Biological Trace Element Research (2022) 200:4903–4915
https://doi.org/10.1007/s12011-021-03077-3

Association Between Essential and Non-essential Metals, Body Composition, and Metabolic Syndrome in Adults

Yi Jing Ngu[1] · Anatoly V. Skalny[2,3] · Alexey A. Tinkov[2,4] · Chien-Sung Tsai[5,6] · Chun-Chao Chang[7,8] · Yung-Kun Chuang[9] · Vladimir N. Nikolenko[2] · Dmitry A. Zotkin[2] · Ching-Feng Chiu[1] · Jung-Su Chang[1,10,11,12]

Received: 27 October 2021 / Accepted: 19 December 2021 / Published online: 7 January 2022

Abstract

Growing evidence indicates that metal exposure is associated with metabolic syndrome (MetS); however, mixed results have been reported. The aim of this study was to clarify associations of exposure to essential and non-essential metals with body composition and risks of obesity and MetS. Anthropometry and blood biochemistry of metabolic parameters were obtained from 150 middle-aged Taiwanese adults. Plasma metals were assessed using inductively coupled plasma mass spectrometry, and body compositions were measured by a bioelectrical impedance analysis (BIA). The essential metals of copper (Cu), manganese (Mn), and chromium (Cr) were positively correlated with the body fat mass but inversely correlated with the skeletal muscle mass (all $p<0.05$). An adjusted logistic regression showed that Mn [odds ratio (OR) = 1.624 (95% confidence interval 1.072, 2.462), $p=0.02$] and, to a lesser extent, Cu [OR = 1.501 (0.985, 2.292), $p=0.059$] predicted abdominal obesity, while plasma Cu [OR = 2.211 (1.146, 4.266), $p=0.02$] and zinc (Zn) [OR = 2.228 (1.048, 4.736) $p=0.04$] predicted MetS. Significant correlations between dyslipidemia and lithium [OR = 1.716 (1.080, 2.726)], Cu [OR = 2.210 (1.415, 3.454)], Mn [OR = 2.200 (1.320, 3.666)], molybdenum [OR = 1.853 (1.160, 2.958)], and Zn [OR = 1.993 (1.186, 3.349)], and between boron [OR = 2.583 (1.137, 5.868)] and hyperglycemia were observed (all $p<0.05$). Exposure to essential metals may affect the body composition and metabolic profiles, exacerbating the risk of MetS.

Keywords Toxic heavy metals · Essential elements · Non-essential metals · Abdominal obesity · Body composition · Metabolic syndrome · Dyslipidemia · Diabetes

Introduction

A worldwide survey in 2015 showed that obesity affects 107.7 million children and 603.7 million adults, with the highest adult obesity (35.3%) observed in Egypt and the highest childhood obesity (12.7%) in the USA [1]. Obesity is the strongest risk factor for metabolic syndrome (MetS). MetS refers to a cluster of metabolic disturbances including abdominal obesity, dyslipidemia, hypertension, and hyperglycemia. MetS is a non-communicable disease with major public health consequences. For example, cardiovascular disease (CVD) (70%) was estimated to be the major cause of death among obese persons [1].

Metals widely exist in the environment, including in the food chain, water, dust, and soils. However, they are also derived from environmental pollutants from domestic, industrial, and medical sources, and technology devices. Although there is yet no consensus on the classification of metals, metals can be broadly categorized as essential [e.g., iron (Fe), copper (Cu), chromium (Cr), manganese (Mn), magnesium (Mg), molybdenum (Mo), and zinc (Zn)], probable essentials [e.g., boron (B) and nickel (Ni)], and non-essentials [e.g., arsenic (As), cadmium (Cd), mercury (Hg), lead (Pb), lithium (Li), and strontium (Sr)] [2]. By acting as cofactors of metalloenzymes, essential metals exert diverse biological functions and are essential for proper functioning of the human body. Metals with high density (> 5 g/cm^3) are often referred as "heavy metals," and they can be either essential or non-essential. Toxic heavy metals are often found in the environment and bioaccumulate in plants, wildlife, and people. They are of major public health concern because of their high toxicity to the human body even at low concentrations at the ppm level. For example, a 2014 World Health Organization (WHO) report emphasizes that Hg is among the top 10 chemicals of major public health concern, and there is a need for policies to reduce Hg exposure particularly in countries with high intake of fish and seafood [3].

✉ Jung-Su Chang
susanchang@tmu.edu.tw

Extended author information available on the last page of the article

Emerging evidence suggests that metal exposure may be associated with risks of obesity [4–6] and MetS [7–9]; however, mixed results have been reported [4, 10, 11]. A recent systematic review and meta-analysis showed that individuals with MetS had a 1.16-fold [pooled effect size (ES) = 1.16, 95% confidence interval (CI) = 1.09, 1.23] higher risk of mixed exposure to toxic heavy metals (As, Cd, Hg, and Pb) compared to those without MetS. However, study heterogeneity was high (I^2 = 75.6%), and a subgroup analysis only found significant relationships between MetS and Hg (pooled ES = 1.26, 95% CI = 1.06, 1.48; I^2 = 67.7%) and Pb (pooled ES = 1.21, 95% CI = 1.00, 1.48; I^2 = 82.9%). Another study evaluated 37 epidemiological studies investigating environmental toxic metal exposure (As, Cd, Hg, Pb, and Cu) and risk of CVD, and the authors concluded that except for Hg exposure, environmental pollutants were associated with an increased risk of CVD [4]. Several factors may contribute to the high study heterogeneity and discrepancies among studies, including study designs (e.g., cross-sectional vs. prospective follow-up study), country and region, participants' age or gender, single vs. multiple metal exposure, and types of metals (non-essential vs. essential). Country and geographic location affect the degree of exposure to environmental pollutants (e.g., type of contaminants and concentrations) particularly nation and race [7]. For example, a population-based study in South Korea showed that Hg exposure predicted risks of obesity and MetS [5, 12, 13], but this relationship was inconclusive in the USA [14, 15]. Seafood has high Hg contaminant levels, and seafood consumption may explain regional differences in Hg exposure and risks of obesity or MetS [16]. Other possibilities include exposure to multiple environmental pollutants [11, 14] or accumulation of less-toxic essential metals, such as Cu, Fe, Zn [17–19], Cr, Mg, and Mn [6, 20, 21]. Overall, relationships between metal exposure and MetS are complicated, and multifactorial mechanisms may be involved.

