RESEARCH ARTICLE

Environmental science and pollution research role of heavy metal concentrations and vitamin intake from food in depression: a national cross-sectional study (2009–2017)

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Abstract

Little is known about associations between depression and serum heavy metal levels, dietary vitamin intakes. Thus, we sought to determine the nature of these associations and to predict risks of depression using marginal effects. A data set of 16,371 individuals aged ≥10 years that participated in Korea National Health and Nutrition Examination Surveys (KNHANES) conducted from 2009 to 2017 (excluding 2014 and 2015) was used to obtain information on sociodemographics, family histories, lifestyles, serum heavy metal levels, food intakes, and depression. Serum cadmium (Cd) and lead (Pb) levels were analyzed by graphite furnace atomic absorption spectrometry and mercury (Hg) levels using a mercury analyzer. Daily vitamin intakes were calculated by 24-h dietary recall. The results obtained showed that females are at higher risk of depression than males. A doubling of serum Cd was associated with a 21% increase in depression (AOR 1.21, 95% CI: 1.07–1.37, $p = 0.002$), whereas twofold increases in daily vitamin B1, B3 and vitamin A intakes reduced the risk of depression by 17% (0.83, 95% CI: 0.73–0.95, $p = 0.005$), 20% (0.80, 95% CI: 0.70–0.91, $p = 0.001$), and 8% (0.92, 95% CI: 0.85–0.99, $p = 0.020$), respectively. Interactions between heavy metals, vitamin intakes, and sex did not influence the risk of depression. The result shows that increased daily dietary vitamin intake might protect the public against depression. Further studies are needed to reduce the risks posed by heavy metals and to determine more comprehensively the effects of daily dietary vitamin intake on depression.

Keywords Heavy metals · Depression · Cadmium · Food intakes

Introduction

The public health burden imposed by depression is massive. More than 264 million people worldwide were affected before the COVID-19 (coronavirus disease-19) pandemic (WHO 2021), and recent evidence indicates that its prevalence has increased considerably since (Czeisler et al. 2020; Ettman et al. 2020; Gao et al. 2020; Huang and Zhao 2020). South Korea has witnessed a third wave of COVID-19, and the number of individuals that experience depressive symptoms has increased in line with the number of infections (Seong et al. 2021). Depression can result in suicide, which was

reported recently to be the second-most common cause of death among 15- to 29-year-olds (WHO 2021). Remarkably, South Korea has the highest suicide rate among member countries of the OECD (Organization for Economic Co-operation and Development) (Lee et al. 2018). Several socio-environmental, psychological, and physical factors, such as alcohol overconsumption, smoking, overweightedness/obesity, inactivity, and coincident chronic diseases, have been associated with the development of depression symptoms (Association AP 2013). However, increasing evidence shows that these factors do not fully explain the prevalence of depression (Lahouaoui et al. 2019), and interestingly, environmental heavy metals have also been reported to be risk factors of mental illness, especially depression (Angeli et al. 2013; Arbi et al. 2017; Poursafa et al. 2014; Valera et al. 2012).

Heavy metals have long been documented as environmental risk factors for multi-organ dysfunction. These metals are persistent environmental pollutants, which means humans are exposed to them in industrial environments and generally in food, water, and air (Ali et al. 2019). Notably, rapid

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industrialization and urbanization have increased the likelihood of heavy metal exposure (Duc et al. 2021a; Nguyen and Kim 2021; Nguyen et al. 2021; Poursafa et al. 2014). Mercury (Hg), cadmium (Cd), and lead (Pb) are three of the most toxic heavy metals studied in recent years. Sources of Cd exposure include contaminated foods and smoking (Satarug et al. 2017). Sources of Hg exposure include cosmetic preparations, fossil fuels, air, contaminated waste, and food, especially contaminated seafood and fish (Çamur et al. 2016; Garí et al. 2013, Wolkin et al. 2012), and sources of Pb exposure include petrol, cigarette smoke, industrial processes, domestic Pb-based paints, soil, air, water, and contaminated food (Aelion et al. 2012; Hrubá et al. 2012). Reportedly, Cd plays a vital role in the pathogenesis of depression (Orisakwe 2014), and several studies have concluded depression is associated with exposure to Pb and Hg (Ng et al. 2013a; Orisakwe 2014). Although numerous researchers have attempted to evaluate the relationship between heavy metals and depression, little is known about their impacts in the Korean population (Park et al. 2016a).

Depressed patients are frequently not correctly diagnosed, and others who do not have a depressive disorder are too frequently misdiagnosed and prescribed antidepressants (WHO 2021). Recent guidelines suggest combinations of psychological and pharmacological treatments for depression management based on considerations of depression severity (Olfson et al. 2016). Growing evidence, both direct and indirect, indicates vitamin deficiency, especially B vitamin deficiency, is associated with symptoms of psychiatric disorders including depression. B vitamins play vital roles in neurochemical pathways related to noradrenergic, dopaminergic, serotonergic, and cholinergic systems and the GABA (γ-aminobutyric acid) and glutamate neurotransmitter systems. Vitamin B deficiency can, therefore, affect several mechanisms associated with depression, such as monoamine reduction, abnormal neurotransmitter release, reduction or interruption of serotonin transmission, and abnormal dopaminergic and noradrenergic activities (Furmaga et al. 2011). Recent studies have increased understanding of the impacts of different diets on depression. For example, it has been established that daily vitamin intake and vegetable and fruit consumption reduce depression risk in the general population (Firth et al. 2020). However, little is known about the association between daily dietary vitamin intake and depression in the Korean population.

