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Demographic and lifestyle correlates of brain-derived neurotrophic factor in a working population: The Furukawa Nutrition and Health Study

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ABSTRACT

This study aimed to examine the cross-sectional association of demographic and lifestyle factors with serum brain-derived neurotrophic factor (BDNF) concentrations in a Japanese working population. Participants were 1678 men and 172 women aged 19–69 years who received health check-ups and participated in a nutrition and health survey. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression (CES-D) scale. Dietary intake was assessed using a validated self-administered diet history questionnaire. Serum BDNF concentrations were measured using a solid phase sandwich enzyme-linked immunosorbent assay. Multiple linear regression analysis was used to estimate the mean and 95% confidence interval of serum BDNF concentrations according to demographic and lifestyle factors. Higher body mass index (BMI) was significantly associated with higher circulating BDNF concentrations. Current smokers had significantly higher mean BDNF concentrations than never-smokers. BDNF concentrations were not associated with folate and 25-hydroxyvitamin D concentrations in serum, or dietary eicosapentaenoic acid and docosahexaenoic acid intake. Serum BDNF concentrations were not associated with depressive symptoms or CES-D score per se. In this study, higher BMI and smoking were associated with higher concentrations of serum BDNF, while nutrients that have been linked to depression were not associated with BDNF concentrations among Japanese workers.

1. Introduction

The proportion of the global population with depression in 2015 is estimated to be 4.4% and increased by 18.4% between 2005 and 2015 (WHO, 2017). Depression, a common illness affecting an estimated over 300 million people, results from a complex interaction of social, psychological, and biological factors (WHO, 2018). Brain-derived neurotrophic factor (BDNF) is a dimeric protein found throughout the brain, with particular abundance in the hippocampus and cerebral cortex, and plays an important role in the survival, growth, and differentiation of neurons (Lewin and Barde, 1996). A meta-analysis showed that serum BDNF concentrations were significantly lower in depressed patients than non-depressed subjects and that BDNF concentrations increased after antidepressant treatment (Sen et al., 2008). A large body of evidence indicates a significant role for BDNF in the pathophysiology of depression.

Increasing attention has been paid to the role of lifestyles for the prevention of depression. Epidemiological evidence suggests that folate (Bender et al., 2017), vitamin D (Anglin et al., 2013), and n-3 polyunsaturated fatty acids (eicosapentaenoic acid and docosahexaenoic acid) (Grosso et al., 2016) are associated with a lower risk of depression. Moreover, non-dietary factors including smoking (Luger et al., 2014), physical activity (Schuch et al., 2018), and obesity (Jung et al., 2017) have been linked to depression. Work-related factors such as long working hours (Virtanen et al., 2012), shift work (Togo et al., 2017), and high job strain (Theorell et al., 2015) have also been reported to be associated with depressive symptoms. To date, the association of these dietary and non-dietary factors with BDNF concentration has been limited and inconsistent. It is important to clarify whether and, if any, how lifestyle factors are related to BDNF for the understanding of mechanism behind their association with depression. Furthermore, previous studies did not observe the association between BDNF concentrations and depressive symptoms (Goltz et al., 2017; Terracciano et al., 2011), though it is suggested that BDNF may be a biomarker for psychiatric disorders. Here, we examined the association of serum BDNF concentration with demographic, lifestyle factors including dietary factors, and depressive symptoms in a Japanese working population.

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2. Methods

2.1. Study procedure and participants

As part of the Japan Epidemiology Collaboration on Occupational Health Study, the Furukawa Nutrition and Health Study, a nutritional epidemiological survey was conducted during the periodic health examination among workers of a manufacturing company and its affiliated companies in Chiba Prefecture and Kanagawa Prefecture, Japan, in April 2012 and May 2013, respectively. Prior to the health checkup, we asked approximately 2800 workers to participate in the survey and to complete two types of survey questionnaires: one specifically inquired about diet and the other about overall health-related lifestyle. Of these, 2162 participants (1930 men and 232 women aged 18–70 years) agreed to participate in the survey with a response rate of about 77%. On the day of the health checkup, research staff checked the questionnaires for completeness and, where necessary, clarified details with the subjects. Participants were asked to donate 7 ml of venous blood. Additionally, we obtained health checkup data including the results of anthropometric and biochemical measurements and information on history of disease. The study protocol was approved by the Ethics Committee of the National Center for Global Health and Medicine, Japan. Written informed consent was obtained from all participants prior to the survey.

Of the 2162 participants, we excluded 58 participants who reported a history of cancer, cardiovascular disease, chronic hepatitis, chronic kidney disease including nephritis, and pancreatitis. We further excluded 218 participants who lacked data on BDNF. Finally, we excluded those with missing data on covariates used in the present analysis, leaving 1850 participants (1678 men and 172 women) for analysis.

