Impacts of Antioxidant Vitamins, Curry Consumption and Heavy Metal Levels on The Metabolic Syndrome With Comorbidities: A National Cross-Sectional Study

Hai Nguyen Duc
Sunchon National University
Hojin Oh
Sunchon National University
Min-Sun Kim (minsun@scnu.ac.kr)
Sunchon National University

Research Article

Keywords: metabolic syndrome (MetS), COVID-19, lifestyle risk factors

Posted Date: February 24th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-225694/v1

Abstract

The burden of metabolic syndrome (MetS) is increasing worldwide especially in the coronavirus disease 2019 (COVID-19). This phenomenon can be related to environmental, dietary, and lifestyle risk factors. We aimed to determine the association between the levels of serum heavy metals, vitamins, and curry intake, subsequently predict the risks for MetS by margin effects. Daily intake of vitamins was measured by 24-h recall was calculated using a food frequency questionnaire. Heavy metals were quantified by graphite furnace atomic absorption spectrometry, and mercury analyzer. The risk of MetS was significantly lower in the high curry consumption than in the low curry consumption, risks of Mets were reduced by 7%, 13%, 1%, and 1%, when the levels of vitamin B1, B2, B3, and C intake increased by one mg, respectively. However, risks of Mets were increased by 9%, 3%, 5%, when the levels of serum Pb, Hg, and CRP increased by one unit. The potential health benefits resulting from vitamin and curry supplementation could guard the public against the dual burden of communicable and non-communicable diseases. Further works are required to thwart risk factors related to heavy metals and determine the mechanistic dual effects of vitamins and curry in MetS.

Introduction

Food is emerging as a significant modifiable contributor to chronic disease with empirical evidence that dietary modifications have clear positive as well as negative impacts on the lifelong health [1]. In fact, consumption of fatty, high-saturated, and low-energy diets as well as inactive physical activity, overuse of tobacco and alcohol has been increasing, which was contributing to the growth of non-communicable diseases (NCDs), especially Metabolic syndrome (MetS) [1,2]. MetS is commonly known as a collection of metabolic disorders, including resistance to insulin, dyslipidemia, central obesity, and hypertension. Besides, MetS was the risk factor for the development of type 2 diabetes and cardiovascular diseases [3]. Of note, recent evidence suggested that MetS affects the progression and prognosis of coronavirus disease 2019 (COVID-19), and increased metabolic severity has been correlated with worse COVID-19 consequences [4,5]. It makes the situation get worse once COVID-19 has spread around the world.

In addition to lifestyle and genetic factors, the effects of heavy metal on the risk factors of MetS [6-9]. Remarkedly, the risk of exposure to heavy metals released by vehicles, factories, or contaminated seafood is increasing, especially lead (Pb), mercury (Hg), and cadmium (Cd) without biological roles in human body systems, but accumulate in bones, kidney cortex, and lungs [10]. Heavy metals catalyze the release of reactive oxygen species as well as inflammatory mediators and antithrombotic substances that cause damage to vascular endothelial cells and exacerbate hypertension[7,11]. Therefore, Pb and Cd disrupt blood clotting and increase the risk of CVD, while Hg accelerated the process of carotid atherosclerosis [6,12].

Increasing evidence shows that vitamin supplementation could reverse CVDs, and diabetes, and mental illness [13]. Additionally, curcumin, curcuma longa dried rhizome, is also supportive for the prevention and/or treatment of CVDs due to its anti-oxidant and anti-inflammatory properties [14]. In this study, we present tentative evidence that increased daily intake of vitamins and curry is related to better performance of MetS among the Korean population with various non-communicable diseases. On the other hand, the association of heavy metal levels with MetS is also provided.

Methods

Study population. We used a stratified, multi-stage, cluster-sampling method that regarded the geographic zone, level of urbanization, economic development condition, gender, and age distribution, conducted by the Korean Ministry of Health and Welfare, specifically the KNHANES IV (2009), KNHANES V (2010–2012), KNHANES VI (2013) and the KNHANES VII (2016-2017) [58]. Subjects surveyed were randomly selected from 10,533 households (2009), 8,958 (2010), 8,518 (2011), 8,058 (2012), 8,018 (2013), 8,150 (2016), and 8,127 (2017). In this study, subjects who (1) have fully take part in three parts including a health interview survey, a health examination survey, and a nutrition survey, (2) with adequate information on metabolic syndrome were selected. Of the 60,362 participants who underwent the survey from 2009-2013, and 2016-2017, we excluded 106 records missing MetS. A total of 60,256 was eligible for data analysis. Written informed consent was required for both patients and family members; parental informed consent was obtained on behalf of all minors before examinations, which were performed by the Health and Nutrition Examination Department of the Korea Centers for Disease Control and Prevention. A detailed description of the plan, operation and license of the survey can be found on the KNHANES website (http://knhanes.cdc.go.kr/). This study was approved by the KNHANES inquiry commission and the Institutional Review Board of Sunchon National University as following by the guidelines set out in the Declaration of Helsinki.

Parameters. Information on sociodemographic characteristics, lifestyle, current medications, medical, and family history was collected during the health interview. Alcohol intakes were classified as low and high (high-risk drinking was defined as > 5 drinks per day and ≥ 1 month). Subjects with a lifetime history of smoking of >100 cigarettes in their lifetime and still smoked daily or occasionally were classified as current smokers; others were classified as ex/non-smokers. Physical activity was dichotomized as regular or irregular. Regular physical activity was defined as: (1) vigorous physical activity, ≥20 minutes per session ≥3 days a week (2) moderate physical activity; ≥30 minutes per session ≥5 days per week, and (3) walking; ≥30 minutes per session ≥5 days a week.

Dyslipidemia was defined as one or more of the following: LDL-C ≥160 mg/dL, triglyceride ≥200 mg/dL, HDL-C <40 mg/dL. Hypertension was defined as having either systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or on anti-hypertensive medication. Type 2 diabetes mellitus was defined as having a fasting plasma glucose of ≥126 mg/dl or on anti-diabetic medication, or HbA1c≥6·5%. Stroke, angina, myocardial infarction (MI), MI or angina, and other diseases were defined as physician diagnosis, the current presence or treatment for stroke, angina, MI, MI or angina, and other diseases. Depression was defined as physician diagnosis, the current presence or treatment for depression, or if participants have experienced depression in the past year or despair to the point where it disturbs their daily routine for 2 weeks in a row or longer [59]. Comorbidities have defined any diseases such as CVDs, hypertension, hyperlipidemia, type 2 diabetes, cancers, thyroid, kidney, arthritis, osteoarthritis, rheumatoid arthritis, depression are present in the participants with MetS. A family history of cardiovascular disease was defined as having at least one parent or sibling with a diagnosis of hypertension, ischemic heart disease, or stroke. A family history of type 2 diabetes or hyperlipidemia was defined as having at least one parent or sibling with a diagnosis of type 2 diabetes or hyperlipidemia.

Laboratory measurements. The height, weight, waist circumference, and blood pressure were measured during medical checkups using the standard procedure. BMI (kg/m^2) was estimated using the formula: BM= weight (kg)/ $height^2$ (m^2). Waist circumstance (cm) was measured at the midpoint between the bottom of the rib cage and the iliac crest of the mid-axillary line when exhaling. Blood pressure was calculated three times with intervals of 5 minutes using a mercury sphygmomanometer with a subject seated after a 5-minute stabilization period. Final blood pressure was the average of the second and third measurements. Blood samples after ≥ 8 hours of fasting were collected and analyzed at the Neodin Medical Institute in Korea. An enzymatic assay was then used to determine levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, low-density lipoprotein cholesterol (LDL-C), and fasting glucose using the Hitachi automated analyzer 7600 (Hitachi, Japan).