Currently, few studies have investigated relationships between metal exposure and body composition. Since MetS is intertwined with obesity, the aim of this study was to clarify relationships of metal exposure and body composition with risks of obesity and MetS in 150 middle-aged Taiwanese adults. Specifically, we aimed to investigate (1) relationships of essential and non-essential metals with body composition and abdominal obesity, and (2) the predictive effects on MetS and its individual components.

Materials and Methods

Participants and Sample Inclusion and Exclusion

This study used non-probability volunteering sampling as the sampling method. Informed written consent was collected by face-to-face interview from 150 Taiwanese adults (100 men and 50 women) aged 20–64 years before the enrollment to the study. Inclusion criteria were (1) Taiwanese citizen; (2) speak fluent Chinese; and (3) adults. Subjects were excluded if they were (1) aged < 20 or ≥ 65 years; (2) pregnant or lactating; (3) anemia (men: Hb < 13 g/dL and women Hb < 12 g/dL); (4) disease history of cancer, hepatitis, nephritis, and dialysis; and (5) excessive alcohol intake (alcohol intake < 20 g/week for women or < 30 g/week for men). A total of 150 (100 men and 50 women) were entered for the analysis.

Anthropometric Parameters and Body Composition

Anthropometric parameters such as body weight, body height, waist circumference (WC), hip circumference (HC), and the waist/hip (W/H) ratio of each participant were measured by trained staff. The WC was measured around the midpoint between the lower margin of the last rib and the top of the iliac crest. The W/H ratio was calculated as the WC divided by the HC. The body mass index (BMI) was calculated as weight (in kg) / (height squared in m^2). The body composition was measured using a bioelectrical impedance analysis (BIA) (X-SCAN Plus-II analyzer, Jawon, Korea) to record the total body fat mass (BFM) (%), skeletal muscle mass (SMM) (%), visceral fat (%), subcutaneous fat (%), and ratio of BFM/SMM.

Blood Biochemistry

Fasting blood samples were collected from overnight-fasted participants. Blood analyses included a complete blood cell count, blood glucose, insulin and lipid profiles [total cholesterol (TC), low- (LDL-C) and high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs)], which were performed in a certified medical laboratory (Le-Zen Clinical Laboratory, Taipei, Taiwan). Plasma metal levels were assessed in Tri-Service Hospital (Taipei, Taiwan) using inductively coupled plasma mass spectrometry (ICP-MS) with a NexION 300D (PerkinElmer, Shelton, CT, USA) equipped with an ESI SC-2 DX4 autosampler (Elemental Scientific, Omaha, NE, USA). Blood plasma were diluted (1:20 v:v) with a diluent consisting of 0.05% Triton X-100 (Sigma-Aldrich, Co., MO, USA), and 1% HNO_3 (ULTREX® II Ultrapure Reagent, J.T.Baker, Co., Canada) in 18.2 MΩ cm distilled deionized water. Analysis of essential, probably essential, and non-essential metal contents was performed using the NexION 300D (PerkinElmer) equipped with an ESI SC-2 DX4 autosampler (Elemental Scientific). A standard 0, 10, 20, 30, 40, and 50 µg/L solution of each metals from Universal Data Acquisition Standards Kit (PerkinElmer) was employed to calibrate the system. Certipur® Certified Reference Material (Merck, Germany) was used in this study as a quality control.

Definitions

Dyslipidemia was classified if an individual had at least one of the following criteria: (1) total C of ≥ 240 mg/dL; (2) LDL-C of ≥ 160 mg/dL; (3) HDL-C of < 40 mg/dL; (4) TC/HDL-C ratio of ≥ 5, and (5) TGs of ≥ 200 mg/dL [22]. The homeostatic model assessment of insulin resistance (HOMA-IR) index was calculated as fasting insulin (μU/L) × fasting glucose (nmol/L)/22.5. Diabetes was defined as glycated hemoglobin (HbA1C) of ≥ 6.5% or fasting plasma glucose of ≥ 126 mg/dL. Hypertension was defined as systolic blood pressure of ≥ 130 mm/Hg and diastolic blood pressure of ≥ 85 mm/Hg. The criteria of MetS were based on the modified National Cholesterol Education Program Adult Treatment Panel III for the Asia Pacific [23]. MetS was confirmed if individuals had three or more of the following criteria: (1) fasting plasma glucose of ≥ 100 mg/dL; (2) fasting TGs of ≥ 150 mg/dL; (3) HDL-C of < 40 mg/dL; (4) systolic blood pressure of ≥ 130 mmHg or diastolic blood pressure of ≥ 85 mmHg; and (5) a WC in males of ≥ 90 cm and in females of ≥ 80 cm, which was also defined as abdominal obesity or central obesity. Toxicity of non-essential elements was defined according to the Agency for Toxic Substances and Disease Registry (ATSDR) as: As > 1 μg/L and Cd > 0.315 μg/L in blood.