2.2. Blood measurements

At the time of the survey, venous blood donated for the study was drawn into an anticoagulant-free vacuum tube and centrifuged to separate the serum. After conducting measurements for insulin, the remaining serum sample was stored at −80 °C until analysis. Serum folate, 25-hydroxyvitamin D, and BDNF concentrations were determined at an external laboratory (LSI Medience Corporation, Tokyo, Japan). Folate was measured using a chemiluminescent immunoassay, with intra-assay coefficients of variation of 3.1% at 2.6 ng/mL and 3.3% at 18.7 ng/mL. 25-hydroxyvitamin D was measured using a competitive protein binding assay, with intra-assay coefficients of variation of 10.9% at 13.3 ng/mL and 8.9% at 21.3 ng/mL. Serum BDNF concentrations were measured using a solid phase sandwich enzyme-linked immunosorbent assay using a Human BDNF Quantikine ELISA kit (R&D Systems, Minneapolis, MN, USA) in a single assay, with intra-assay coefficients of variation of 3.9% at 17.5 ng/mL and 5.6% at 39.2 ng/mL.

2.3. Other variables

The questionnaire inquired about marital status, shift work, overtime work, job grade, smoking, alcohol consumption, physical activity during work and housework or on the commute to work, and leisure-time physical activity. Physical activity during work and housework, commutes and leisure time were expressed as the sum of metabolic equivalents (METs) multiplied by the duration (in hours) across all levels of physical activity. Body height was measured to the nearest 0.1 cm with subjects standing without shoes. Body weight in light clothes was measured to the nearest 0.1 kg. BMI was calculated as weight in kilograms divided by the square of height in meters.

Depressive symptoms were assessed using the Japanese version (Shima et al., 1985) of the Center for Epidemiologic Studies Depression (CES-D) scale (Radloff, 1977), which was incorporated into the lifestyle questionnaire. This scale consists of 20 questions addressing 6 symptoms of depression. Each question is scored on a scale of 0–3 according to the frequency of the symptom, and the total CES-D score ranges from 0 to 60. The criterion validity of the CES-D scale has been well established both in Western (Radloff, 1977) and Japanese (Shima et al., 1985) participants. Depressive symptoms were defined as present when participants had a CES-D score ≥16. A cutoff value ≥19, which may be suitable for Japanese populations (Wada et al., 2007), was also used. Moreover, we defined severe depressive symptoms by a CES-D score ≥28 according to a study by Terracciano et al. (2011).

Dietary habits during the preceding month were assessed using a validated, brief self-administered diet history questionnaire (BDHQ) (Sasaki, 2004) covering 56 foods and beverages commonly consumed by Japanese populations. Dietary intake of energy and selected nutrients, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), was estimated using an ad hoc computer algorithm for BDHQ according to the Standard Tables of Food Composition in Japan. In a validation study of the BDHQ against 16-day weighted dietary records among 92 men and 92 women aged 31–76 years, the Pearson correlation coefficients for energy-adjusted intake of EPA and DHA were 0.31 and 0.30 in men, and 0.40 and 0.30 in women, respectively (Kobayashi et al., 2012).

2.4. Statistical analysis

For characteristics of participants, data were expressed as mean and percentages for continuous variables and categorical variables, respectively. Factors considered in the analysis were age, sex, site, BMI, marital status, job grade, overtime work, shift work, smoking status, alcohol consumption, physical activity during work and housework or on the commute to work, leisure-time physical activity, history of diabetes, serum folate concentration, serum 25-hydroxyvitamin D concentration, EPA intake, and DHA intake. To examine the association between these factors and serum BDNF concentration, we used multiple linear regression analysis to calculate the mean and 95% confidence interval (CI) of serum BDNF concentration for each exposure category with adjustment for other covariates. Moreover, we examined the association between depressive symptoms or mental disease under physician treatment and BDNF concentration using the above analysis method to confirm whether BDNF reflects the depressive status of the study population. Two-side P values <0.05 were regarded as statistically significant. All analyses were performed using Statistical Analysis System (SAS) version 9.3 (SAS Institute, Cary, NC, USA).

3. Results

The characteristics of the study participants are shown in Table 1. Ninety one percent of participants were men. Mean ± standard deviation (SD) of age was 43.5 ± 9.2 years. Mean ± SD (range) of serum BDNF concentrations were 30.1 ± 6.7 (1.0–62.3) ng/mL in all, 30.3 ± 6.7 (1.0–62.3) ng/mL in men, and 28.4 ± 6.1 (11.2–44.9) ng/mL in women. Men had a higher BMI and were more likely to be current smokers and alcohol drinkers and to be engaged in shift work, overtime work, and work-related and leisure-time physical activity than women. In addition, men had lower serum folate concentrations, but higher serum 25-hydroxyvitamin D concentrations than women.

Multivariable-adjusted mean serum BDNF concentrations according to demographic and lifestyle factors are shown in Table 2. Serum BDNF concentrations were significantly higher in participants aged 40–49 years than those aged <30 years in both the age-, sex-, and site-adjusted model and fully adjusted model. Serum BDNF concentrations were significantly positively associated with BMI in both models. The multivariable-adjusted mean BDNF concentrations were 29.3, 29.9, 30.6, 30.7, and 30.6 ng/mL for those with BMIs <21.0, 21.0–22.9, 23.0–24.9, 25.0–26.9, and ≥27.0 kg/m^2, respectively (P for trend = 0.003). Serum BDNF concentrations in current smokers were also significantly higher than those in never-smokers: the multivariable-adjusted mean BDNF concentration was 29.2 ng/mL in never-smokers,

Table 1
Characteristics of participants.