This study was undertaken to determine relations between the prevalence of depression and serum heavy metal (Hg, Pb, and Cd) levels and dietary vitamin intakes in a nationally representative cohort in the hope that the knowledge gained regarding environmental predisposing factors will aid the prevention and early management of depression.

irm if it is correct." –>Materials and methods

Study population

Information on the design and data collection methods used in Korea National Health and Nutrition Examination Surveys (KNHANES) has been published elsewhere (Duc et al. 2021b). In the present study, we used data from KNHANES studies conducted between 2009 and 2017. Totals of 10,533 (2009), 8958 (2010), 8518 (2011), 8058 (2012), 8018 (2013), 8150 (2016), and 8127 (2017) subjects participated in these studies. Of the 60,362 individuals that participated during 2009–2013 and 2016–2017, we excluded 43,509 without serum Pb, Cd, or Hg data and 482 without depression data. Consequently, the data of 16,371 individuals that participated in KNHANES were included in the analysis.

Determination of serum Pb, Hg, and Cd levels

Serum Hg, Pb, and Cd levels were analyzed as previously described (Nguyen and Kim 2021; Nguyen et al. 2021). Briefly, serum Cd and Pb concentrations were measured by the NEODIN Medical Institute, which is certified by the Korean Ministry of Health and Welfare. The methods used met the requirements of the German External Quality Assessment Scheme, the US CDC, and the Korea Occupational Safety and Health Administration program. Pb and Cd levels were determined by graphite furnace atomic absorption spectrometry (model AAnalyst 600, Perkin Elmer, Turku, Finland) with Zeeman background correction. Total serum Hg levels were determined using a direct mercury analyzer (model DMA-80 Analyzer, Bergamo, Italy). Limits of detection (LODs) Pb, Hg, and Cd were 0.223, 0.05, and 0.087 µg/L, respectively. Commercial standards (Lyphochek Whole Blood Metals, Bio-Rad, CA, USA) were used as reference materials for internal quality assurance and quality control.

Urinary cotinine and smoking verification

Urinary cotinine analysis was conducted by gas chromatography and mass spectrometry (PerkinElmer Clarus 600T) on spot urine samples. The detection limit was 1.26 ng/mL. Standard reference materials were used for internal quality assurance and control purposes (ClinChek, RECIPE, Munich, Germany). Urinary cotinine levels were measured using a standard G-EQUAS protocol. Subjects with a level of ≥50 ng/mL were defined as cotinine-verified smokers (Benowitz et al. 2002; Jung-Choi et al. 2012).

Laboratory measurements

Blood samples were collected during mornings after an overnight fast. Serum concentrations of alanine aspartate aminotransferase (ALT), aspartate aminotransferase (AST), triglycerides, high-density lipoprotein cholesterol (HDL-C), and glucose were measured using an automatic analyzer (Hitachi 7600, Hitachi, Tokyo, Japan). Serum low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation serum [LDL-C = serum total cholesterol – serum HDL-C – (serum triglyceride)/5]. hs-CRP levels were analyzed by immunoturbidimetry using a Cobas 8000 modular analyzer (Roche, Mannheim, Germany) (Yun et al. 2021). Clinical analyses were performed by the Neodin Medical Institute, a laboratory certified by the Korean Ministry of Health and Welfare.

Food intakes

Daily food intakes were calculated using the 24-h recall method. Before assessing food intakes, all subjects were instructed to maintain their normal dietary habits. Daily dietary vitamin intakes were defined as self-assessed mean 24-h dietary intakes and calculated using Can-Pro 3.0 nutrient intake assessment software developed by the Korean Nutrition Society (Duc et al. 2021b). Total vitamin A intakes were measured by summing vitamin A and b-carotene intakes and dividing by 6 (Park et al. 2015).

A semi-quantitative food frequency questionnaire (FFQ), which addressed the intakes of 63 food products, was completed by each subject. Food intake levels were categorized on a monthly, weekly, or daily basis as "never or rarely in any given month," "once a month," "once or twice a month," "once a week," "two to four times a week," "five to six times a week," "daily," "twice daily," or "three or more times daily." Three food groups (green vegetables, white vegetables, and fruit) were chosen from the 63 food items. The green vegetable group included cucumber, spinach, radish leaves, and pepper; the white vegetable group included cabbage, pumpkin, radish, sprout, Korean cabbage, carrot, and tomato; and the fruit group included tangerine, pear, persimmon, watermelon, strawberry, apple, grape, peach, banana, and citrus. Participants were classified based on vegetable and fruit consumption frequencies as low, medium, or high consumers (Duc et al. 2021a; Nguyen and Kim 2021; Park et al. 2015).

Parameters

During medical checkups, information on age, education, smoking history, and alcohol intake was collected using the standard KNHANES questionnaire. Waist circumference (cm) was measured at the midpoint between the bottom of the rib cage and the iliac crest at the mid-axillary line while exhaling.

Blood pressure was measured after a 5-min rest period with participants in a seated position on right arms in triplicate with 5-min intervals between measurements using a mercury sphygmomanometer, and measurements were averaged.