Statistical Analysis

Analyses were carried out using IBM® SPSS® 21, SAS vers. 9.4, GraphPad Prism 5 and R software (version 1.4.1717). A normality test was carried out to test the distribution of each variable. Variables that were not normally distributed were log-transformed to meet the normality assumption for the analysis. Categorical data are presented as the number [percentage (%)], and continuous data are presented as the mean ± standard deviation (SD). Plasma metal concentrations were divided into tertiles (T) using SPSS by assigning T1 to the smallest value. Mann–Whitney test was used to identify the difference of metals concentration between two groups. A general linear model was used to analyze the p-trend between variables for continuous data, and chi-squared was used for categorical data. A multivariate linear regression analysis adjusted for age, sex, and smoking status was employed to evaluate relationships between metal exposure and body composition (W/H ratio, BMI, total body fat mass, subcutaneous fat mass, visceral fat mass, skeletal muscle mass, and ratio of body fat mass/skeletal muscle mass) as well as metabolic profiles (e.g., fasting plasma glucose, HOMA-IR, HDL, LDL, and TC). A multivariate logistic regression adjusted for age, sex, smoking, and BMI was conducted to estimate the odds ratio (OR) and 95% CI of MetS, and its components (dyslipidemia, diabetes, and hypertension). In Fig. 1, cut-off points for tertile (T) groups of each metal were As: < 1.0, 1.0–2.8 μg/L, > 2.8; Hg: < 0.9, 1.0–1.4, > 1.4 μg/L; Li: < 1.0, 1.0–1.4, > 1.4 μg/L; Sr: < 31.50, 31.50–43.10, > 43.10 μg/L; B: < 12.0, 12.0–28.40, > 28.40 μg/L; Cr: < 0.7, 0.7–1.2, > 1.2 μg/L; Cu: < 886.3, 886.3–1061.6, > 1061.6 μg/L; Ni: < 0.4, 0.4–1.6, > 1.6 μg/L; Mg: < 21,781, 21,781–25,894 μg/L, > 25,894; Mn: < 1.4, 1.4–1.7, > 1.7 μg/L; Mo: < 0.9, 0.9–1.2, > 1.2 μg/L, and Zn: < 764.5, 764.5–951.9, > 951.9 μg/L. Differences were considered significant at $p \leq 0.05$.

Results

Baseline Characteristics

Table 1 shows the general characteristics of study participants. In total, 150 participants were included in the analysis. The mean age was 42.6 ± 12.4 year and mean BMI was 24.8 ± 4.4 kg/m^2. The majority of study participants were male (70.7%), and 18.7% had a smoking history. Almost half of participants had abdominal obesity (45.3%) and dyslipidemia (55.3%), and one-quarter had hypertension (22.0%). Individuals with MetS had lower skeleton muscle mass but higher levels of fat mass, non-essential metals (Cd, Li, and Sr), and essential metals (B, Cu, Ni, Mg, Zn) compared to those without MetS (all $p < 0.05$) (Table 1).

MetS was confirmed if individuals had three or more of the following criteria: (1) fasting plasma glucose ≥ 100 mg/dL; (2) fasting TGs ≥ 150 mg/dL; (3) HDL-C < 40 mg/dL; (4) systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg; and (5) a WC in males ≥ 90 cm and in females ≥ 80 cm.

Associations Between Plasma Metals and Body Composition

We first investigated relationships between plasma metals and the most common anthropometric indices used to screen for abodominal obesity (the waist (W)/hip (H) circumference ratio) or obesity (BMI). Table 2 shows no significant relationship between plasma metals and the W/H ratio or BMI after adjusting for age, gender, and smoking, except between plasma B and BMI ($\beta = 0.834$ (0.017, 1.650), $p < 0.05$). We next investigated relationships between plasma metal exposure and body composition. For non-essential metals, a significant positive correlation was found between plasma Li and the body fat mass (%) ($\beta = 1.454$ (0.005, 2.902), $p < 0.05$) after adjusting for covariates (Table 2, non-essential metals). Cr, Cu, and Mn essential metals were significantly positively correlated with the body fat mass (%) but inversely correlated with the skeletal muscle mass (%) (Table 2, essential metals)