	All	Men	Women
No of participants	1850	1678	172
Age (mean ± SD, year)	43.5 ± 9.2	43.6 ± 9.2	43.2 ± 8.8
BMI (mean ± SD, kg/m^2)	23.4 ± 3.4	23.5 ± 3.3	21.6 ± 3.4
Site A (survey in April 2012, %)	55.0	54.9	55.8
Married (%)	69.9	71.7	52.9
Job grade (low, %)	66.2	63.2	95.3
Shift work (yes, %)	20.2	22.2	0.6
Overtime work (≥30 hours/month, %)	25.3	26.9	9.9
Work-related physical activity (mean ± SD, MET-hour/day)	14.0 ± 16.9	14.5 ± 17.3	9.2 ± 10.9
Leisure-time physical activity (mean ± SD, MET-hour/week)	8.2 ± 15.6	8.4 ± 15.6	6.3 ± 16.0
Current smoker (%)	29.6	31.6	9.9
Alcohol consumption (≥1 day/week, %)	54.5	57.4	26.2
History of diabetes (yes, %)	2.9	3.1	1.2
Serum folate concentrations (mean ± SD, ng/mL)	5.2 ± 2.9	5.0 ± 2.7	7.2 ± 3.9
Serum 25(OH)D concentrations (mean ± SD, ng/mL)	21.5 ± 5.3	21.6 ± 5.3	20.3 ± 5.1
EPA intake (mean ± SD, % energy)	0.12 ± 0.08	0.12 ± 0.08	0.13 ± 0.08
DHA intake (mean ± SD, % energy)	0.21 ± 0.12	0.21 ± 0.11	0.24 ± 0.12
CES-D score (mean ± SD)	12.4 ± 7.8	12.4 ± 7.9	12.0 ± 7.2
Depressive symptoms (CES-D ≥ 16, %)	28.0	28.1	27.3
Depressive symptoms (CES-D ≥ 19, %)	18.7	18.9	16.9

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CES-D, Center for Epidemiologic Studies Depression Scale; MET, metabolic equivalent.

31.3 ng/mL in current smokers with a consumption of <20 cigarettes/day, and 32.1 ng/mL in current smokers with a consumption of ≥20 cigarettes/day. Moreover, BDNF concentrations were significantly lower in alcohol drinkers consuming ≥46 g of ethanol/day and unmarried participants than nondrinkers and married participants, respectively, in the fully adjusted model. Women, participants in the highest quartile of leisure-time physical activity, those without a history of diabetes, and those with high serum 25-hydroxyvitamin D concentrations had significant lower serum BDNF concentrations than men, those in the lowest quartile of leisure-time physical activity, those with a history of diabetes, and those in the lowest quartile of serum 25-hydroxyvitamin D concentration, respectively, in the age-, sex-, and site-adjusted model. After adjustment for all covariates, however, these associations disappeared.

Regarding nutritional factors, serum BDNF concentrations were not associated with serum folate and dietary EPA and DHA intake. There were no significant differences in serum BDNF concentration between participants with and without depressive symptoms (for both criteria of CES-D score ≥16 and ≥19). The multivariable-adjusted mean serum BDNF concentrations were 30.1 ng/mL and 30.2 ng/mL (CES-D score ≥16; $P = 0.86$), and 29.9 ng/mL and 30.2 ng/mL (CES-D score ≥19; $P = 0.48$) in participants with and without depressive symptoms, respectively. When we defined severe depressive status as CES-D score ≥28, serum BDNF concentrations were significantly lower in participants with CES-D ≥28 than those with CES-D <16; the multivariable-adjusted mean BDNF concentrations were 28.8 ng/mL and 30.2 ng/mL, respectively ($P = 0.06$). Serum BDNF did not differ between participants with ($n = 39$) and without ($n = 1811$) mental disease who were under treatment (31.3 and 30.1 ng/ml in participants with and without a current medical history of mental disease, respectively; $P = 0.28$).

4. Discussion

In this cross-sectional study of Japanese workers, higher BMI, current smoking, and age 40–49 years were associated with higher serum BDNF concentration, whereas heavy alcohol consumption (≥46 g of ethanol/day) was associated with lower serum BDNF concentration. Nutritional factors including serum folate and 25-hydroxyvitamin D concentrations and dietary EPA and DHA intake were not associated with serum BDNF. To our knowledge, this is among a few studies to report the association of serum BDNF concentration with demographic and lifestyle factors.