Physical activity was dichotomized as regular or irregular. Regular physical activity was defined as follows: (1) participation in vigorous physical activity (running, fast cycling, climbing, football, fast swimming, basketball, squash, singles tennis, rope jumping, or occupational or recreational activities involving the carrying of heavy objects), ≥20 min per session for ≥3 days per week; (2) or participation in moderate physical activity (slow swimming, volleyball, doubles tennis, or occupational or recreational activity involving the carrying of light objects), ≥30 min per session for ≥5 days per week; or (3) walking for ≥30 min per session ≥5 days per week. Alcohol consumption was defined as low- or high-risk drinking (high-risk drinking was defined as >5 drinks per day for ≥1 month) (Duc et al. 2021b).

Depression

In this study, the outcome variable depression was defined based on physician's diagnosis or the current presence or treatment for depression (Duc et al. 2021b).

Statistical analysis

The statistical analysis was performed using STATA software (version 16·0; StataCorp, TX, USA). Baseline characteristics of participants are presented as frequencies and percentages for categorical variables and as means and standard deviations or medians and interquartile ranges for continuous variables. Student's t-test or Mann–Whitney test was used to analyze continuous variables and the χ^2 test was used for categorical variables.

The serum heavy metal (Cd, Pb, Hg) levels and daily vitamin intake levels (vitamin B1, B2, B3, C, total vitamin A) were $\log_2$ transformed because their distributions were right skewed. Serum heavy metal levels and daily vitamin intakes are presented as geometric means (GMs) and 95% confidence intervals (CIs).

Associations between depression and serum heavy metal and daily vitamin intake levels were examined by logistic regression. Potential covariates were obtained from the literature, chosen based on subjective prior knowledge, or identified by univariate analysis based on a p-value ≤ 0.25. Ten events per variable were carefully considered before entering these variables in the full model (Hosmer Jr et al. 2013). Logistic regression models were used to identify risk factors associated with depression. The potential factors included were sex (male, female), residential area (rural vs. urban), monthly household income (<2000, ≥2000 and <4000, ≥4000 and <6000, ≥6000), physical activity (not regular,

regular), occupation (managers, professional, office worker, clerical, service, sales, agricultural, forestry and fishery workers, craftsmen, elementary occupations, unemployed, and plant or machine operators or assemblers), BMI (<18.5, ≥18.5 but <25, ≥25 but <30, and ≥30 kg/m^2), high-risk drinking (yes, no), educational level (≤middle school, high school, ≥college), and cotinine-verified smoker (yes, no). Interactions between heavy metal levels and daily vitamin intakes were also evaluated. Marginal effects were then used to predict the risks of depression. Statistical tests were two sided, and p-values < 0.05 were considered statistically significant.

Results

Our study included 16,371 individuals that participated in KNHANES (2009–2013, 2016–2017); the mean (SD) age of participants was 42.62 (18.12) and 8485 (51.8%) were women. The percentage of participants with depression was 3.64% (596/16,371, 95% CI: 3.36–3.94). Mean serum Cd, Pb, and Hg levels were 1.02 (0.67) (95% CI: 1.01–1.03), 2.06 (1.10) (95% CI: 2.04–2.07), and 4.06 (3.52) (95% CI: 4.01–4.12), respectively. Daily intakes of vitamins B1, B2, B3, and C were 1.46 (0.89) mg (95% CI: 1.44–1.47), 1.37 (0.81) mg (95% CI: 1.36–1.39), 15.99 (9.64) mg (95% CI: 15.84–16.15), and 93.83 (97.59) mg (95% CI: 92.23–95.44), respectively.

Table 1 shows the demographic distribution of participants with depression. Those with depression were significantly more likely to be female, young adults, married, unemployed, to have a low educational level, a low-income monthly household, a healthy BMI (18.5 ≤ BMI < 25 kg/m^2) or to be overweight (25 ≤ BMI < 30 kg/m^2), to have a family history of CVDs or hyperlipidemia, or to be non-smokers. Cardiometabolic risk factors (total cholesterol, triglyceride, waist circumference, fasting glucose, and systolic and diastolic blood pressure), HbA1c, hemoglobin, and energy intake were significantly higher in participants with depression. Geometric mean serum Cd was significantly higher for participants with depression than for those without, but no significant difference was observed for serum Pb or Hg. On the other hand, daily vitamins B1, B2, B3, C, and A and retinol intakes were significantly lower for those with depression (Table 2).

Table 3 presents adjusted odds ratios (AOR) for associations between depression status and heavy metal concentrations and daily vitamin intakes. Results showed a significant relationship between serum Cd levels and depression after adjustment for potential confounders. A doubling of serum Cd was associated with a 21% increase in depression (AOR 1.21, 95% CI: 1.07–1.37, p = 0.002). On the other hand, the risk of depression decreased as vitamin intake increased. A twofold increase in daily vitamin B1, B3, or A intake reduced

the risk of depression by 17% (0.83, 95% CI: 0.73–0.95, p = 0.005), 20% (0.80, 95% CI: 0.70–0.91, p = 0.001), and 8% (0.92, 95% CI: 0.85–0.99, p = 0.020), respectively. Interactions between heavy metals, vitamin intakes, and sex were not found to influence the prevalence of depression.

Figure 1 shows the marginal effects of serum Cd and daily vitamin B1, B3, or A intake on the prevalence of depression by sex after adjustment for potential confounders among all study subjects. An increase in serum Cd was associated with an increase in the prevalence of depression in males and females, and increases in daily vitamin B1, B3, or A intake were related to reduced risks of depression in males and females.