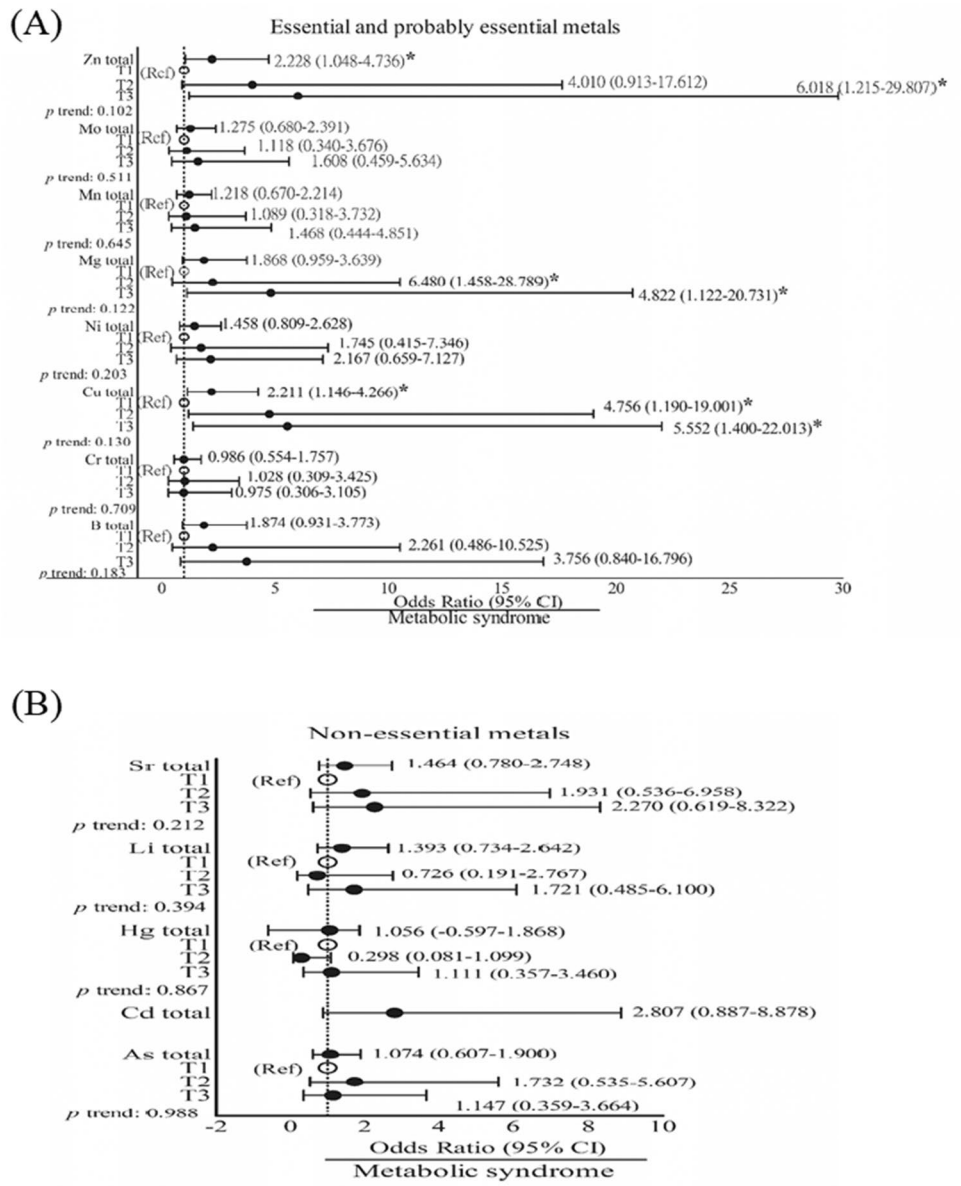

Fig. 1 Adjusted odds ratio (ORs) and 95% confidence intervals (CI) of essential and probably essential metals (**A**) and non-essential metals (**B**) for predicting metabolic syndrome (MetS) according to total and tertile (T) groups of plasma metals ($n = 150$). The multivariate model was adjusted for age, gender, body mass index, and smoking. Black, filled circles represent total predictive effects of each metal. Unfilled circles indicate the reference (Ref, T1) and black, filled circles represent T2 and T3 groups, respectively. *$p < 0.05$

(all $p < 0.05$). Positive trends between plasma levels of B and Cu and the ratio of body fat mass/skeletal muscle mass were also observed (both $p < 0.05$).

Associations Between Plasma Metals and Metabolic Components

Table 3 shows that no significant correlations between non-essential metals and metabolic components (total C, HDL, LDL, HOMA-IR, fasting plasma glucose) were observed (Table 3, non-essential metals), except for plasma Li and fasting plsma glucose levels ($\beta = 3.810$ (0.972, 8.592), $p < 0.05$). In contrast, significant positive correlations were found between TC and the essential metals Cu [$\beta = 32.928$ (6.259, 59.598)], Mn [$\beta = 45.308$ (10.771, 79.846)], and Zn [$\beta = 31.814$ (3.389, 60.239)], and between LDL-C and Cu [$\beta = 31.642$ (7.850, 55.433)] and Mg [$\beta = 34.383$ (3.285, 65.481)] (all $p < 0.05$). Significant positive relationships between fasting plasma glucose levels and plasma B [$\beta = 3.918$ (0.661, 7.175)] and Mo [$\beta = 9.790$ (2.615, 16.964)], as well as HOMA-IR and plasma Mo [$\beta = 0.633$ (0.001, 1.266)], were found (Table 3, essential metals) (all $p < 0.05$).

Predictive Effects of Metal Exposure on MetS and Its Individual Components

We next investigated predictive effects of metal exposure on the risks of MetS and its individual components. After adjusting for age, gender, BMI, and smoking, plasma Cu (OR = 2.211 (1.146, 4.266), $p = 0.02$) and Zn (OR = 2.228 (1.048, 4.736)

Table 1 Baseline characteristics of participants ($n=150$)