Published studies have reported inconsistent findings regarding the association between BDNF and BMI. Consistent with our present finding, circulating BDNF was previously shown to be positively associated with BMI in US women (Golden et al., 2010) and in a Japanese study among patients with type 2 diabetes (Suwa et al., 2006). In contrast, a study in Turkey observed that serum BDNF concentrations were lower in obese (BMI ≥30 kg/m^2) than non-obese participants (BMI <25.0 kg/m^2) (Celik Guzel et al., 2014). Moreover, serum BDNF concentrations were not associated with BMI among apparently healthy men and women in Hong Kong (Chan et al., 2008) and the Netherlands (Bus et al., 2011). Similarly, there was no association between plasma BDNF and BMI among depressed and control participants in an elderly US population (Pillai et al., 2012). BDNF is involved in not only neurological development but also body weight control and energy homeostasis, and BDNF deficiency causes decreased satiety and hyperphagia through impairment in hypothalamic and hippocampal functions including the mechanisms associated with appetite regulation (Rosas-Vargas et al., 2011). However, the following is also suggested. Proinflammatory cytokines can stimulate BDNF secretion from monocytes (Kerschensteiner et al., 1999; Schulte-Herbruggen et al., 2005); thus, the elevated BDNF levels may be indicative of an inflammatory state associated with greater adiposity (Thorand et al., 2006; Warnberg et al., 2006). Given the inconsistent epidemiological data and different mechanistic explanation, further investigation is required for the association between obesity and BDNF.

Our finding that serum BDNF concentrations were higher in current smokers than in never-smokers is consistent with those from large-scale studies in the Netherlands (Bus et al., 2011, 2012; Jamal et al., 2015) and Thailand (Suriyaprom et al., 2013). Moreover, serum BDNF concentrations tended to increase with the total number of smoking years in the Dutch study (Jamal et al., 2015) and with the number of cigarettes smoked per day in the Thai study (Suriyaprom et al., 2013). In animal studies, BDNF mRNA and protein expression is increased in the hippocampus after nicotine infusion (Andresen et al., 2009). Acute nicotine administration reduces BDNF mRNA expression due to its inhibitory effect on BDNF mRNA (Kenny et al., 2000). However, after chronic administration, tolerance to the inhibitory effect of nicotine on BDNF mRNA develops, leading to increased BDNF expression (Kenny et al., 2000).

Folate, vitamin D, EPA, and DHA have been reported to be associated with depressive symptoms (Anglin et al., 2013; Bender et al., 2017; Grosso et al., 2016). However, in the present study, serum

Table 2
Multivariable-adjusted mean serum brain-derived neurotrophic factor concentrations (ng/mL) in relation to demographic and lifestyle factors.