Determination of Pb, Hg, and Cd in blood. Pb, Hg, and Cd analyzes were decribed in the previous study [9]. In brief, these tests were performed by the Neodin Medical Institute, which was approved by the Korean Ministry of Labor for Heavy Metal Analysis. Furthermore, these tests also were met the criteria of the Korea Occupational Safety and Health Administration, the German External Quality Assessment Scheme, and the U.S. CDC. Pb and Cd were measured by graphite furnace atomic absorption spectrometry (model AAnalyst 600; Perkin Elmer, Turku, Finland) using Zeeman background correction, and total Hg was calculated by a direct mercury analyzer (model DMA-80 Analyzer; Bergamo, Italy) and gold amalgam (KCDC 2013). Limits of detection (LODs) were 0.223 μg/dL, 0.05 μg/L, 0.087 μg/L for Pb, Hg, and Cd, respectively. Commercial standard reference materials purchased from Bio-Rad for internal quality assurance and control (Lyphocheck Whole Blood Metals Control; Bio-Rad, Hercules, CA, USA).

Metabolic syndrome. MetS were defined using American Heart Association/National Heart, Lung, and Blood Institute criteria for clinical diagnosis that included abdominal obesity, elevated triglycerides, increased waist circumference, decreased HDL, elevated blood pressure, and elevated plasma glucose [60]. Participants with three or more of the following five risk factors were defined with metabolic syndrome. (1) Elevated waist circumference (WC ≥ 80 cm in women), (2) Elevated triglycerides (TG ≥ 150 mg/dL or receiving medication for elevated triglycerides), (3) Low high-density lipoprotein cholesterol (HDL-C < 50 mg/dL in women or receiving medication to increase HDL-C), (4) Elevated blood pressure (systolic blood pressure≥ 130 mmHg and/or ≥ 85 mmHg diastolic blood pressure or on antihypertensive drug treatment and a history of hypertension), (5) Elevated fasting glucose (≥ 100 mg/dL or receiving medical treatment for elevated glucose) [60,61].

Vitamin intake. Daily food intake was calculated using the 24-h recall method. Before evaluating the food intake, all participants were instructed to uphold their normal dietary habits. A semi-quantitative questionnaire on food frequency, which addressed the intakes of 63 food products, was completed by each participant. The levels of participants of food consumption were calculated using nine categories: never or rarely," "once a month," "two to three times a month". Often a week," "three or four times a week," "five to six times a week," "once a week," "five to six times a week. Day," "twice a day," and "every day, three or more times. The daily intake of thiamine was determined by summing the mean of the 24-hour dietary intakes using the Can-Pro 3.0 nutrient intake assessment software developed by the Korean Nutrition Society. The daily total energy intakes were measured using the Estimated Energy Requirement (EER) in Korea [62].

The curry consumption was estimated using the KNHANES food frequency questionnaire. Curry rice was the only food in the surveyed foods related to curry consumption. According to the frequency of their curry consumption, subjects were divided into two groups: the low curry consumption group ("almost never", or "once a month"), and the high curry consumption group ("2-3 times a month" or "once a week" or "2-6 times per week").

Statistical analysis. All statistical analyses were undertaken using STATA software (version 16.0; StataCorp, Texas, USA). The baseline characteristics of participants were summarized using frequency and proportion for categorical variables; mean and standard deviation for continuous variables. Student's t-test for continuous variables and χ^2 test for categorical variables.

Logistic regression models ascertained the risk factors associated with MetS, including age group (≤29, 30-39, 40-49, 50-59, ≥60), sex, residential area (rural vs urban), marital status (married, living alone), education level (≤ middle school, high school, ≥ college), monthly household income (< 2,000, ≥ 2,000 and < 4,000, ≥ 4,000 and < 6,000, ≥ 6,000), smoking status (current smoker, non/ex-smoker), high-risk drinking (yes, no), physical activity (not regular, regular), BMI groups (<18.5, ≥ 18.5 and < 25, ≥ 25 and < 30, ≥ 30), and comorbidities. The margin effects were used to predict the risks for MetS. Statistical tests were two-sided, *p*-value < 0.05 was considered statistically significant.

Results

Our study included 60,256 participants of the KNANES 2009-2103, 2016-2017 survey; the mean age of participants was 40.8±22.8, 32,827 (54.5%) were women. Most subjects reported never or rarely consumed curry (53%), 46% at least occasionally consumed curry (2-3 times a month" or "once a week), while only 1% (67/10,874) of subjects reported often consumed curry (2-4 times a week" or "5-6 times a week). Subjects with MetS included significantly more who were female, aged 60 years or over, being unemployed or elementary occupations, living rural or alone, were low educated, were low-income monthly household, being underweight (BMI < 25 Kg/m^2), overweight (BMI ≥ 25 and < 30 Kg/m^2), and being obese (BMI≥ 30 Kg/m^2), having a family history of CVDs, diabetes. In addition, levels of total cholesterol, LDL-C, triglyceride, HbA1c, fasting glucose, waist circumference, aspartate aminotransferase (AST), alanine aminotransferase (ALT), systolic and diastolic blood pressure were significantly higher in subjects with MetS compared with subjects without MetS. Remarkedly, the risk of MetS was significantly higher in subjects with comorbidities than subjects without comorbidities, in subjects with low curry consumption than subjects with high curry consumption. The characteristics of the study population by MetS are shown in Table 1.

The average daily intake of vitamin B1, B2, B3, and C was 1.35±0.86 mg (95% CI 1.34–1.36); 1.28±0.82 mg (95% CI 1.28–1.29); 14.64±9.08 mg (95% CI 14.56–14.72); 90.1±95.76 mg (95% CI 89.3–90.9), respectively. The average levels of serum Pb, Hg, Cd, and C-reactive protein (CRP) were 2.06±1.10 μg/L (95% CI 2.04–2.07); 4.08±3.53 μg/L (95% CI 4.02–4.13); 1.02±0.67 μg/L (95% CI 1.01–1.03), 1.20±2.02 mg/L (95% CI 1.17–1.24), respectively. The levels of vitamin B1, B2, B3, and C intake were significantly lower in subjects with MetS compared with subjects without MetS. By contrast, the levels of serum Pb, Hg, Cd, and CRP were significantly higher in subjects with MetS compared with subjects without MetS. (shown in Figure 1).

After adjustment for comorbidities, the risk of MetS was significantly lower in subjects with high curry consumption than subjects with low curry consumption, risks of Mets were reduced by 44% (OR 0.56; 95% CI, 0.54—0.58, p<0.001), 38% (OR 0.62; 95% CI, 0.61—0.64, p<0.001), 7% (OR 0.93; 95% CI, 0.92—0.93, p<0.001), 1% (OR 0.99; 95% CI, 0.98—0.99, p<0.001), when the levels of vitamin B1, B2, B3 and C intake increased by one mg, respectively. However, risks of Mets were increased by 19% (OR 1.19; 95% CI, 1.15—1.24, p<0.001), 3% (OR 1.03; 95% CI, 1.02—1.05, p<0.001), 113% (OR 2.13; 95% CI, 2.00—2.27, p<0.001), 6% (OR 1.06; 95% CI, 1.03—1.09, p<0.001), when the levels of serum Pb, Hg, Cd, and CRP increased by one unit. The marginal effect of the levels of vitamin intake, curry consumption, heavy metals and serum CRP on MetS by comorbidities was shown in Figure 2.

After adjustment for potential confounders, adjusted odds ratio followed the similar pattern. The risk of MetS was significantly lower in the high curry consumption than in the low curry consumption (OR 0.85; 95% CI, 0.74—0.98, p=0.028), risks of Mets were reduced by 7% (OR 0.93; 95% CI, 0.87—0.99, p=0.016), 13% (OR 0.87; 95% CI, 0.81—0.93, p<0.001), 1% (OR 0.99; 99% CI, 0.98—0.99, p<0.001), 1% (OR 0.99; 95% CI, 0.98—0.99, p=0.001), when the levels of vitamin B1, B2, B3 and C intake increased by one mg, respectively. Similarly, risks of Mets were increased by 9% (OR 1.09; 95% CI, 1.02—1.15, p=0.006), 3% (OR 1.03; 95% CI, 1.01—1.05, p=0.003), 5% (OR 1.06; 95% CI, 1.02—1.08, p<0.001), when the levels of serum Pb, Hg, and CRP increased by one unit. Crude odds ratio and adjusted odds ratio (95% confidence interval) for the risks of Metabolic syndrome was shown in Figure 3.