Discussion

Our findings provide epidemiological evidence that adds to earlier experimental results and support associations between the risk of depression and serum heavy metal levels and dietary intakes of vitamin B1, B3, or A in the Korean population. Marginal effects analysis was used to quantify the effects of heavy metals and dietary daily vitamin intakes on the prevalence of depression by sex. The study identified associations between depression and heavy metal concentrations and vitamin intakes in the Korean population. To summarize, an increase in serum Cd was associated with an increased risk of depression, and remarkably, the risk of depression was found to rapidly decrease when vitamin B1, B3, or total vitamin A intake increased. These findings contribute to our understanding of the effects of heavy metals and dietary vitamin intakes on the pathogenesis of depression.

Environmental toxic metal exposures have become a major public health issue over the last few decades due to their potential adverse impacts on human health (WHO 2017), and the risks associated with human exposure to heavy metals have increased globally in parallel with urbanization and industrialization (Wang et al. 2018). In the present study, we found that the risk of depression in a nationally representative cohort was associated with serum Cd levels, which were significantly higher in subjects with depression. Somewhat surprisingly, the association between serum Cd and depression was similar for current smokers and non-smokers, which we attribute to confounding by other compounds, like lead and cotinine, in cigarette smoke (Scinicariello and Buser 2015). Furthermore, our findings are consistent with those of previous studies (Kim et al. 2016; Orisakwe 2014). The mechanism whereby Cd-induced neurotoxicity underlies neuropsychiatric disorders is not well understood, even in animal models. However, several explanations have been proposed. First, Cd can cross and disrupt the blood–brain barrier, and thus, Cd could induce oxidative stress, and thus, mitochondrial dysfunction and even neuronal cell apoptosis in brain tissue (Chen et al. 2011; Gonçalves et al. 2010). Second, Cd can

Table 1 Characteristics of study subjects with or without depression

Variables	N	Depression		p-values
		No	Yes	
Demographic and social characteristics				
Sex *(%)*	16,371			
Male	7886	7751 (49.1)	135 (22.7)	<0.001
Female	8485	8024 (50.9)	461 (77.3)	
Age group *(%)*	16,371			
≤29	4538	4469 (28.3)	69 (11.6)	<0.001
30–39	2755	2682 (17.0)	73 (12.3)	
40–49	2817	2714 (17.2)	103 (17.3)	
50–59	2891	2734 (17.3)	157 (26.3)	
60–69	2294	2165 (13.7)	129 (21.6)	
70–79	928	867 (5.5)	61 (10.2)	
≥80	148	144 (1.0)	4 (0.7)	
Marital status *(%)*	16,364			
Married	11,395	10,882 (69.0)	513 (86.1)	<0.001
Living alone	4969	4886 (31.0)	83 (13.9)	
Residential areas *(%)*	16,371			
Urban	13,421	12,930 (82.0)	491 (82.4)	0.795
Rural	2950	2845 (18.0)	105 (17.6)	
Occupation *(%)*	15,170			
Managers, professional	2052	2012 (13.8)	40 (6.8)	<0.001
Office worker, clerical workers	1518	1487 (10.2)	31 (5.2)	
Service workers, sales workers	2012	1947 (13.4)	65 (10.9)	
Agriculture, forestry and fishing workers	757	728 (5.0)	29 (4.8)	
Craft, plant and machine operators and assemblers	1638	1611 (11.1)	27 (4.5)	
Elementary occupations	1259	1202 (8.3)	57 (9.6)	
Unemployed	5934	5587 (38.2)	347 (58.2)	
Education level *(%)*	16,333			
≤Middle school	5915	5639 (35.8)	276 (46.3)	<0.001
High school	5331	5137 (32.7)	194 (32.6)	
≥College	5087	4961 (31.5)	126 (21.1)	
Monthly household income *(%)**	16,264			
<2000	4327	4062 (25.9)	265 (44.6)	<0.001
≥2000 and <4000	5320	5167 (33.0)	153 (25.8)	
≥4000 and <6000	3599	3506 (22.4)	93 (15.6)	
≥6000	3018	2935 (18.7)	83 (14.0)	
BMI group *(%)*	16,339			
<18.5	1165	1143 (7.3)	22 (3.6)	0.004
≥18.5 and <25	10,197	9827 (62.4)	370 (62.1)	
≥25 and <30	4300	4122 (26.2)	178 (29.9)	
≥30	677	651 (4.1)	26 (4.4)	
Smoking status *(%)*	14,354			
Non/ex-smoker	10,729	10,246 (74.5)	483 (81.2)	<0.001
Current smoker	3625	3513 (25.5)	112 (18.8)	
Cotinine verified smokers *(%)*	16,371			
No	8059	7741 (49.1)	318 (53.4)	0.040
Yes	8312	8034 (50.9)	278 (46.6)	
High-risk drinking status *(%)*	16,356			

Table 1 (continued)