	No of participants	Age-, sex-, and site-adjusted model[1]		Multivariable-adjusted model[2]	
		BDNF[3] (ng/mL)	Trend *P*[4]	BDNF[3] (ng/mL)	Trend *P*[4]
Age[5] (year)					
<30 (ref)	87	29.1 (27.7–30.4)	0.012	29.1 (27.7–30.5)	0.040
30–39	589	30.3 (29.8–30.8)		30.2 (29.6–30.7)	
40–49	739	30.8 (30.3–31.3)[6]		30.9 (30.4–31.4)[6]	
50–59	307	29.7 (29.0–30.4)		29.7 (29.0–30.5)	
≥60	128	27.4 (26.3–28.5)		27.4 (26.2–28.6)	
Sex[7]					
Men (ref)	1678	30.3 (30.0–30.6)	<0.001	30.2 (29.9–30.5)	0.16
Women	172	28.4 (27.4–29.4)[6]		29.4 (28.3–30.5)	
Site[8]					
A (survey in April 2012) (ref)	1018	28.8 (28.4–29.2)	<0.001	28.8 (28.4–29.2)	<0.001
B (survey in May 2013)	832	31.7 (31.3–32.2)[6]		31.8 (31.3–32.2)[6]	
BMI (kg/m^2)					
<21.0 (ref)	428	29.4 (28.8–30.0)	0.001	29.3 (28.7–30.0)	0.003
21.0–22.9	498	29.9 (29.3–30.4)		29.9 (29.3–30.5)	
23.0–24.9	439	30.4 (29.8–31.0)[6]		30.6 (30.0–31.2)[6]	
25.0–26.9	252	30.7 (29.9–31.5)[6]		30.7 (29.9–31.5)[6]	
≥27.0	233	30.9 (30.1–31.7)[6]		30.6 (29.8–31.5)[6]	
Marital status					
Married (ref)	1294	30.2 (29.9–30.6)	0.45	30.4 (30.0–30.7)	0.031
Others	556	30.0 (29.4–30.5)		29.6 (29.0–30.2)[6]	
Job grade					
Low (ref)	1225	30.3 (29.9–30.6)	0.14	30.2 (29.9–30.6)	0.23
Middle	357	30.1 (29.5–30.8)		30.2 (29.5–30.9)	
High	268	29.5 (28.7–30.3)		29.6 (28.8–30.4)	
Overtime work (hour/month)					
<10 (ref)	554	29.8 (29.2–30.4)	0.49	29.8 (29.2–30.3)	0.34
10–29	828	30.4 (29.9–30.8)		30.3 (29.9–30.8)	
≥ 30	468	30.1 (29.5–30.7)		30.2 (29.6–30.8)	
Shift work					
Day shift (ref)	1095	30.0 (29.6–30.4)	0.15	30.1 (29.8–30.5)	0.94
Flexible work	368	29.8 (29.1–30.5)		30.1 (29.4–30.8)	
Midnight shift or shiftwork	387	30.7 (30.1–31.4)		30.1 (29.3–30.9)	
Smoking status					
Never (ref)	734	29.2 (28.7–29.7)	<0.001	29.2 (28.8–29.7)	<0.001
Past	569	29.9 (29.3–30.4)		29.9 (29.3–30.4)	
<20 cigarettes/day	343	31.4 (30.7–32.1)[6]		31.3 (30.6–32.0)[6]	
≥20 cigarettes/day	204	32.1 (31.3–33.0)[6]		32.1 (31.1–33.0)[6]	
Alcohol drinking					
Nondrinker (ref)	600	30.6 (30.1–31.1)	0.12	30.5 (29.9–31.0)	0.12
Occasional	241	29.9 (29.1–30.7)		30.2 (29.4–31.0)	
<23 g of ethanol/day	498	29.6 (29.1–30.2)[6]		29.8 (29.2–30.4)	
23-<46 g of ethanol/day	349	30.6 (29.9–31.3)		30.5 (29.8–31.2)	
≥46 g of ethanol/day	162	29.3 (28.3–30.3)[6]		29.0 (28.0–30.1)[6]	
Work-related physical activity					
Quartile 1 (ref)	486	29.9 (29.3–30.4)	0.09	30.0 (29.4–30.6)	0.85
Quartile 2	439	29.8 (29.2–30.5)		30.2 (29.5–30.8)	
Quartile 3	461	30.3 (29.7–30.9)		30.4 (29.8–31.0)	
Quartile 4	464	30.5 (29.9–31.1)		30.0 (29.3–30.7)	
Leisure-time physical activity					
Quartile 1 (ref)	496	30.7 (30.2–31.3)	0.003	30.5 (29.9–31.0)	0.075
Quartile 2	431	30.3 (29.7–30.9)		30.3 (29.6–30.9)	
Quartile 3	455	30.1 (29.5–30.7)		30.1 (29.5–30.7)	
Quartile 4	468	29.4 (28.8–30.0)[6]		29.7 (29.1–30.3)	
History of diabetes					
No (ref)	1796	30.1 (29.8–30.34	0.023	30.1 (29.8–30.4)	0.12
Yes	54	32.1 (30.4–33.9)[6]		31.5 (29.8–33.3)	
Serum folate concentrations					
Quartile 1 (ref)	466	30.6 (30.0–31.2)	0.08	30.2 (29.6–30.8)	0.87
Quartile 2	454	30.3 (29.7–30.9)		30.1 (29.6–30.7)	
Quartile 3	474	29.9 (29.3–30.5)		30.1 (29.5–30.6)	
Quartile 4	456	29.8 (29.2–30.4)		30.1 (29.5–30.7)	
Serum 25(OH)D concentrations					
Quartile 1 (ref)	467	30.6 (30.0–31.2)	0.013	30.4 (29.8–31.0)	0.18
Quartile 2	461	30.6 (30.0–31.2)		30.5 (30.0–31.1)	
Quartile 3	459	29.6 (29.0–30.2)[6]		29.6 (29.0–30.2)	
Quartile 4	463	29.7 (29.1–30.3)[6]		30.0 (29.4–30.6)	
EPA intake					
Quartile 1 (ref)	462	30.2 (29.6–30.8)	0.39	29.9 (28.7–31.2)	0.89
Quartile 2	463	30.1 (29.5–30.7)		30.1 (29.2–30.9)	
Quartile 3	463	30.3 (29.7–30.9)		30.4 (29.5–31.2)	
Quartile 4	462	29.9 (29.3–30.5)		30.2 (28.7–31.6)	
DHA intake					

(*continued on next page*)

Table 2 (*continued*)

	No of participants	Age-, sex-, and site-adjusted model[1]		Multivariable-adjusted model[2]	
		BDNF[3] (ng/mL)	Trend P[4]	BDNF[3] (ng/mL)	Trend P[4]
Quartile 1 (ref)	462	30.2 (29.6–30.8)	0.39	30.3 (29.0–31.5)	0.80
Quartile 2	463	30.1 (29.5–30.7)		30.1 (29.3–31.0)	
Quartile 3	463	30.3 (29.7–30.9)		30.2 (29.3–31.1)	
Quartile 4	462	29.8 (29.3–30.4)		29.9 (28.5–31.4)	

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; ref, reference.
[1] Adjusted for age (year, continuous), sex, and site (survey in April 2012 or in May 2013).
[2] Adjusted for all confounders which were noted in Table.
[3] BDNF concentrations (ng/mL) are expressed as mean (95%CI).
[4] Based on multiple linear regression with assignment of ordinal number or median value for each category.
[5] Except for age from adjustment factors.
[6] There was significant difference compared with the reference category of the variable.
[7] Except for sex from adjustment factors.
[8] Except for site from adjustment factors.