Figure 4 shows the marginal effect of the levels of vitamin intake, curry consumption, heavy metals, and CRP on MetS by age group after adjustment for potential cofounders among the Korean population. The effect of vitamin and curry intake showed a similar trend. The probability of MetS decreased when the levels of vitamin or curry intake increase. While, the probability of MetS increased once the levels of serum Pb, Hg, and CRP increased.

Discussion

Our findings include epidemiological evidence that draws upon an important volume of earlier experimental knowledge to support the association between vitamin, curry consumption, heavy metals, and effectiveness for MetS among subjects with comorbidities. We also identified the association between MetS, vitamin heavy metals, and comorbidities on a national level in Korea. We found that levels of vitamin intake and high curry consumption showed an inverse correlation with MetS, while levels of serum heavy metals and CRP showed a positive correlation with MetS. These findings partly contribute to the dual effects of vitamin, curry, and heavy metal consumption in Korea.

The dramatic global rise of urbanization and industrialization has increased the risk of exposure to pollutants, particularly heavy metals[15]. Besides, the growing global burden of NCDs has made the prevention and management of NCDs a priority, especially in the context of COVID-19 pandemic. Because the COVID-19 pandemic has also been connected with NCDs related to disease-induced morbidity and mortality, especially preventive measures such as the impact of social distancing and stay-at-home orders [16].

In this study, we found that the levels of heavy metals and cardiometabolic risk factors have positively correlated with MetS. These findings are in agreement with the previous study[9,17]. Heavy metals such as Pb, Hg, and Cd are toxic to the human body and can trigger different diseases, especially CVDs [18]. Heavy metals can increase the levels of reactive oxygen species and reactive nitrogen species leading to increased oxidative stress, consequently, cause DNA damage and oxidize protein thiol groups [19]. Furthermore, heavy metals destroy blood clotting and provoke the production of inflammatory cytokines and anti-thrombotic agents [6,7]. Recent data also indicate that, increased risk of the development of MetS with higher quartiles of CRP level in obese and non-obese women[20]. Therefore, the special concern should be given to the harmful impacts of multiple environmental pollutants, along with heavy metals on MetS. It is crucial to developing a prevention strategy targeting the high-risk population to slow down this progression to postpone risk factors related to heavy metals and reduce prevalence.

MetS is a risk factor for the formation of type 2 diabetes and CVDs [21]. While vitamin B1 plays an important role in intracellular glucose metabolism since it acts as a coenzyme for the α-ketoglutarate dehydrogenase complexes, transketolase, and pyruvate dehydrogenase [22]. Our study showed the levels of vitamin intake were significantly lower in subjects with MetS compared with subjects without MetS. Additionally, levels of HbA1c, fasting glucose were significantly higher in participants with MetS compared with those without MetS. It has been shown that reduced vitamin B1 in diabetic vascular cells exacerbates metabolic dysfunction in hyperglycemia [23]. The relationship between diabetes and vitamin B1 has been reported by genetic studies such as T*k*, α-1-antitrypsin, *SLC19A2* gene, and *p53* [24-27]*.* Vitamin B1 and its derivatives could thwart the biochemical pathways of caspase activation like improved flux via the polyol or hexosamine biosynthesis pathway, the making of advanced glycation end-products, induction of protein kinase C activity produced by hyperglycemia [28-31]. These data support our finding for the consumption of sufficient vitamin B1 presented an inverse correlation with MetS. Our findings were in line with the previous results of a significant reduction in plasma fasting glucose concentrations at a daily dose of 150 mg thiamine per 1 month in patients with drug-naïve type 2 diabetes [32]. Besides, the consumption of sufficient vitamin B1 also reported an inverse related to dyslipidemia [33]. Vitamin B1 thwarts the adverse consequence of high endothelial glucose levels by dropping the glycation of intracellular proteins [34]; vitamin B1 also plays a vital role in averting the development of atherosclerotic plaque as it had a positive effect against glucose-and insulin-mediated development of human infragenicular arterial smooth muscle cells [35]. Several studies also showed the regular vitamin B1 administration increases the functions of endothelial cells and slows the development of atherosclerosis [36], and short-term vitamin B1 treatment has regenerated the function of endothelial cells in healthy smokers with endothelial dysfunction caused by smoking [37]. Our findings long-established the role of vitamin B1 in the reversal of MetS, which is a risk factor that impacts the progression and prognosis of COVID-19.

Oxidative stress could play a significant part in MetS etiology[38]. Subjects with MetS have increased systemic oxidative damage due to upregulation of reactive oxygen species (ROS) and/or reduced antioxidant protection due to antioxidant enzymes[39]. Our findings show that intake of vitamin B2, B3, and C can reduce MetS, which was in line with the previous studies [40-42]. It could be explained that vitamin B2 could prevent the pro-inflammatory activity of adipocyte and macrophage co-cultures, thus decreasing the possibility of mild inflammation associated with obesity [40]. While vitamin B2 deficiency could increase the proinflammatory activity of adipocyte cells, resulting in chronic inflammation in obesity[43]. Vitamin B3 has also been found to be an efficient antioxidant in ROS production and to prevent DNA damage in lymphocytes[44]. It supports the previous study about vitamin B3 treatment has favored the normalization of low HDL-C atherogenic dyslipidemia [45]. Furthermore, a positive correlation has been reported between diets enriched with specific antioxidants such as vitamin C for oxidative stress [46]. These findings highlight the value of urgent efforts to establish targeted vitamin supplementation in Korea. We believe these strategies would effectively diminish the prevalence of MetS; therefore, it could support patients through the COVID-19 pandemic and reduce the morbidity and mortality of this syndrome.

Our analyses revealed that the risk of MetS was significantly lower among the high curry consumption group. These findings support our hypothesis that high curry consumption is related to reducing the risk of type 2 diabetes, which was in agreement with previous studies [47]. Curcumin could improve endothelial function and reducing oxidative stress and inflammatory markers (IL-6, TNF alpha, endothelin-1) in type 2 diabetes patients, and it also helps to enhance the function of β cells. [48,49]. Of note, curcumin has also an impact on insulin secretion in healthy participants [50]. On the other hand, Curcumin has the potential benefit of reducing triglyceride, total cholesterol, LDL-C, and increasing HDL-C in patients with acute coronary syndrome [51]. Recent data indicated that curcumin has a preventive stroke effect by reducing the oxidative stress levels related to signaling the uncoupling of protein 2 to strengthen endothelial vascular function [52]. Curcumin also has a profound effect on the microglial response, facilitate microglial M2 polarization, and prevents the pro-inflammatory response of microglia. Additionally, curcumin posttreatment among ischemic stroke patients diminishes brain damage and strengthens vascular endothelial function [53]. These data showed the potential benefits of curcumin in diabetes and CVDs. Consequently, curcumin is not only a promising therapeutic alternative for type 2 diabetes because of its anti-inflammatory property but also a preventive strategy for CVDs.

To our knowledge, this large-scale study is the first to report the dual effect of vitamin, curry, heavy metal consumption, and MetS on a national level in Korea. However, this study has several limitations. First, the cross-sectional method could not evaluate causality between MetS, and levels of thiamine and curry, heavy metal consumption. Second, as no physiological markers of antioxidant status in KNHANES were measured, oxidation status and vitamin levels in plasma and tissues were not evaluated. Third, vitamin consumption is measured from 24-h recall data which is based on recall; therefore, participants could be under-or overestimated their food consumption. However, the 24-h recall may be an effective technique to assess food intake, especially, before evaluating the food consumption, all participants were instructed to uphold their usual dietary habits. Finally, there were few individuals who consumed curry with high frequency, which could be underestimated the association between curry consumption and MetS.

The prevalence of MetS and exposure to heavy metal in Korea tends to be increasing [54-56], it gets worse during the COVID-19 pandemic [57]. MetS are significant factors of risk for severe COVID-19, but the mechanisms have been somewhat uncertain. Furthermore, the dramatic global rise of urbanization and industrialization has increased the risk of exposure to heavy metals. It is critical to developing a prevention strategy targeting the high-risk population to slow down this progression to postpone risk factors related to heavy metals and reduce prevalence. Vitamins and curry supplements could reverse MetS, these results indicate that the potential health benefits resulting from thiamine and curry supplementation could guard the public against the dual burden of communicable and non-communicable diseases in Korea. However, further works are required to determine the mechanistic dual effects of vitamins and curry in MetS.