Variables	N	Depression		p-values
		No	**Yes**	
No	14,809	14,293 (90.7)	516 (86.6)	0.001
Yes	1547	1467 (9.3)	80 (13.4)	
Physical activity *(%)*	16,371			
Not regular	13,116	12,644 (80.2)	472 (79.2)	0.565
Regular	3255	3131 (19.8)	124 (20.8)	
Family history of CVDs *(%)*	13,450			
No	7836	7599 (58.6)	237 (49.0)	<0.001
Yes	5614	5367 (41.4)	247 (51.0)	
Family history of diabetes *(%)*	13,310			
No	10,644	10,283 (80.1)	361(76.5)	0.054
Yes	2666	2555 (19.9)	111(23.5)	
Family history of hyperlipidemia *(%)*	12,945			
No	12,104	11,688 (93.6)	416 (90.6)	0.011
Yes	841	798 (6.4)	43 (9.4)	

*Thousand won

CVDs, cardiovascular diseases

adversely affect the central nervous system by triggering vascular damage via endothelial oxidative stress (Angeli et al. 2013), which several authors have concluded is a risk factor for depression (Bonaccorso et al. 2002; Förstl et al. 1991). Third, Cd-induced changes in dopamine, norepinephrine, serotonin, or thyroid hormone concentrations may be related to depression (Demartini et al. 2014; Lafuente et al. 2003; Takiguchi and Si 2006).

Several studies have reported that elevated serum levels of Hg and Pb were associated with depression, though we found no evidence of these associations (Bouchard et al. 2009; Kim et al. 2020). For example, Bouchard et al. found higher serum Pb levels were related to increased risks of major depression and panic disorders among young US adults (Bouchard et al. 2009), and Kyung et al. reported that higher levels of serum Hg were related to depression risk in Korean women, especially in those with lower fish intakes (Kim et al. 2020). Several authors have reported Pb can disrupt catecholaminergic systems and lead to depression and anxiety disorders (Kala and Jadhav 1995; Lasley et al. 1984). In rats, Pb reduced serotoninergic activity in numerous brain regions, including frontal cortex, nucleus accumbens, and brainstem (Kala and Jadhav 1995). Ng et al. found that higher total serum Hg was not related to an increased risk of depression among US adults (Ng et al. 2013b), and Park et al. failed to find an association between serum Hg and depression in Korean adults (Park et al. 2016b), and both of these studies concur with our findings. We believe these discrepancies were probably caused by different sample sizes, analysis methods, and population

differences. Moreover, like Cd, Hg can cross the blood–brain barrier and induce neurotoxic symptoms (Castro-González and Méndez-Armenta 2008), and exposure to inorganic mercury, especially methylmercury, can induce neuropsychiatric symptoms by inducing oxidative stress in the central nervous system (Maximino et al. 2011).

Deficiency of any B vitamin can result in homocysteine accumulation and detrimental cellular effects, and vitamin B deficiency is known to play a role in the development of depression (Folstein et al. 2007). Vitamin B1 is important for carbohydrate metabolism and nerve function, and its deficiency can negatively impact the central nervous system (Abdou and Hazell 2015). Furthermore, the relationship between thiamine deficiency and depression among adults has been well demonstrated (Pepersack et al. 1999; Zhang et al. 2013). Our results show that vitamin B1 consumption is inversely associated with depression in the Korean population, which concurs with a previous study, in which vitamin B1 supplementation for 6 weeks reduced depressive symptoms in 80 elderly women (Smidt et al. 1991). Other studies have also reported vitamin B1 supplementation can reduce depressive symptoms and improve cognitive function among patients with geriatric depression, and in a case report, it reduced depressive symptoms in a 50-year-old man admitted to a psychiatric clinic (Bell et al. 1992; Jong and Hoek 2008). Our recent study also showed an increase in daily vitamin B1 intake was negatively associated with the prevalence of depression (Duc et al. 2021b).

Table 2 Food intake and laboratory measurements of study subjects with or without depression

Variables	N	Depression		p-values
		No	Yes	
Food intake				
Energy intake *(kcal)*	14,225	2042.72 ± 7.63	1691.60 ± 32.80	<0.001
Vitamin B1 intake *(mg)* ‡	14,225	1.26 (1.24–1.27)	0.99 (0.94–1.04)	<0.001
Vitamin B2 intake *(mg)* ‡	14,225	1.17 (1.16–1.18)	0.95 (0.90–1.01)	<0.001
Vitamin B3 intake *(mg)* ‡	14,225	13.82 (13.69–13.95)	10.80 (10.28–11.35)	<0.001
Vitamin C intake *(mg)* ‡	14,225	62.79 (61.79–63.80)	52.75 (48.50–57.39)	0.001
Total vitamin A intake *(mg)* ‡	14,225	481.40 (473.67–489.26)	392.76 (358.76–429.99)	<0.001
Retinol *(μg)* ‡	14,225	52.45 (50.95–53.99)	32.29 (26.96–38.67)	<0.001
Green vegetables (%)§	4246			
Low consumption	3168	3039 (74.4)	129 (80.6)	0.051
Medium consumption	816	797 (19.5)	19 (11.9)	
High consumption	262	250 (6.1)	12 (7.5)	
White vegetables (%)§	4257			
Low consumption	3324	3195 (78.0)	129 (80.6)	0.311
Medium consumption	716	689 (16.8)	27 (16.9)	
High consumption	217	213 (5.2)	4 (2.5)	
Fruits (%)§	4258			
Low consumption	3580	3440 (83.9)	140 (87.5)	0.275
Medium consumption	318	306 (7.5)	12 (7.5)	
High consumption	360	352 (8.6)	8 (5.0)	
Laboratory measurements				
Waist circumference *(cm)*	16,343	79.86 ± 0.09	81.27 ± 0.42	0.002
Total cholesterol *(mg/dL)*	16,370	185.80 ± 0.30	192.82 ± 1.56	<0.001
LDL-C *(mg/dL)*	8090	111.97 ± 0.37	115 (44–174)	0.126
Triglyceride *(mg/dL)* †	16,370	101 (42–154)	148.00 ± 5.82	<0.001
HDL-C *(mg/dL)*	16,368	50.35 ± 0.10	50.09 ± 0.53	0.611
HbA1c *(%)*	12,377	5.71 ± 0.01	5.84 ± 0.04	0.002
Fasting glucose (mg/dL)	16,368	97.33 ± 0.17	99.12 ± 0.90	0.048
hs-CRP *(mg/L)*	5055	1.22 ± 0.03	1.16 ± 0.11	0.652
Hemoglobin *(g/dL)*	16,367	14.14 ± 0.01	13.62 ± 0.06	<0.001
Systolic blood pressure *(mmHg)*	16,358	116.64 ± 0.13	119.52 ± 0.70	<0.001
Diastolic blood pressure *(mmHg)*	16,358	75.04 ± 0.09	75.93 ± 0.41	0.047
AST *(IU/L)*	16,370	22.00 ± 0.12	22.59 ± 0.44	0.331
ALT *(IU/L)*	16,370	21.39 ± 0.16	21.34 ± 0.63	0.959
Serum Cd *(μg/L)* ‡	16,371	0.81 (0.80–0.81)	1.11 (1.06–1.16)	<0.001
Serum Pb *(μg/dL)* ‡	16,371	1.84 (1.82–1.85)	1.85 (1.79–1.91)	0.748
Serum Hg *(μg/L)* ‡	16,371	3.26 (3.23–3.29)	3.09 (2.93–3.25)	0.039