concentrations or dietary intake of these nutrients were not associated with serum BDNF concentration. In a randomized controlled trial among 26 older adults in Australia (Pirotta et al., 2015), serum BDNF concentrations did not change after 10 weeks of intervention in either the vitamin D supplement or placebo group. In a randomized controlled trial among 110 injured patients vulnerable to posttraumatic stress disorder and depression in Japan (Matsuoka et al., 2014), there was no difference in serum BDNF between the DHA supplement and placebo groups after 12 weeks. Similarly, in a randomized controlled study among 25 diabetic patients with major depression in the Netherlands (Bot et al., 2011), 12-week supplementation with omega-3 ethyl-eicosapentaenoic acid (E-EPA) had no effect on serum BDNF concentration. Regarding folate, in a cross-sectional US study among 496 middle-aged and elderly men and women (mean age approximately 70 years) (Golden et al., 2010), plasma BDNF concentrations were inversely associated with plasma folate in women but not in men. In a Japanese study among women aged 11–19 years (Tsuchimine et al., 2015), serum folate concentrations were lower in patients with depression ($n = 24$) than in healthy controls ($n = 26$), but serum BDNF did not differ between the two groups. Animal studies have shown that n-3 polyunsaturated fatty acid supplementation increases brain BDNF levels (Venna et al., 2009). In animal studies, BDNF can cross the blood-brain barrier (Pan et al., 1998) and cortical levels of BDNF are correlated with serum BDNF levels (Karege et al., 2002). However, the correlation between peripheral serum BDNF levels and brain BDNF levels in humans remains to be elucidated (Krishnan and Nestler, 2008).

A meta-analysis reported lower serum BDNF concentrations in depressed participants than in healthy control participants, suggesting that BDNF may be a biomarker for psychiatric disorders (Sen et al., 2008). Contrary to our expectation, however, we did not observe an association between serum BDNF concentration and depressive symptoms (as assessed using CES-D) among apparently healthy participants. Similarly, an Italian study did not observe an association between serum BDNF concentration and CES-D score ($r = -0.032$, $P = 0.15$) in a community-based cohort (2099 men and women aged 51.4 ± 15.3 years) (Terracciano et al., 2011). A German study also reported no association of serum BDNF with depressive symptoms (as assessed using the Patient Health Questionnaire) in a population-based cohort (3926 men and women aged 20–79 years) (Goltz et al., 2017). In the meta-analysis, most of the studies examined outpatients or inpatients diagnosed with major depressive disorders (Sen et al., 2008). In contrast, the present and the previous (Italian and German) studies examined apparently healthy populations for an outcome of depressive symptoms (not major depressive disorders). When we defined the outcome as severe depressive symptoms (CES-D score ≥28), we observed that serum BDNF concentrations were lower in participants with severe depressive symptoms than without depressive symptoms. The Italian study reported similar findings (Terracciano et al., 2011). The CES-D scale was developed for use in epidemiological studies of depressive symptomatology in general populations (Radloff, 1977), not for the diagnosis of clinical depression. The lack of an association between BDNF and depressive symptoms might be because the criteria CES-D score ≥16 included many participants with light to moderate depressive symptoms.

Strengths of the present study include a high study participation rate; measurement of circulating BDNF, folate, and 25-hydroxyvitamin D concentrations; use of validated questionnaires for diet and depressive symptoms; and adjustment for known and suspected risk factors of depressive symptoms. Because this study was conducted in employees of one particular company during nonselective recruitment for the annual health checkup and had a high study participation rate, the possibility of bias associated with selective study participation is low. Our study also had some limitations. First, associations derived under a cross-sectional design cannot indicate causality. To minimize the possibility of reverse causality, we excluded participants with a history of serious diseases that might affect depressive symptoms or lifestyle factors including dietary habits. Second, because lifestyle factors were self-reported and serum BDNF were measured using single assay, measurement error due to incorrect recall and random variation is inevitable. Third, we did not obtain information for antidepressive medication, which may influence serum BDNF concentrations (Sen et al., 2008). We confirmed that serum BDNF concentrations did no differ between participants with and without mental disease under treatment. Fourth, although we adjusted for important risk factors for depressive symptoms, we cannot rule out the possibility of bias due to unrecognized confounders or residual confounding. Finally, because the study participants were workers of one particular company and most of them (91%) were men, the present findings may not be applicable to the general population.

In conclusion, we observed that lifestyle factors including BMI, smoking, and alcohol consumption were significant predictors of serum BDNF concentration. In contrast, dietary factors including serum folate and 25-hydroxyvitamin D, and dietary intake of DHA and EPA were not associated with serum BDNF concentration. Our finding may be useful for the understanding of mechanism behind the association between lifestyle factors and depression.

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Declaration of interest

None to declare.

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References

Andresen, J.H., Loberg, E.M., Wright, M., Goverud, I.L., Stray-Pedersen, B., Saugstad, O.D., 2009. Nicotine affects the expression of brain-derived neurotrophic factor mRNA and protein in the hippocampus of hypoxic newborn piglets. J. Perinat. Med. 37, 553–560.

Anglin, R.E., Samaan, Z., Walter, S.D., McDonald, S.D., 2013. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. Br. J. Psychiatry 202, 100–107.

Bender, A., Hagan, K.E., Kingston, N., 2017. The association of folate and depression: a meta-analysis. J. Psychiatr. Res. 95, 9–18.