Declarations

Acknowledgements

The authors are grateful to all research staff for their excellent contributions in data collection in the survey.

Author contributions

Study concept and design (H.N.D and M.S.K.); acquisition of data (H.N.D and M.S.K); analysis and interpretation of data (H.N.D, H.O. and M.S.K); statistical analysis (H.N.D and M.S.K), drafting of the manuscript (H.N.D and M.S.K).

Competing interests

The author(s) declare no competing interests.

Ethics declarations

Funding

This study supported by grants National Research Foundation of Korea (NRF) grant funded by the Korean government (MEST) (grant nos. NRF2013R1A1A3008851 and 2018R1D1A1B07049610).

References

1. WHO. *Diet, nutrition, and the prevention of chronic diseases: report of a joint WHO/FAO expert consultation*. Vol. 916 (World Health Organization, 2003).
2. Song, S. & Song, H. Dietary and Lifestyle Factors Associated with Weight Status among Korean Adolescents from Multicultural Families: Using Data from the 2017-2018 Korea Youth Risk Behavior Surveys. *Korean Journal of Community Nutrition* **24**, 465-475 (2019).
3. Huang, P. L. A comprehensive definition for metabolic syndrome. *Disease models & mechanisms* **2**, 231-237 (2009).
4. Costa, F. F. *et al.* Metabolic syndrome and COVID-19: An update on the associated comorbidities and proposed therapies. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* (2020).
5. le Roux, C. W. COVID-19 alters thinking and management in metabolic diseases. *Nature Reviews Endocrinology*, 1-2 (2020).
6. Arbi, S., Oberholzer, H. M., Van Rooy, M. J., Venter, C. & Bester, M. J. Effects of chronic exposure to mercury and cadmium alone and in combination on the coagulation system of Sprague-Dawley rats. *Ultrastructural Pathology* **41**, 275-283 (2017).
7. Angeli, J. K. *et al.* Cadmium exposure induces vascular injury due to endothelial oxidative stress: the role of local angiotensin II and COX-2. *Free radical biology and medicine* **65**, 838-848 (2013).
8. Valera, B. *et al.* Cardiac autonomic activity and blood pressure among Inuit children exposed to mercury. *Neurotoxicology* **33**, 1067-1074 (2012).
9. Poursafa, P. *et al.* Association of serum lead and mercury level with cardiometabolic risk factors and liver enzymes in a nationally representative sample of adolescents: the CASPIAN-III study. *Environmental Science and Pollution Research* **21**, 13496-13502 (2014).
10. Kim, N. H. *et al.* Erratum: Environmental Heavy Metal Exposure and Chronic Kidney Disease in the General Population. *Journal of Korean Medical Science* **30**, 507 (2015).
11. Yamamoto, C., Kaji, T., Sakamoto, M. & Kozuka, H. Cadmium stimulation of plasminogen activator inhibitor-1 release from human vascular endothelial cells in culture. *Toxicology* **83**, 215-223 (1993).
12. Salonen, J. T., Seppänen, K., Lakka, T. A., Salonen, R. & Kaplan, G. A. Mercury accumulation and accelerated progression of carotid atherosclerosis: a population-based prospective 4-year follow-up study in men in eastern Finland. *Atherosclerosis* **148**, 265-273 (2000).

13. Eshak, E. & Arafa, A. Thiamine deficiency and cardiovascular disorders. *Nutrition, Metabolism and Cardiovascular Diseases* **28**, 965-972 (2018).
14. Kunnumakkara, A. B. *et al.* Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. *British journal of pharmacology* **174**, 1325-1348 (2017).
15. Wang, M., Liu, R., Chen, W., Peng, C. & Markert, B. Effects of urbanization on heavy metal accumulation in surface soils, Beijing. *Journal of Environmental Sciences* **64**, 328-334 (2018).
16. Czeisler, M. É. *et al.* Mental health, substance use, and suicidal ideation during the COVID-19 pandemic—United States, June 24–30, 2020. *Morbidity and Mortality Weekly Report* **69**, 1049 (2020).
17. Kelishadi, R. *et al.* Association of blood cadmium level with cardiometabolic risk factors and liver enzymes in a nationally representative sample of adolescents: the CASPIAN-III study. *Journal of environmental and public health* **2013** (2013).
18. Gupta, V. K., Singh, S., Agrawal, A., Siddiqi, N. J. & Sharma, B. Phytochemicals mediated remediation of neurotoxicity induced by heavy metals. *Biochemistry research international* **2015** (2015).
19. Jomova, K. & Valko, M. Advances in metal-induced oxidative stress and human disease. *Toxicology* **283**, 65-87 (2011).
20. Song, Y., Yang, S. K., Kim, J. & Lee, D.-C. Association between C-reactive protein and metabolic syndrome in Korean adults. *Korean Journal of family medicine* **40**, 116 (2019).
21. Rochlani, Y., Pothineni, N. V., Kovelamudi, S. & Mehta, J. L. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. *Therapeutic advances in cardiovascular disease* **11**, 215-225 (2017).
22. vinh quoc Luong, K. & Nguyen, L. T. H. The impact of thiamine treatment in the diabetes mellitus. *Journal of clinical medicine research* **4**, 153 (2012).
23. Thornalley, P. *et al.* High prevalence of low plasma thiamine concentration in diabetes linked to a marker of vascular disease. *Diabetologia* **50**, 2164-2170 (2007).
24. Thameem, F., Wolford, J. K., Bogardus, C. & Prochazka, M. Analysis of slc19a2, on 1q23. 3 encoding a thiamine transporter as a candidate gene for type 2 diabetes mellitus in pima indians. *Molecular Genetics and Metabolism* **72**, 360-363 (2001).
25. Kalis, M., Kumar, R., Janciauskiene, S., Salehi, A. & Cilio, C. M. α 1-antitrypsin enhances insulin secretion and prevents cytokine-mediated apoptosis in pancreatic β-cells. *Islets* **2**, 185-189 (2010).
26. Rodríguez, M. R. Importance of water-soluble vitamins as regulatory factors of genetic expression. *Revista de investigacion clinica; organo del Hospital de Enfermedades de la Nutricion* **54**, 77 (2002).
27. Yang, Z. *et al.* The expression of p53, MDM2 and Ref1 gene in cultured retina neurons of SD rats treated with vitamin B1 and/or elevated pressure. *Yan ke xue bao (2016)* **20**, 259-263 (2004).
28. Berrone, E., Beltramo, E., Solimine, C., Ape, A. U. & Porta, M. Regulation of intracellular glucose and polyol pathway by thiamine and benfotiamine in vascular cells cultured in high glucose. *Journal of Biological Chemistry* **281**, 9307-9313 (2006).

29. Ayo, S. H., Radnik, R., Garoni, J., Troyer, D. A. & Kreisberg, J. I. High glucose increases diacylglycerol mass and activates protein kinase C in mesangial cell cultures. *American Journal of Physiology-Renal Physiology* **261**, F571-F577 (1991).

30. Babaei-Jadidi, R., Karachalias, N., Ahmed, N., Battah, S. & Thornalley, P. J. Prevention of incipient diabetic nephropathy by high-dose thiamine and benfotiamine. *Diabetes* **52**, 2110-2120 (2003).

31. Kohda, Y. *et al.* Prevention of incipient diabetic cardiomyopathy by high-dose thiamine. *The Journal of toxicological sciences* **33**, 459-472 (2008).

32. González-Ortiz, M., Martínez-Abundis, E., Robles-Cervantes, J. A., Ramírez-Ramírez, V. & Ramos-Zavala, M. G. Effect of thiamine administration on metabolic profile, cytokines and inflammatory markers in drug-naïve patients with type 2 diabetes. *European journal of nutrition* **50**, 145-149 (2011).