†Median (IQR); ‡geometric mean (95% confidence interval) and *p*-value using Mann–Whitney test; §data available in 2012, 2013, and 2016

BMI, body mass index (kg/m^2); *AST*, aminotransferase; *ALT*, alanine aminotransferase

Vitamin B1 intake may also protect against heavy metal–induced stress. In an in vivo study conducted using Sprague–Dawley rats injected with 5 mg of CdCl2•H2O/kg, vitamin B1 appeared to have protective effects (Casas et al. 1995). Another study reported that vitamin B1 might be more therapeutically effective than thiol chelating agents at protecting rats from the toxic effects of Cd (Tandon and Prasad 2000). Dhawan et al. reported that a mixture of vitamins B1 and C increased the urinary elimination of Pb, reduced hepatic and renal Pb stress, and reversed the Pb-induced

Table 3 Adjusted odds ratio (AOR) for the risk of depression

Variables	95%CI	*p*-value ¶
Heavy metals		
Log$_2$ serum Cd	1.21 (1.07–1.37)	0.002
Sex—log2 serum Cd	*Male—log$_2$ serum Cd (Ref)*	
	1.25 (0.95–1.65)	0.118
Log$_2$ serum Hg	0.95 (0.85–1.08)	0.438
Sex—log$_2$ serum Hg	*Male—log$_2$ serum Hg (Ref)*	
	1.03 (0.79–1.35)	0.553
Log$_2$ serum Pb	1.03 (0.87–1.22)	0.726
Sex—log$_2$ serum Pb	*Male—log$_2$ serum Cd (Ref)*	
	1.47 (1.01–2.15)	0.046
Food intake		
Log$_2$ vitamin B1 intake	0.83 (0.73–0.95)	0.005
Sex—log$_2$ vitamin B1 intake	*Male—log$_2$ vitamin B1 intake (Ref)*	
	0.89 (0.63–1.25)	0.503
Log$_2$ vitamin B2 intake	0.93 (0.93–1.05)	0.250
Sex- log$_2$ vitamin B2 intake	*Male—log$_2$ vitamin B2 intake (Ref)*	
	0.84 (0.62–1.13)	0.245
Log$_2$ vitamin B3 intake	0.80 (0.70–0.91)	0.001
Sex—log$_2$ vitamin B3 intake	*Male—log$_2$ vitamin B3 intake (Ref)*	
	1.08 (0.79–1.48)	0.611
Log$_2$ vitamin C intake	0.83 (0.96–0.100)	0.055
Sex—log$_2$ vitamin C intake	*Male—log$_2$ vitamin C intake (Ref)*	
	0.95 (0.78–1.15)	0.568
Log$_2$ total vitamin A intake	0.92 (0.85–0.99)	0.020
Sex—log$_2$ total vitamin A intake	*Male—log$_2$ total vitamin A intake (Ref)*	
	1.03 (0.86–1.23)	0.769
Log$_2$ retinol intake	0.99 (0.95–1.03)	0.671
Sex—log$_2$ retinol intake	*Male—log$_2$ retinol intake (Ref)*	
	1.03 (0.93–1.04)	0.541

Adjusted for sex (male, female), residential area (rural vs. urban), household income (<2000, ≥2000 but <4000, ≥4000 but <6000, and ≥6000 thousand won/month) physical activity (not regular, regular), occupation (managers, professional, office, clerical, service, sales, agricultural, forestry, and fishery workers, craft, plant/machine operators and assemblers, and the unemployed), BMIs were classified as <18.5, ≥18.5 but <25, and ≥25 but <30, ≥30), high-risk drinking (yes, no), education level (≤middle school, high school, ≥college), cotinine-verified smoker (yes, no).

inhibition of 5-aminolevulinic acid dehydratase (δ-ALA-D) in blood (Dhawan et al. 1988). Bratton et al. suggested vitamin B1 interacts with Pb in several ways to protect against tissue accumulation, thereby thwarting clinical signs and death. The authors proposed that therapeutic doses of vitamin B1 may be useful for preventing and treating animals or people exposed to high environmental levels from its toxic effects (Bratton et al. 1981). Reddy et al. theorized Pb may interact with the pyrimidine ring of vitamin B1 and cause its solubilization at physiological pH values, and reported that vitamin B1 treatment can reduce Pb levels in kidneys, blood, and bones (Reddy et al. 2010). Further work is required to determine whether interactions between vitamin 1 and heavy metals influence the risk of depression.