	Total ($n=150$)	MetS(−) ($n=110$)	MetS(+) ($n=40$)	p value
Basic characteristic				
Gender				**0.020**
Male (n, %)	106 (70.7%)	72 (65.5%)	34 (85.0%)	
Female (n, %)	44 (29.3%)	38 (34.5%)	6 (15.0%)	
Age (years)	42.64 ± 12.38	40.63 ± 12.45	48.17 ± 10.46	**0.001**
Abdominal obesity (n, %)	68 (45.3%)	32 (29.1%)	36 (90.0%)	**< 0.001**
Diabetes mellitus (n, %)	19 (12.7%)	8 (7.3%)	11 (27.5%)	**0.001**
Dyslipidemia (n, %)	83 (55.3%)	53 (48.2%)	30 (75.0%)	**0.003**
Hypertension (n, %)	33 (22.0%)	9 (8.2%)	24 (60.0%)	**< 0.001**
Smoking (n, %)	28 (18.7%)	18 (16.4%)	10 (25.0%)	0.230
Anthropometry				
BMI (kg/m^2)	24.89 ± 4.48	23.56 ± 3.56	28.54 ± 4.76	**< 0.001**
Waist circumference (cm)	88.08 ± 11.94	83.94 ± 9.49	99.44 ± 10.60	**< 0.001**
Hip circumference (cm)	100.02 ± 8.00	97.75 ± 6.30	106.28 ± 8.89	**< 0.001**
W/H ratio	87.86 ± 7.56	85.79 ± 7.04	93.56 ± 5.90	**< 0.001**
Body fat mass (%)	26.92 ± 5.85	25.68 ± 5.68	30.32 ± 4.96	**< 0.001**
Subcutaneous fat (%)	16.68 ± 8.58	15.33 ± 8.42	20.37 ± 8.00	**0.001**
Visceral fat mass (%)	4.08 ± 3.66	3.39 ± 0.98	6.04 ± 6.65	**< 0.001**
Skeleton muscle mass (%)	67.34 ± 5.79	68.56 ± 5.62	63.99 ± 4.92	**< 0.001**
Body fat mass/skeleton muscle mass (ratio)	0.41 ± 0.13	0.38 ± 0.12	0.48 ± 0.12	**< 0.001**
Non-essential metals (As, Cd, Hg, Li, Sr) (μg/L)				
Arsenic (As)	2.74 ± 3.32	2.70 ± 3.32	2.86 ± 3.73	0.868
Cadmium (Cd)	0.02 ± 0.05	0.02 ± 0.51	0.03 ± 0.05	**0.035**
Mercury (Hg)	1.43 ± 1.33	1.45 ± 1.47	1.40 ± 0.85	0.932
Lithium (Li)	1.62 ± 3.16	1.58 ± 3.66	1.73 ± 0.93	**0.001**
Strontium (Sr)	39.95 ± 17.70	38.70 ± 19.31	43.38 ± 11.78	**0.004**
Essential or probably essential metals (B, Cu, Cr, Ni, Mg, Mn, Mo, Zn) (μg/L)				
Boron (B)	33.61 ± 45.03	27.51 ± 39.35	**50.39 ± 55.02**	**< 0.001**
Chromium (Cr)	1.20 ± 1.02	1.11 ± 0.96	1.45 ± 1.15	0.074
Copper (Cu)	1007.89 ± 238.07	988.55 ± 253.29	**1061.06 ± 182.42**	**0.014**
Nickel (Ni)	1.22 ± 1.29	1.10 ± 1.30	**1.55 ± 1.21**	**0.025**
Magnesium (Mg)	24,286.22 ± 5508.84	23,917.82 ± 6061.52	**25,299.29 ± 3437.70**	**0.021**
Manganese (Mn)	1.72 ± 1.12	1.74 ± 1.25	1.65 ± 0.61	0.563
Molybdenum (Mo)	1.14 ± 0.52	1.11 ± 0.51	1.23 ± 0.53	0.064
Zinc (Zn)	896.57 ± 259.43	877.22 ± 279.29	**949.77 ± 187.51**	**0.016**

Significance p value < 0.05

Continuous variables are presented as the mean ± standard deviation, and categorical data as the number (n) (percentage, %).

$p=0.04$) independently predicted MetS, and to a lesser extent, so did Cd (OR = 2.807 (0.887, 8.878), $p=0.08$), B (OR = 1.874 (0.931, 3.773), $p=0.08$), and Mg (OR = 1.868 (0.959, 3.639), $p=0.07$) (Table 4, Fig. 1). Plasma Mn independently predicted abdominal obesity (OR = 1.624 (1.072–2.462), $p=0.02$), and Cd (OR = 2.269 (0.918–5.604), $p=0.08$) and Cu (OR = 1.501 (0.985–2.288), $p=0.06$) had borderline predictive effects on abdominal obesity. Five metals exerted strong predictive effects on dyslipidemia: plasma Li (OR = 1.883 (1.184, 2.993), $p=0.007$), Cu (OR = 2.108 (1.361, 3.266), $p=0.001$), Mg (OR = 1.940 (1.179, 3.193), $p=0.009$), Mo (OR = 1.794 (1.131, 2.844), $p=0.01$), and Zn (OR = 1.993 (1.186, 3.349), $p=0.009$). Plasma B levels (OR = 2.606 (1.162, 5.842), $p=0.02$) and, to a lesser extent, Mo (OR = 2.021 (0.955, 4.280), $p=0.07$) were positively correlated with diabetes (Table 4).

Discussion

To our knowledge, this is one of the few studies to have investigated relationships between exposure to 13 (five non-essential and eight essential/probably essential)

Table 2 Linear regression coefficients (β) and 95% confidence intervals (CIs) of body compostion indices stratifed by non-essential and essential metals ($n = 150$) after adjusting for age, gender, and smoking