33. Al-Attas, O. *et al.* Metabolic benefits of six-month thiamine supplementation in patients with and without diabetes mellitus type 2. *Clinical Medicine Insights: Endocrinology and Diabetes* **7**, CMED. S13573 (2014).

34. La Selva, M. *et al.* Thiamine corrects delayed replication and decreases production of lactate and advanced glycation end-products in bovine retinal and human umbilical vein endothelial cells cultured under high glucose conditions. *Diabetologia* **39**, 1263-1268 (1996).

35. Avena, R., Arora, S., Carmody, B. J., Cosby, K. & Sidawy, A. N. Thiamine (vitamin B1) protects against glucose-and insulin-mediated proliferation of human infragenicular arterial smooth muscle cells. *Annals of vascular surgery* **14**, 37-43 (2000).

36. Arora, S. *et al.* Thiamine (vitamin B1) improves endothelium-dependent vasodilatation in the presence of hyperglycemia. *Annals of vascular surgery* **20**, 653-658 (2006).

37. Stirban, A. *et al.* Benfotiamine counteracts smoking-induced vascular dysfunction in healthy smokers. *International journal of vascular medicine* **2012** (2012).

38. Avignon, A., Hokayem, M., Bisbal, C. & Lambert, K. Dietary antioxidants: do they have a role to play in the ongoing fight against abnormal glucose metabolism? *Nutrition* **28**, 715-721 (2012).

39. Palmieri, V. O., Grattagliano, I., Portincasa, P. & Palasciano, G. Systemic oxidative alterations are associated with visceral adiposity and liver steatosis in patients with metabolic syndrome. *The Journal of nutrition* **136**, 3022-3026 (2006).

40. Mazur-Bialy, A. I. & Pocheć, E. Riboflavin reduces pro-inflammatory activation of adipocyte-macrophage co-culture. Potential application of vitamin B2 enrichment for attenuation of insulin resistance and metabolic syndrome development. *Molecules* **21**, 1724 (2016).

41. Park, S., Ham, J.-O. & Lee, B.-K. Effects of total vitamin A, vitamin C, and fruit intake on risk for metabolic syndrome in Korean women and men. *Nutrition* **31**, 111-118 (2015).

42. Abdullah, K., Alam, M. M., Iqbal, Z. & Naseem, I. Therapeutic effect of vitamin B3 on hyperglycemia, oxidative stress and DNA damage in alloxan induced diabetic rat model. *Biomedicine & Pharmacotherapy* **105**, 1223-1231 (2018).

43. Mazur-Bialy, A. I. & Pocheć, E. Vitamin B2 deficiency enhances the pro-inflammatory activity of adipocyte, consequences for insulin resistance and metabolic syndrome development. *Life sciences*

178, 9-16 (2017).

44. Abdullah, K., Qais, F. A., Ahmad, I. & Naseem, I. Inhibitory effect of vitamin B3 against glycation and reactive oxygen species production in HSA: An in vitro approach. *Archives of biochemistry and biophysics* **627**, 21-29 (2017).
45. Adiels, M. *et al.* Niacin action in the atherogenic mixed dyslipidemia of metabolic syndrome: Insights from metabolic biomarker profiling and network analysis. *Journal of clinical lipidology* **12**, 810-821. e811 (2018).
46. Khalil, A. *et al.* Antioxidant-rich food intakes and their association with blood total antioxidant status and vitamin C and E levels in community-dwelling seniors from the Quebec longitudinal study NuAge. *Experimental gerontology* **46**, 475-481 (2011).
47. Srinivasan, M. Effect of curcumin on blood sugar as seen in a diabetic subject. *Indian journal of medical sciences* **26**, 269 (1972).
48. Usharani, P., Mateen, A., Naidu, M., Raju, Y. & Chandra, N. Effect of NCB-02, atorvastatin and placebo on endothelial function, oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus. *Drugs in R & D* **9**, 243-250 (2008).
49. Chuengsamarn, S., Rattanamongkolgul, S., Luechapudiporn, R., Phisalaphong, C. & Jirawatnotai, S. Curcumin extract for prevention of type 2 diabetes. *Diabetes care* **35**, 2121-2127 (2012).
50. Wickenberg, J., Ingemansson, S. L. & Hlebowicz, J. Effects of Curcuma longa (turmeric) on postprandial plasma glucose and insulin in healthy subjects. *Nutrition journal* **9**, 43 (2010).
51. Alwi, I. *et al.* The effect of curcumin on lipid level in patients with acute coronary syndrome. *Acta Med Indones* **40**, 201-210 (2008).
52. Lan, C. *et al.* Curcumin prevents strokes in stroke-prone spontaneously hypertensive rats by improving vascular endothelial function. *BMC cardiovascular disorders* **18**, 1-10 (2018).
53. Liu, Z. *et al.* Curcumin protects against ischemic stroke by titrating microglia/macrophage polarization. *Frontiers in aging neuroscience* **9**, 233 (2017).
54. Lim, S. *et al.* Components of Metabolic Syndrome in Korean Adults: A Hospital-Based Cohort at Seoul National University Bundang Hospital. *Journal of obesity & metabolic syndrome* **28**, 118 (2019).
55. Huh, J. H. *et al.* Metabolic syndrome severity score in Korean adults: analysis of the 2010–2015 Korea National Health and Nutrition Examination Survey. *Journal of Korean medical science* **34** (2019).
56. Lee, J.-m. *et al.* Association between heavy metal exposure and prevalence of metabolic syndrome in adults of South Korea. *Korean Journal of Family Practice* **7**, 172-178 (2017).
57. Lancet, T. COVID-19: a new lens for non-communicable diseases. *Lancet (London, England)* **396**, 649 (2020).
58. Welfare, K. M. o. H. a. *Korea National Health & Nutrition Examination Survey*, <https://knhanes.cdc.go.kr/knhanes/eng/index.do. Jan 20, 2021> (2021).

59. Lee, K.-J. & Kim, J.-I. Relating factors for depression in Korean working women: secondary analysis of the fifth Korean National Health and Nutrition Examination Survey (KNHANES V). *Asian nursing research* **9**, 265-270 (2015).
60. Gregory, C. O., McCullough, M. L., Ramirez-Zea, M. & Stein, A. D. Diet scores and cardio-metabolic risk factors among Guatemalan young adults. *British journal of nutrition* **101**, 1805-1811 (2008).
61. Organization, W. H. Western Pacific Region, International Association for the Study of Obesity. The Asia-Pacific Perspective. *Redefining obesity and its treatment* (2000).
62. Paik, H. Y. Dietary Reference Intakes for Koreans (KDRIs). *Asia Pacific Journal of Clinical Nutrition* **17** (2008).

Tables

Table 1. Demographic distribution of participants by metabolic syndrome in Korean, 2009-2013 and 2016-2017.

Variables	No.	Metabolic syndrome		*ORs 95%CI*	*p*-value
		Yes	No		
Sex *(%)*	60,256				
Male	27,429	8,239 (38.1)	19,190 (49.7)	1 (refer)	
Female	32,827	13,373 (61.9)	19,454 (50.3)	1.60 (1.55—1.66)	<0.001
Age (year) †	60,256	39.6±28.0	41.6±19.1		<0.001
Age group *(%)*					
<29	19,626	8,353 (38.7)	11,273 (29.2)	1 (refer)	
30-39	8,332	1,219 (5.6)	7,113 (18.4)	0.23 (0.22—0.25)	<0.001
40-49	8,656	1,946 (9.0)	6,710 (17.4)	0.39 (0.37—0.41)	<0.001
50-59	8,554	2,861 (13.2)	5,693 (14.7)	0.68 (0.64—0.72)	<0.001
>60	15,088	7,233 (33.5)	7,855 (20.3)	1.24 (1.19—1.30)	<0.001
Marital status *(%)*	60,126				
Married	39,286	12,929 (60.0)	26,357 (68.3)	1 (refer)	
Living alone	20,840	8,611 (40.0)	12,229 (31.7)	1.44 (1.39—1.49)	<0.001
Residential areas *(%)*	60,256				
Urban	48,396	16,919 (78.3)	31,477 (81.4)	1 (refer)	
Rural	11,860	4,693 (21.7)	7,167 (18.6)	1.22 (1.17—1.27)	<0.001
Occupation *(%)*	44,687				