We also found dietary vitamin B3 intake was associated with a reduced risk of depression, which also agrees with previous studies (Smesny et al. 2010; Thompson and Proctor 1953). In a recent study, it was reported vitamin B3 levels were substantially lower in patients with depression than in controls (Ryan et al. 2020). It may be that vitamin B3 is transformed in vivo into nicotinamide, which has benzodiazepine-like effects on the γ-aminobutyric acid (GABA) system (Möhler et al. 1979; Tallman et al. 1980). In addition, vitamin B3 has been associated with the kynurenine pathway and interacts with brain receptors, which play important roles in the pathogenesis of depression (Mikkelsen et al. 2016; Miller et al. 2009).
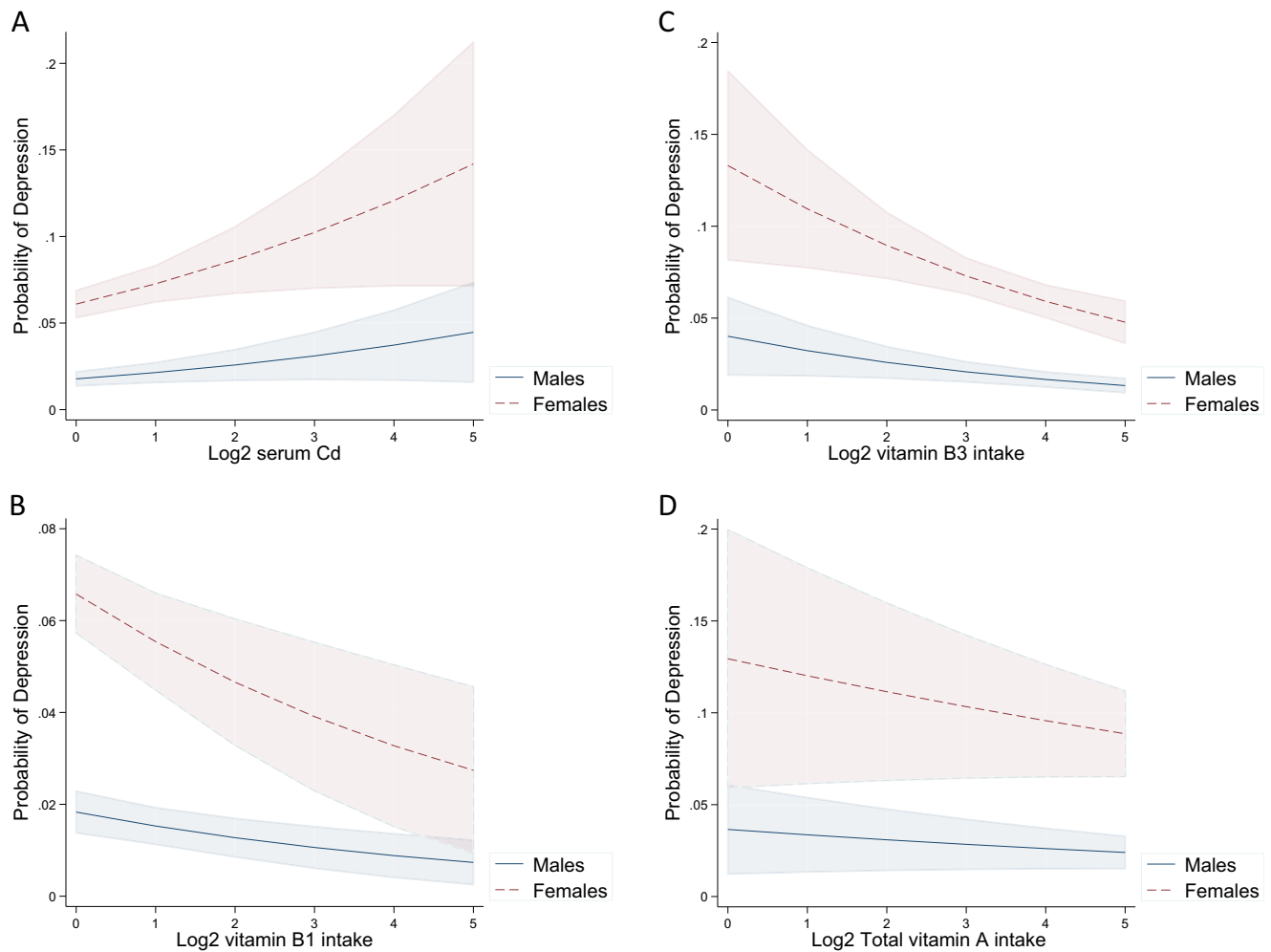
Fig. 1 Marginal effects of serum Cd (**A**), vitamin B1 (**B**), vitamin B3 (**C**), and total vitamin A levels (**D**) on depression by sex for all study subjects after adjustment for potential confounders