Metal	W/H ratio	BMI (kg/m^2)	Body fat mass (%)	Subcutaneous fat (%)	Visceral fat (%)	Skeletal muscle mass (%)	Body fat mass/ skeletal muscle mass
Non-essential metals (As, Cd, Hg, Li, Sr)							
Arsenic (As)	−0.409 (−1.538, 0.721)	−0.250 (−0.942, 0.443)	−0.351 (−1.200, 0.498)	−0.823 (−2.278, 0.633)	−0.370 (−1.029, 0.288)	0.342 (−0.496, 1.180)	−0.006 (−0.024, 0.012)
Cadmium (Cd)	−1.241 (−8.180, 5.698)	4.097 (−1.081, 9.274)	2.463 (−3.849, 8.776)	3.593 (−3.42, 10.603)	2.101 (−8.111, 12.313)	−2.472 (−8.712, 3.769)	0.077 (−0.068, 0.222)
Mercury (Hg)	0.684 (−1.309, 2.676)	0.345 (−0.889, 1.579)	0.723 (−0.727, 2.173)	−0.224 (−2.682, 2.233)	−0.298 (−1.346, 0.749)	−0.731 (−2.164, 0.702)	0.017 (−0.014, 0.048)
Lithium (Li)	1.472 (−0.381, 3.325)	1.060 (−0.174, 2.294)	**1.454 (0.005, 2.902)***	0.856 (−1.616, 3.328)	−0.183 (−1.237, 0.871)	−1.425 (−2.857, 0.007)	0.026 (−0.005, 0.057)
Strontium (Sr)	0.737 (−2.362, 3.837)	0.387 (−1.680, 2.454)	0.751 (−1.682, 3.184)	−0.888 (−4.996, 3.219)	−1.593 (−3.342, 0.157)	−0.763 (−3.167, 1.641)	0.014 (−0.038, 0.065)
Essential or probably essential metals (B, Cu, Cr, Ni, Mg, Mn, Mo, Zn)							
Boron (B)	0.910 (−0.338, 2.158)	**0.834 (0.017, 1.650)***	0.905 (−0.067, 1.877)	0.623 (−1.062, 2.309)	0.342 (−0.403, 1.086)	−0.884 (−1.845, 0.076)	**0.022 (0.002, 0.042)***
Chromium (Cr)	0.429 (−1.281, 2.139)	0.536 (−0.601, 1.674)	**1.467 (0.144, 2.790)***	0.503 (−1.763, 2.770)	0.169 (−0.800, 1.138)	**−1.442 (−2.75, −0.134)***	0.027 (−0.001, 0.055)
Copper (Cu)	2.832 (−1.817, 7.482)	0.845 (−2.268, 3.957)	**4.076 (0.465, 7.686)***	1.291 (−4.905, 7.487)	0.747 (−1.923, 3.417)	**−4.000 (−7.569, −0.43)***	**0.081 (0.004, 0.158)***
Nickel (Ni)	−0.545 (−2.581, 1.491)	0.494 (−0.768, 1.756)	0.451 (−1.027, 1.929)	0.406 (−1.274, 2.086)	0.611 (−0.660, 1.881)	−0.449 (−1.911, 1.013)	0.015 (−0.018, 0.047)
Magnesium (Mg)	−3.223 (−9.266, 1.093)	−0.497 (−4.540, 3.547)	3.961 (−0.760, 8.682)	3.105 (−4.93, 11.144)	1.146 (−2.363, 4.654)	−3.877 (−8.543, 0.789)	0.081 (−0.020, 0.181)
Manganese (Mn)	1.026 (−1.261, 3.313)	0.602 (−0.924, 2.128)	**1.979 (0.207, 3.752)***	0.802 (−2.242, 3.847)	0.032 (−1.272, 1.335)	**−1.959 (−3.71, −0.207)***	0.037 (−0.001, 0.075)
Molybdenum (Mo)	0.100 (−2.746, 2.946)	−0.508 (−2.404, 1.388)	−1.561 (−3.782, 0.661)	−3.668 (−7.393, 0.058)	**−1.622 (−3.226, −0.017)***	1.551 (−0.645, 3.746)	−0.031 (−0.078, 0.016)
Zinc (Zn)	−1.401 (−6.000, 3.919)	−1.187 (−4.491, 2.117)	1.209 (−2.684, 5.102)	−2.220 (−8.808, 4.368)	−1.007 (−3.825, 1.811)	−1.198 (−5.046, 2.649)	0.029 (−0.053, 0.112)

Significance p value < 0.05

Adjusted for age, gender, and smoking, *$p < 0.05$; variables were log-transformed for the analysis to meet the normality assumption.

W/H, waist/hip ratio; *BMI*, body mass index.

metals and body composition. The current study indicates that for middle-aged adults, plasma metal levels were not correlated with common anthropometric indices used to screen for abdominal obesity (W/H ratio) or obesity (BMI). In contrast, body fat mass (Cr, Cu, and Mn), skeletal muscle mass (Cr, Cu, and Mn), and the ratio of body fat mass/skeletal muscle mass (B and Cu) were sensitive to exposure to essential metals. Compared to non-essential xenobiotic metals (e.g., As, Cd, Hg, and Sr), essential metals independently predicted dyslipidemia (Cu, Mg, Mn, and Zn), hyperglycemia (B, Cr, Cu, Mn, and Mo), and MetS (Cu and Zn), and these effects were

Table 3 Linear regression coefficients (β) and 95% confidence intervals (CIs) of metabolic componets stratifed by non-essential and essential metals ($n = 150$) adjusted for age, gender, and smoking