Variables	No.	Metabolic syndrome		*ORs 95%CI*	*p*-value
		Yes	No		
Managers, professional	5,358	621 (5.6)	4,737 (14.1)	1 (refer)	
Office worker, clerical workers	3,790	497 (4.5)	3,293 (9.8)	1.15 (1.01—1.31)	0.029
Service workers, sales workers	5,407	1,217 (11.0)	4,190 (12.5)	2.22 (1.99—2.46)	<0.001
Agriculture, forestry and fishing workers	2,848	900 (8.1)	1,948 (5.8)	3.52 (3.14—3.95)	<0.001
Craft, plant and machine operators and assemblers	4,029	677 (6.1)	3,352 (10.0)	1.54 (1.37—1.73)	<0.001
Elementary occupations	3,730	1,111 (10.1)	2,619 (7.7)	3.24 (2.90—3.61)	<0.001
Unemployed	19,525	6,036 (54.6)	13,489 (40.1)	3.41 (3.12—3.73)	<0.001
Education level *(%)*	55,326				
≤ Middle school	27,702	13,669 (76.4)	14,033 (37.5)	1 (refer)	
High school	14,342	2,689 (15.0)	11,653 (31.1)	0.24 (0.23—0.25)	<0.001
≥ College	13,282	1,544 (8.6)	11,738 (21.4)	0.14 (0.13—0.14)	<0.001
Monthly household income *(%)* §	59,628				
< 2,000	16,917	7,264 (34.0)	9,653 (25.2)	1 (refer)	
≥ 2,000 and < 4,000	19,423	6,922 (32.4)	12,501 (32.7)	0.74 (0.71—0.77)	<0.001
≥ 4,000 and < 6,000	13,065	4,176 (19.6)	8,889 (23.2)	0.62 (0.60—0.65)	<0.001

Variables	No.	Metabolic syndrome		*ORs 95%CI*	*p*-value
		Yes	No		
≥ 6,000	10,223	2,982 (14.0)	7,241 (18.9)	0.55 (0.52—0.58)	<0.001
BMI group *(%)*	56,009				
<18.5	8,945	5,057 (29.0)	3,888 (10.1)	5.71 (5.43—6.01)	<0.001
≥ 18.5 and < 25	31,942	5,925 (33.9)	26,017 (67.5)	1 (refer)	
≥ 25 and < 30	13,096	5,337 (30.6)	7,759 (20.1)	3.02 (2.89—3.16)	<0.001
≥ 30	2,026	1,137 (6.5)	889 (2.3)	5.62 (5.12—6.16)	<0.001
Curry consumption *(%)*	10,874				
Rarely or never	5,812	1,587 (61.9)	4,225 (50.8)	1 (refer)	
Often and occasionally	5,062	977 (38.1)	4,085 (49.2)	0.64 (0.58—0.70)	<0.001
Smoking status *(%)*	42,803				
Non/ex-smoker	32,992	9,413 (84.5)	23,579 (74.5)	1 (refer)	
Current smoker	9,811	1,728 (15.5)	8,083 (25.5)	0.54 (0.51—0.57)	<0.001
Drinking status *(%)*	47,435				
Often	15,884	4,814 (42.8)	11,070 (30.6)	1 (refer)	
Occasionally	22,403	4,511 (40.1)	17,892 (49.4)	0.58 (0.55—0.61)	<0.001
Never or rarely	9,148	1,915 (17.0)	7,233 (20.0)	0.61 (0.57—0.65)	<0.001
Physical activity *(%)*	60,256				

Variables	No.	Metabolic syndrome		*ORs 95%CI*	*p*-value
		Yes	No		
Not regular	51,088	19,677 (91.1)	31,411 (81.3)	1 (refer)	
Regular	9,168	1,935 (8.9)	7,233 (18.7)	0.43 (0.40—0.45)	<0.001
Family history of CVDs *(%)*	60,256				
No	51,088	4,337 (50.0)	17,727 (60.2)	1 (refer)	
Yes	9,168	4,331 (50.0)	11,703 (39.8)	1.51 (1.44—1.59)	<0.001
Family history of diabetes *(%)*	37,720				
No	30,335	6,375 (75.5)	23,960 (81.8)	1 (refer)	
Yes	7,385	2,071 (24.5)	5,314 (18.2)	1.46 (1.38—1.55)	<0.001
Family history of hyperlipidemia *(%)*	36,414				
No	34,145	7,525 (94.2)	26,620 (93.6)	1 (refer)	
Yes	2,269	461 (5.8)	1,808 (6.4)	0.90 (0.81—1.00)	0.055
Comorbidities ¶					
Type 2 diabetes mellitus	3,793	2,525 (13.9)	1,268 (3.3)	4.67 (4.35—5.01)	<0.001
Hypertension	9,837	5,927 (32.6)	3,910 (10.3)	4.21 (4.03—4.41)	<0.001
Dyslipidemia	5,532	3,332 (32.8)	2,200 (6.0)	7.59 (7.15—8.06)	<0.001
Stroke	906	486 (2.7)	420 (1.12)	2.45 (2.15—2.80)	<0.001

Variables	No.	Metabolic syndrome		*ORs 95%CI*	p-value
		Yes	No		
MI or angina	1,130	565 (3.4)	565 (1.6)	2.21 (1.96—2.48)	<0.001
MI	393	178 (1.0)	215 (0.6)	1.73 (1.42—2.12)	<0.001
Angina	810	421 (2.3)	389 (1.0)	2.29 (1.99—2.63)	<0.001
Asthma	1,965	804 (4.5)	1,161 (3.1)	1.47 (1.34—1.61)	<0.001
Thyroid disease	1,607	585 (3.3)	1,022 (2.7)	1.20 (1.08—1.33)	0.001
Osteoarthritis	4,984	2,706 (15.1)	2,278 (6.1)	2.74 (2.58—2.91)	<0.001
Rheumatoid arthritis	880	378 (2.1)	502 (1.3)	1.58 (1.38—1.81)	<0.001
Arthritis	5,628	2,948 (17.5)	2,680 (7.3)	2.68 (2.53—2.83)	<0.001
Kidney failure	178	89 (0.5)	89 (0.2)	2.09 (1.56—2.81)	<0.001
Depression	1,785	706 (3.9)	1,079 (2.9)	1.38 (1.25—1.52)	<0.001
Waist circumference *(cm)* †	56,935	77.6 ±10.5	74.2±19.0	–	<0.001
Total cholesterol *(mg/dL)* †	47,054	195.9±40.9	183.8±35.6	–	<0.001
LDL-C *(mg/dL)* †	10,339	117.4±36.3	111.3±31.9	–	<0.001
Triglyceride *(mg/dL)*	47,054	194.7±136.4	110.9±87.7	–	<0.001
HDL-C *(mg/dL)* †	47,054	44.3±9.8	51.6±12.0	–	<0.001
HbA1c *(%)* †	33,118	6.4±1.2	5.6±0.7	–	<0.001
Fasting glucose *(mg/dL)* †	46,984	113.7±32.0	93.8±16.6	–	<0.001

Variables	**No.**	**Metabolic syndrome**		***ORs 95%CI***	***p*-value**
		Yes	**No**		
Energy intake *(Kcal)* †	53,701	1680.9±797.4	2026.6±880.2	–	<0.001
Hemoglobin *(g/dL)* †	46,846	13.7±1.5	14.0±1.6	–	<0.001
ALT *(U/L)* †	47,054	24.9±17.9	19.7±17.7	–	<0.001
AST *(U/L)* †	47,054	24.8±12.9	21.3±13.1	–	<0.001
Systolic blood pressure *(mmHg)* †	50,220	130.3±17.4	114.4±15.2	–	<0.001
Diastolic blood pressure *(mmHg)*	50,220	78.8±11.4	73.6±10.4	–	<0.001

†: mean ± SD, two-sample t test with unequal variances, except for ALT with equal variances; ¶: reference with no comorbidities; §: thousand won. AST: aspartate aminotransferase. ALT: alanine aminotransferase, MI: myocardial infraction. BMI: Body mass index (kg/m^2), CVDs: Cardiovascular disease, HDL: High-density lipoprotein, LDL-C: low-density lipoprotein cholesterol.