Exposure to heavy metals induces the formation of reactive oxygen species (ROS) (Duc et al. 2021a; Nguyen and Kim 2021), and ROS-induced oxidative stress is related to the pathogenesis of depression (Michel et al. 2012). Vitamin B3 has significant antioxidant properties (Cho et al. 2009), and thus, might protect against oxidative stress induced by heavy metals. In an in vivo study, vitamin B3 appeared to protect rat fertility from the adverse effects of MeHg (Frenedoso da Silva et al. 2014). Paula et al. also suggested that vitamin B3 co-administration might reverse GSH depletion and attenuate malondialdehyde and nitric oxide levels and DNA damage in rats exposed to MeHg. The authors suggested that the mechanism underlying these effects might be associated with the intrinsic antioxidant potential of vitamin B3 (Silva de Paula et al. 2016). Although data is lacking regarding relationships between vitamin B3, heavy metals, and depression, vitamin B3 supplementation is viewed as a candidate treatment for depression. Further studies are needed to assess the effectiveness of vitamin B3 in depression.

On the other hand, an increase in daily retinol intake was not associated with a decrease in the prevalence of depression, which was in line with a previous study (Nguyen et al. 2017), but we found total vitamin A intake was negatively associated with depression. This observation supports the result of a previous study, in which low serum levels of carotenoids were related to depressive symptoms and increase risk of new depressive symptoms in individuals older than 65 (Milaneschi et al. 2012). Although the mechanism whereby vitamin A affects depression has not been determined, the mechanism seems to be associated with oxidative stress and inflammation. Several studies have reported depressive patients had higher oxidative stress levels and lower antioxidant capacities than non-depressed patients (Kodydková et al. 2009; Maes et al. 2010). Furthermore, depressive mood is also strongly associated with impaired inflammatory status and antioxidant capacity, and it has been documented that depressive mood is strongly associated with impaired antioxidant defense and inflammatory status (Cumurcu et al. 2009). Notably, Bremner and Ludot reported that retinoic acid, the active form of

vitamin A, can cause suicide and depression in some susceptible patients (Bremner et al. 2012; Ludot et al. 2015). Furthermore, associations between vitamin A and heavy metals have also been reported. Cd may impair vitamin A release, particularly from stores to serum (Sugawara and Sugawara 1978), and Sugawara found that Cd at 6.2 mg/kg considerably reduced serum levels of vitamin A for 2 weeks after final injections in rats, but had no effect on hepatic vitamin A contents (Sugawara and Sugawara 1979). Furthermore, Engström et al. concluded that an adequate vitamin A status can help minimize the negative impact of Cd on bone mineral density (Engström et al. 2011). Taken together, it is evident that further work is needed to improve understanding of the association between vitamin A and heavy metals.

Conclusions

To the best of our knowledge, this large-scale study is the first to report the effects of dietary vitamin intake and serum heavy metal levels on depression in a nationally representative sample of the Korean population. However, this study has several limitations. First, the cross-sectional method used in KNHANES did not allow causality to be established between depression and vitamin intakes or serum heavy metal levels. Second, the cross-sectional method used in KNHANES prevented us from accessing the vitamin effect thresholds or plateaus. Third, as no physiological markers of antioxidant status was measured during KNHANES, oxidation statuses and vitamin concentrations in plasma and tissues were not evaluated. Fourth, we investigated associations between vitamins and heavy metals in a background of depression, and thus, the impacts of relationships between macronutrients (protein, fats, carbohydrates) and heavy metals on depression need further study. Fifth, vitamin intakes were calculated using 24-h recall data, and thus, may have been under- or overestimated; though before evaluating food intakes, all participants were instructed to maintain their usual dietary habits.

Rapid industrialization and urbanization have increased exposure to heavy metals, and exposure to these metals and dietary and lifestyle changes may have increased the incidence of depression. Our findings indicate that an increase in serum Cd is associated with an increased risk of depression and that higher vitamin B1, B3, or A intake reduced the risk of depression in a nationally representative Korean cohort.

Eating a balanced diet every day provides the nutrients necessary to maintain health. Fruits and vegetables are sources of vitamins, and thus, balanced diets containing vegetables and fruits may reduce the risk of depression. Further studies are needed to identify the risk factors of heavy metal exposure and to determine the effects of dietary vitamin intake on depression risk.

Data availability The datasets analyzed during the current study are available in the NHANES repository. (http://knhanes.cdc.go.kr/).

Declarations

Ethics approval and consent to participate Before examinations, all that participated in KNHANES provided written informed consent. KNHANES studies were performed by the Health and Nutrition Examination Department of the Korea Centers for Disease Control and Prevention (KCDC). This study was approved by the KNHANES inquiry commission and the Institutional Review Board of Sunchon National University. These surveys were conducted with the approval of the IRB of the KCDC (2009-01CON-03-2C, 2010-02CON-21-C, 2011-02CON-06-C, 2012-01EXP-01-2C, 2013-07CON-03-4C, 2013-12EXP-03-5C, 2015-01-02-6C, 2018-01-03-P-A). Between 2016 and 2019, KNHANES was exempt from research ethics review as stipulated by the Korean Bioethics and Safety Act.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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