Bot, M., Pouwer, F., Assies, J., Jansen, E.H., Beekman, A.T., de Jonge, P., 2011. Supplementation with eicosapentaenoic omega-3 fatty acid does not influence serum brain-derived neurotrophic factor in diabetes mellitus patients with major depression: a randomized controlled pilot study. Neuropsychobiology 63, 219–223.

Bus, B.A., Molendijk, M.L., Penninx, B.J., Buitelaar, J.K., Kenis, G., Prickaerts, J., et al., 2011. . Determinants of serum brain-derived neurotrophic factor. Psychoneuroendocrinology 36, 228–239.

Bus, B.A., Tendolkar, I., Franke, B., de Graaf, J., den Heijer, M., Buitelaar, J.K., et al., 2012. . Serum brain-derived neurotrophic factor: determinants and relationship with depressive symptoms in a community population of middle-aged and elderly people. World J. Biol. Psychiatry 13, 39–47.

Celik Guzel, E., Bakkal, E., Guzel, S., Eroglu, H.E., Acar, A., Kucukyalcin, V., et al., 2014. . Can low brain-derived neurotrophic factor levels be a marker of the presence of depression in obese women. Neuropsychiatr. Dis. Treat. 10, 2079–2086.

Chan, K.L., Tong, K.Y., Yip, S.P., 2008. Relationship of serum brain-derived neurotrophic factor (BDNF) and health-related lifestyle in healthy human subjects. Neurosci. Lett. 447, 124–128.

Golden, E., Emiliano, A., Maudsley, S., Windham, B.G., Carlson, O.D., Egan, J.M., et al., 2010. . Circulating brain-derived neurotrophic factor and indices of metabolic and cardiovascular health: data from the Baltimore Longitudinal Study of Aging. PLoS One 5, e10099.

Goltz, A., Janowitz, D., Hannemann, A., Nauck, M., Hoffmann, J., Seyfart, T., et al., 2017. Association of brain-derived neurotrophic factor and vitamin D with depression and obesity: a population-based study. Neuropsychobiology 76, 171–181.

Grosso, G., Micek, A., Marventano, S., Castellano, S., Mistretta, A., Pajak, A., et al., 2016. Dietary n-3 PUFA, fish consumption and depression: a systematic review and meta-analysis of observational studies. J. Affect. Disord. 205, 269–281.

Jamal, M., Van der Does, W., Elzinga, B.M., Molendijk, M.L., Penninx, B.W., 2015. Association between smoking, nicotine dependence, and BDNF Val66Met polymorphism with BDNF concentrations in serum. Nicotine Tob. Res. 17, 323–329.

Jung, S.J., Woo, H.T., Cho, S., Park, K., Jeong, S., Lee, Y.J., et al., 2017. Association between body size, weight change and depression: systematic review and meta-analysis. Br. J. Psychiatry 211, 14–21.

Karege, F., Schwald, M., Cisse, M., 2002. Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets. Neurosci. Lett. 328, 261–264.

Kenny, P.J., File, S.E., Rattray, M., 2000. Acute nicotine decreases, and chronic nicotine increases the expression of brain-derived neurotrophic factor mRNA in rat hippocampus. Brain Res. Mol. Brain Res. 85, 234–238.

Kerschensteiner, M., Gallmeier, E., Behrens, L., Leal, V.V., Misgeld, T., Klinkert, W.E., et al., 1999. Activated human T cells, B cells, and monocytes produce brain-derived neurotrophic factor in vitro and in inflammatory brain lesions: a neuroprotective role of inflammation. J. Exp. Med. 189, 865–870.

Kobayashi, S., Honda, S., Murakami, K., Sasaki, S., Okubo, H., Hirota, N., et al., 2012. Both comprehensive and brief self-administered diet history questionnaires satisfactorily rank nutrient intakes in Japanese adults. J. Epidemiol. 22, 151–159.

Krishnan, V., Nestler, E.J., 2008. The molecular neurobiology of depression. Nature 455, 894–902.

Lewin, G.R., Barde, Y.A., 1996. Physiology of the neurotrophins. Annu. Rev. Neurosci. 19, 289–317.

Luger, T.M., Suls, J., Vander Weg, M.W., 2014. How robust is the association between smoking and depression in adults? A meta-analysis using linear mixed-effects models. Addict. Behav. 39, 1418–1429.

Matsuoka, Y., Nishi, D., Tanima, Y., Itakura, M., Kojima, M., Hamazaki, K., et al., 2014. Serum pro-BDNF/BDNF as a treatment biomarker for response to docosahexaenoic acid in traumatized people vulnerable to developing psychological distress: a randomized controlled trial. Transl. Psychiatry 5, e596.

Pan, W., Banks, W.A., Fasold, M.B., Bluth, J., Kastin, A.J., 1998. Transport of brain-derived neurotrophic factor across the blood-brain barrier. Neuropharmacology 37, 1553–1561.

Pillai, A., Bruno, D., Sarreal, A.S., Hernando, R.T., Saint-Louis, L.A., Nierenberg, J., et al., 2012. Plasma BDNF levels vary in relation to body weight in females. PLoS One 7, e39358.