Figures

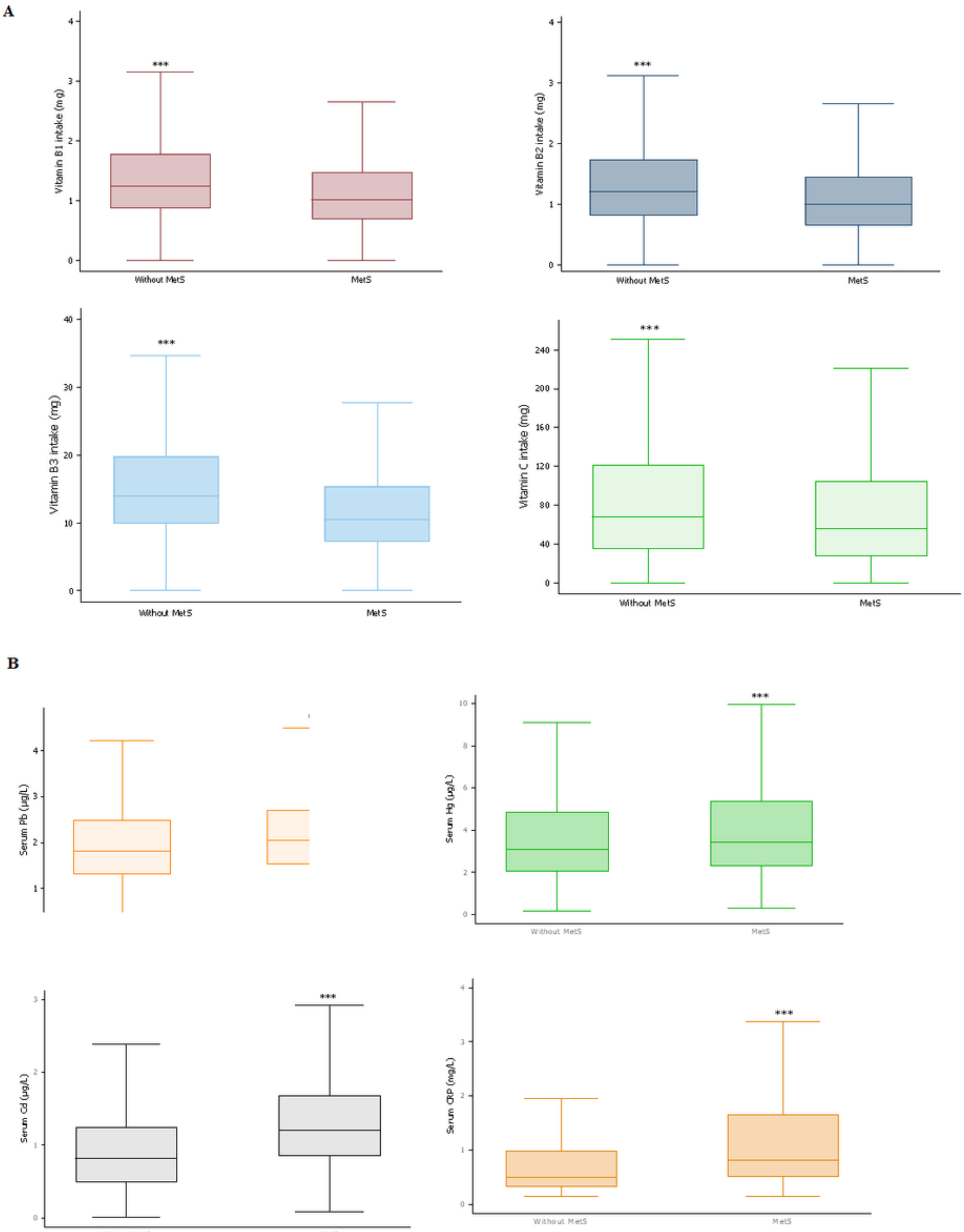

Figure 1

The levels of vitamin intake (A), serum heavy metals and serum CRP (B) in subjects with or without metabolic syndrome (MetS). Two-sample t test with unequal variances. ***, P<0.001.

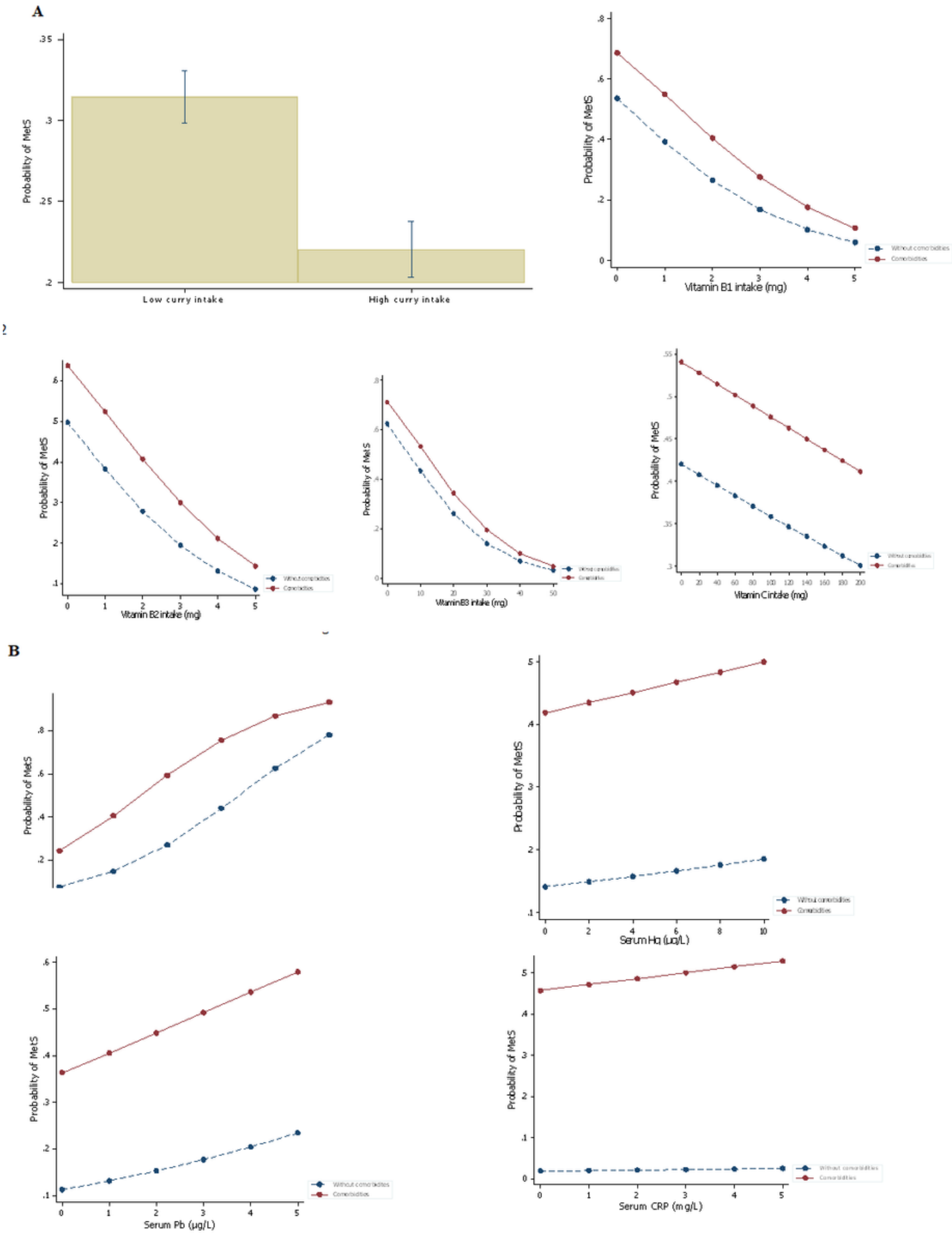

Figure 2

The marginal effect of the levels of vitamin intake, curry consumption (A), heavy metals and serum CRP (B) on MetS by comorbidities among the Korean population, respectively.