Metal	Total cholesterol (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	HOMA-IR index	Fasting plasma glucose (mg/dL)
Non-essential metals (As, Cd, Hg, Li, Sr)					
Arsenic (As)	−0.262 (−6.484, 5.960)	1.544 (−0.801, 3.890)	−1.901 (−7.522, 3.719)	0.040 (−0.200, 0.280)	1.137 (−1.773, 4.046)
Cadmium (Cd)	3.890 (−31.438, 39.219)	−4.241 (−16.498, 8.016)	14.891 (−24.039, 53.821)	1.570 (−0.353, 3.492)	−16.539 (−36.744, 3.666)
Mercury (Hg)	0.875 (−9.921, 11.671)	1.063 (−2.804, 4.931)	−1.572 (−11.230, 8.087)	0.011 (−0.406, 0.428)	−0.478 (−5.264, 4.308)
Lithium (Li)	5.882 (−4.950, 16.714)	−2.183 (−6.071, 1.705)	6.053 (−3.628, 15.734)	0.267 (−0.152, 0.685)	**3.810 (0.972, 8.592)***
Strontium (Sr)	0.613 (−17.437, 18.664)	−0.981 (−7.459, 5.498)	0.254 (−15.898, 16.405)	0.171 (−0.527, 0.869)	−1.453 (−9.453, 6.546)
Essential or probably essential metals (B, Cu, Cr, Ni, Mg, Mn, Mo, Zn)					
Boron (B)	2.497 (−4.811, 9.805)	−1.248 (−3.846, 1.349)	3.075 (−3.410, 9.560)	0.218 (−0.058, 0.494)	**3.918 (0.661, 7.175)***
Chromium (Cr)	−0.933 (−10.892, 9.026)	0.638 (−2.937, 4.212)	−1.502 (−10.411, 7.407)	0.205 (−0.179, 0.589)	2.902 (−1.490, 7.293)
Copper (Cu)	**32.928 (6.259, 59.598)***	−1.979 (−11.736, 7.778)	**31.642 (7.850, 55.433)***	0.431 (−0.618, 1.481)	0.261 (−11.796, 12.317)
Nickel (Ni)	6.730 (−3.863, 18.322)	0.875 (−3.168, 4.918)	5.396 (−4.059, 14.850)	0.355 (−0.077, 0.786)	0.843 (−4.745, 6.430)
Magnesium (Mg)	**45.308 (10.771, 79.846)***	5.726 (−6.913, 18.366)	**34.383 (3.285, 65.481)***	0.023 (−1.343, 1.388)	−0.900 (−16.551, 14.751)
Manganese (Mn)	5.127 (−8,195, 18.448)	−0.927 (−5.716, 3.862)	3.908 (−8.018, 15.834)	0.350 (−0.163, 0.863)	1.383 (−4.531, 7.296)
Molybdenum (Mo)	0.211 (−16.357, 16.778)	−3.526 (−9.447, 2.394)	2.067 (−12.754, 16.888)	**0.633 (0.001, 1.266)***	**9.790 (2.615, 16.964)***
Zinc (Zn)	**31.814 (3.389, 60.239)***	−1.339 (−11.706, 9.028)	21.326 (−4.188, 47.039)	−0.281 (−1.398, 0.835)	0.659 (−12.147, 13.465)

Significance p value < 0.05

Adjusted for age, gender, and smoking, $^*p < 0.05$.

HDL, high-density lipoprotein; *LDL*, low-density lipoprotein; *HOMA-IR*, homeostatic model assessment of insulin resistance: fasting insulin (μU/L) × fasting glucose (nmol/L)/22.5.

independent of the BMI. By contrast, no significant correlation between toxic non-essential heavy metals (As, Cd, Hg, Li, Sr) and MetS was found. According to the ATSDR ToxGuide, normal human blood levels for As and Cd should be < 1 μg/L and < 0.315 μg/L, respectively. In the current study, the mean plasma levels of Cd is 0.02 ± 0.05 μg/L [MetS(−): 0.02 ± 0.51, MetS(−): 0.03 ± 0.05, $p = 0.035$], which is within the normal reference range. However, the mean plasma levels of As in both MetS(−) and MetS(+) groups all exceeded the acceptable range [mean: 2.74 ± 3.32 [MetS(−): 2.70 ± 3.32, MetS(−): 2.86 ± 3.73, $p = 0.868$]]. Our finding is in agreement with a previous study, which showed that blood level of As in healthy Taiwanese adults is above the tolerable range (mean blood As: 7.41 ± 4.70 μg/L) [24]. Hence, it is less likely that no correlation between non-essential metals and MetS observed in the current study is simply due to the exposure dosage. However, since blood levels of metals are indicative of recent exposure rather than whole-body burdens, a longitudinal follow-up study is needed to clarify the causal relationship of non-essential xenobiotic metals exposure and risk of MetS. Overall, the current results provide evidence that exposure to essential metals may promote a risk of MetS, possibly acting through alterations of the body composition and disturbances of blood glucose and lipid homeostasis.

The present study found that plasma Zn and Cu independently predicted MetS, and that there were direct relationships between plasma essential metals (Cu, Mg, Mo, and Zn) and dyslipidemia. These results are in agreement with recent studies which showed that exposure to Cu [25–27], Zn [17, 18], Mg [20], and Mn [21] predicted risks of MetS or its individual components. The pathological effects of non-essential metals on MetS have long been recognized

Table 4 Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for metabolic syndrome (MetS) and its componets stratifed by non-essential and essential metals ($n = 150$)