Pirotta, S., Kidgell, D.J., Daly, R.M., 2015. Effects of vitamin D supplementation on neuroplasticity in older adults: a double-blinded, placebo-controlled randomised trial. Osteoporos. Int. 26, 131–140.

Radloff, L.S., 1977. The CES-D scale: a self-report depression scale for research in the general population. Appl. Psychol. Meas. 1, 385–401.

Rosas-Vargas, H., Martinez-Ezquerro, J.D., Bienvenu, T., 2011. Brain-derived neurotrophic factor, food intake regulation, and obesity. Arch. Med. Res. 42, 482–494.

Sasaki, S., 2004. Development and evaluation of dietary assessment methods using biomarkers and diet history questionnaires for individuals. in: In: Ministry of Health, Labour and Walfare, Japan (ed), Research for Evaluation Methods of Nutrition and Dietary Lifestyle Programs Held on Healthy Japan 21 (head investigator: Tanaka H). Summary report. Tokyo. pp. 10–44 :in Japanese.

Schuch, F.B., Vancampfort, D., Firth, J., Rosenbaum, S., Ward, P.B., Silva, E.S., et al., 2018. . Physical activity and incident depression: a meta-analysis of prospective cohort studies. Am. J. Psychiatry. https://doi.org/10.1176/appi.ajp.2018.17111194.

Schulte-Herbruggen, O., Nassenstein, C., Lommatzsch, M., Quarcoo, D., Renz, H., Braun, A., 2005. Tumor necrosis factor-alpha and interleukin-6 regulate secretion of brain-derived neurotrophic factor in human monocytes. J. Neuroimmunol. 160, 204–209.

Sen, S., Duman, R., Sanacora, G., 2008. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. Biol. Psychiatry 64, 527–532.

Shima, S., Shikano, T., Kitamura, T., Asai, M., 1985. New self-rating scale for Depression (in Japanese). Jpn. J. Clin. Psychiatry 27, 717–723.

Suriyaprom, K., Tungtrongchitr, R., Thawnashom, K., Pimainog, Y., 2013. BDNF Val66Met polymorphism and serum concentrations of BDNF with smoking in Thai males. Genet. Mol. Res. 12, 4925–4933.

Suwa, M., Kishimoto, H., Nofuji, Y., Nakano, H., Sasaki, H., Radak, Z., et al., 2006. Serum brain-derived neurotrophic factor level is increased and associated with obesity in newly diagnosed female patients with type 2 diabetes mellitus. Metabolism 55, 852–857.

Terracciano, A., Lobina, M., Piras, M.G., Mulas, A., Cannas, A., Meirelles, O., et al., 2011. Neuroticism, depressive symptoms, and serum BDNF. Psychosom. Med. 73, 638–642.

Theorell, T., Hammarstrom, A., Aronsson, G., Traskman Bendz, L., Grape, T., Hogstedt, C., et al., 2015. A systematic review including meta-analysis of work environment and depressive symptoms. BMC Public Health 15, 738.

Thorand, B., Baumert, J., Doring, A., Herder, C., Kolb, H., Rathmann, W., et al., 2006. Sex differences in the relation of body composition to markers of inflammation. Atherosclerosis 184, 216–224.

Togo, F., Yoshizaki, T., Komatsu, T., 2017. Association between depressive symptoms and morningness-eveningness, sleep duration and rotating shift work in Japanese nurses. Chronobiol. Int. 34, 349–359.

Tsuchimine, S., Saito, M., Kaneko, S., Yasui-Furukori, N., 2015. Decreased serum levels of polyunsaturated fatty acids and folate, but not brain-derived neurotrophic factor, in childhood and adolescent females with depression. Psychiatry Res. 225, 187–190.

Venna, V.R., Deplanque, D., Allet, C., Belarbi, K., Hamdane, M., Bordet, R., 2009. PUFA induce antidepressant-like effects in parallel to structural and molecular changes in the hippocampus. Psychoneuroendocrinology 34, 199–211.

Virtanen, M., Stansfeld, S.A., Fuhrer, R., Ferrie, J.E., Kivimaki, M., 2012. Overtime work as a predictor of major depressive episode: a 5-year follow-up of the Whitehall II study. PLoS One 7, e30719.

Wada, K., Tanaka, K., Theriault, G., Satoh, T., Mimura, M., Miyaoka, H., et al., 2007. Validity of the Center for Epidemiologic Studies Depression Scale as a screening instrument of major depressive disorder among Japanese workers. Am. J. Ind. Med. 50, 8–12.

Warnberg, J., Nova, E., Moreno, L.A., Romeo, J., Mesana, M.I., Ruiz, J.R., et al., 2006. Inflammatory proteins are related to total and abdominal adiposity in a healthy adolescent population: the AVENA study. Am. J. Clin. Nutr. 84, 505–512.

WHO, 2017. Depression and Other Common Mental Disorders: Global Health Estimates. WHO Document Production Services, Geneva, Switzerland. http://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf (Accessed 4 December 2018).

WHO, 2018. Depression. http://www.who.int/mediacentre/factsheets/fs369/en/ (Accessed 25 May 2018).