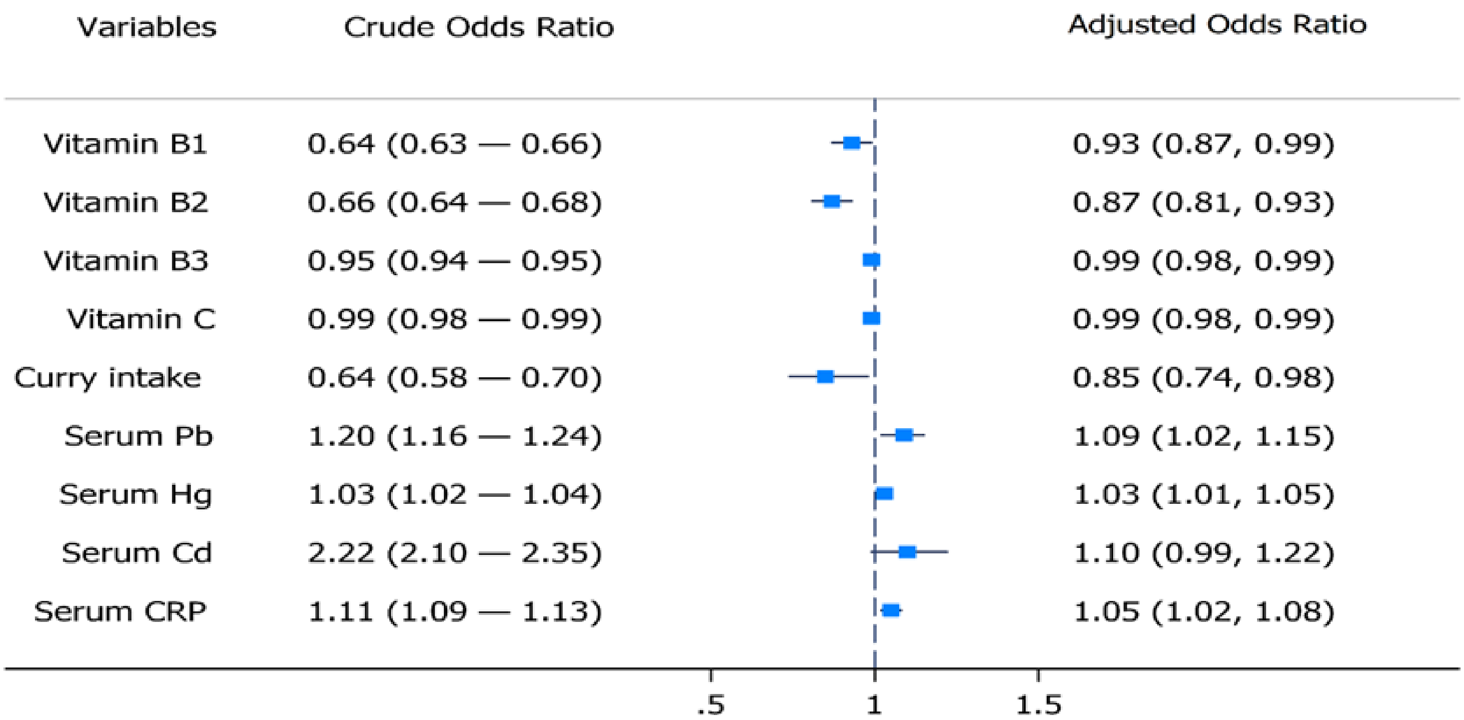

Figure 3

Crude odds ratio and adjusted odds ratio (95% confidence interval) for the risks of Metabolic syndrome. Adjusted for monthly household income, residential areas, energy intake, age group, occupation, sex, family history of CVDs, family history of diabetes mellites, family history of hyperlipidemia, BMI group, smoking status, high risk drinking, physical activity, education level, hypertension, dyslipidemia, type 2 diabetes, stroke, myocardial infarction or angina, myocardial infarction, angina, arthritis, osteoarthritis, rheumatoid arthritis, kidney failure, depression, thyroid disease, and asthma. (shown in the supplementary material).

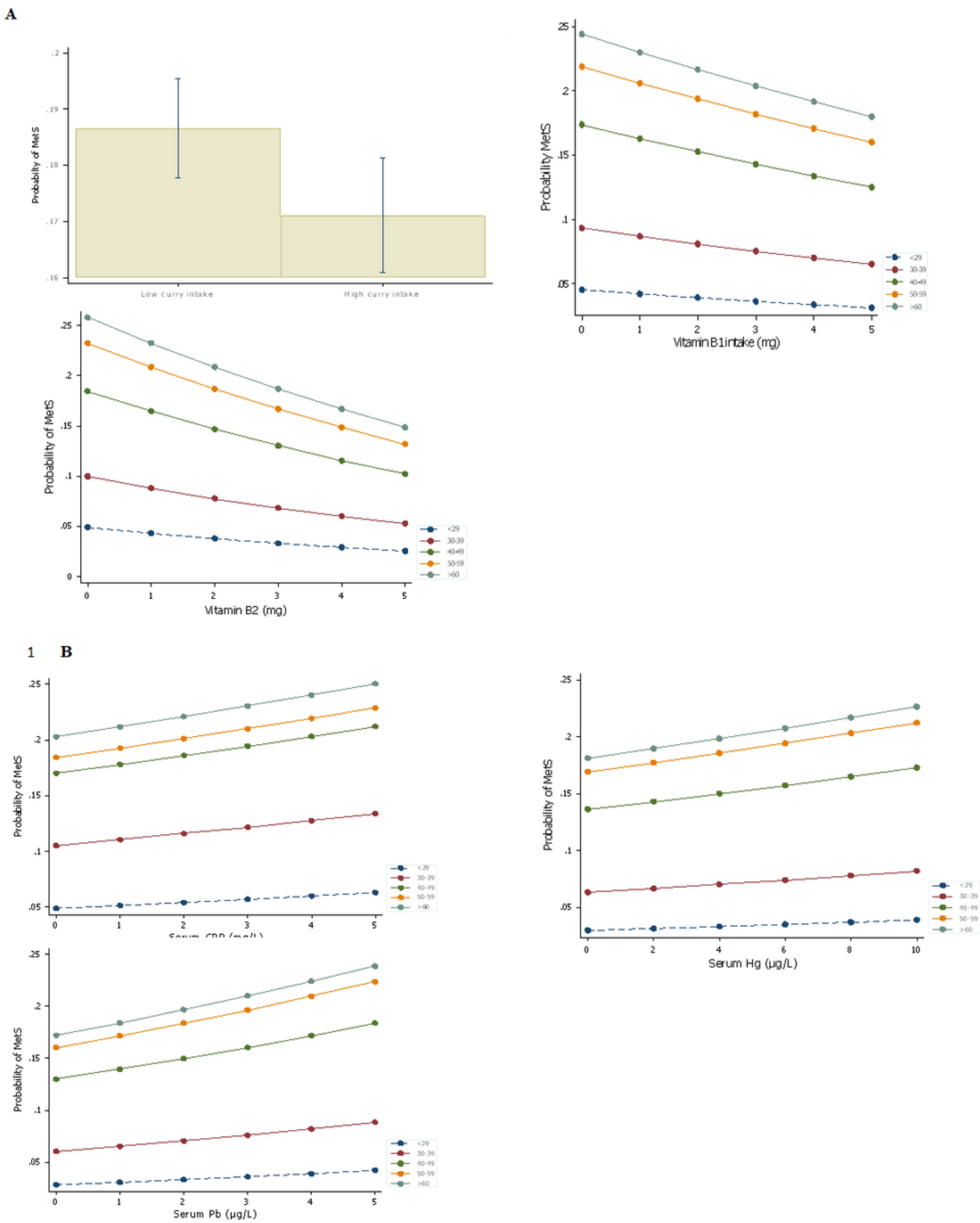

Figure 4

The marginal effect of the levels of vitamin intake, curry consumption (A), heavy metals and serum CRP (B) on MetS by age group after adjustment for potential cofounders among the Korean population, respectively.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.docx