh, T., Mimura, M., Miyaoka, H., Aizawa, Y., 2007. Validity of the Center for Epidemiologic Studies Depression Scale as a screening instrument of major depressive disorder among Japanese workers. *American Journal of Industrial Medicine* 50, 8–12.
- Wang, W., Knovich, M.A., Coffman, L.G., Torti, F.M., Torti, S.V., 2010. Serum ferritin: past, present and future. *Biochimica et Biophysica Acta* 1800, 760–769.
- Whitfield, J.B., Treloar, S., Zhu, G., Powell, L.W., Martin, N.G., 2003. Relative importance of female-specific and non-female specific effects on variation in iron stores between women. *British Journal Haematology* 120, 860–866.