Metal	MetS#		Abdominal obesity&		Dyslipidemia#		Hypertension#		Diabetes#	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Non-essential metals (As, Cd, Hg, Li, Sr)										
Arsenic (As)	1.074 (0.607, 1.900)	0.807	1.167 (0.774, 1.760)	0.461	1.222 (0.805, 1.856)	0.346	1.143 (0.665, 1.964)	0.628	1.470 (0.751, 2.877)	0.261
Cadmium (Cd)	2.807 (0.887, 8.878)	**0.079**	2.269 (0.918, 5.604)	**0.076**	1.350 (1.010, 1.190)	0.522	1.094 (0.375, 3.194)	0.869	1.007 (0.272, 3.725)	0.992
Mercury (Hg)	1.056 (−0.597, 1.868)	0.852	1.077 (0.718, 1.617)	0.719	1.226 (0.813, 1.849)	0.331	1.236 (0.728, 2.098)	0.432	1.484 (0.759, 2.902)	0.249
Lithium (Li)	1.393 (0.734, 2.642)	0.311	1.270 (0.810, 1.993)	0.298	**1.716 (1.080, 2.726)**	**0.022**	1.160 (0.639, 2.106)	0.625	0.995 (0.479, 2.067)	0.989
Strontium (Sr)	1.464 (0.780, 2.748)	0.235	1.267 (0.821, 1.956)	0.285	1.349 (0.870, 2.092)	0.182	1.349 (0.755, 2.411)	0.312	0.846 (0.420, 1.703)	0.639
Essential or probably essential metals (B, Cu, Cr, Ni, Mg, Mn, Mo, Zn)										
Boron (B)	1.874 (0.931, 3.773)	**0.079**	1.010 (0.640, 1.594)	0.967	1.176 (0.742, 1.864)	0.491	0.942 (0.527, 1.683)	0.840	**2.583 (1.137, 5.868)**	**0.023**
Chromium (Cr)	0.986 (0.554, 1.757)	0.962	1.262 (0.833, 1.910)	0.272	1.108 (0.728, 1.687)	0.633	0.922 (0.543, 1.568)	0.765	1.100 (0.571, 2.118)	0.776
Copper (Cu)	**2.211 (1.146, 4.266)**	**0.018**	1.501 (0.985, 2.288)	**0.059**	**2.210 (1.415, 2.454)**	**< 0.001**	1.351 (0.785, 2.324)	0.278	1.239 (0.623, 2.461)	0.541
Nickel (Ni)	1.458 (0.809, 2.628)	0.209	0.967 (0.6333, 1.477)	0.877	1.123 (0.732, 1.723)	0.596	1.404 (0.793, 2.487)	0.244	1.175 (0.581, 2.376)	0.654
Magnesium (Mg)	1.868 (0.959, 3.639)	**0.066**	0.853 (0.527, 1.382)	0.519	**2.200 (1.320, 3.666)**	**0.002**	1.411 (0.769, 2.587)	0.266	0.823 (0.402, 1.686)	0.595
Manganese (Mn)	1.218 (0.670, 2.214)	0.518	1.624 (1.072, 2.462)	0.022	1.343 (0.890, 2.027)	0.160	0.905 (0.531, 1.541)	0.712	1.061 (0.549, 2.051)	0.859
Molybdenum (Mo)	1.275 (0.680, 2.391)	0.449	0.942 (0.602, 1.474)	0.793	**1.853 (1.160, 2.958)**	**0.010**	1.424 (0.797, 2.542)	0.233	2.009 (0.942, 4.284)	**0.071**

Table 4 (continued)

Metal	MetS#		Abdominal obesity&		Dyslipidemia#		Hypertension#		Diabetes#	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Zinc (Zn)	**2.228 (1.048, 4.736)**	**0.037**	1.082 (0.656, 1.783)	0.759	**2.199 (1.287, 3.760)**	**0.004**	1.033 (0.544, 1.961)	0.922	1.223 (0.558, 2.681)	0.616

Significance *p* value < 0.05

#Adjusted for age, gender, body mass index, and smoking, $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$.

&Adjusted for age, gender, and smoking, $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$.

and are well investigated [10]; in contrast, relationships between essential metals and metabolic function are inconsistent [18]. Essential metals play key roles in regulating body metabolism; however, a deficiency or excess may both promote a risk of MetS. For example, a recent meta-analysis showed that compared to those with the lowest dietary intake, individuals with the highest intake of dietary Zn had a 13% decreased risk of type 2 diabetes (OR = 0.87 (95% CI = 0.78, 0.98)); in contrast, plasma/serum Zn levels predicted diabetic risk (OR = 1.64, 95% CI = 1.25, 2.14) [18]. Zn is not only an essential trace element but is also a heavy metal, which means that the human body only requires a small amount. However, like most essential trace elements, Zn has a high dietary absorption rate and can enter the body through a Zn-contaminated soil–water-food-cooking container cycle. Minerals are inorganic elements, which cannot be destroyed by cooking processes (e.g., heat and acid), and tend to accumulate in the body once absorbed. Metallic elements generally exist in the environment and in food. Ingestion of metal-contaminated foodstuffs is the most common route of heavy metal exposure. When exposed to large amounts, they may disturb energy metabolism, possibly through interfering with enzymatic activities and inducing free radical-induced oxidative stress leading to endocrine disorders [26, 28]. Nonetheless, future studies are warranted to investigate consumption of heavy metal-contaminated foods (e.g., type of crops and consumption dosage) and health risks of MetS.

Obesity is a significant public health issue in Taiwan, affecting almost one in two adults (45.3%) in this study. Few studies have investigated relationships between metal exposure and body composition. Interestingly, we found that plasma metal levels were not correlated with conventional anthropometric indices such as the W/H ratio or BMI. Instead, body composition seemed to be more sensitive to plasma levels of essential metals. This suggests that anthropometric indices are not sensitively enough to reflect the exposure of trace elements on the body fat mass, which may be due to the low abundance of trace elements in the human body. Specifically, we found that plasma Mn, and a borderline effect of Cu, independently predicted abdominal obesity after adjusting for covariates. Both Mn and Cu were significantly positively correlated with the total body fat mass but inversely associated with the skeletal muscle mass. These results were in agreement with findings in a nationwide nutrition and health survey in US children and adolescents, which showed that compared to those with the lowest, children with the highest blood levels of Cu (OR = 9.27, 95% CI = 5.43, 15.82) and Mn (OR = 2.29, 95% CI = 1.74, 3.02) had increased risks of obesity [29]. Subsequently, this relationhsip was confirmed in a meta-analysis ($n = 21$ related articles), and the authors showed that compared to controls, the serum Cu level was higher in obese children

[standard mean difference (SMD): 0.74 (0.16, 1.32)] and adults [SMD: 0.39 (0.02, 0.76)] [27]. Direct relationships between essential metals and obesity were observed in studies in US women (Cu, Mn, and Mo) [14] and Chinese adults (Cu, Mn, Zn, Mo, and B) [6]. However, the clinical implication of the role of essential trace elements in the etiology of obesity and MetS remains difficult to interpret. This is due in part to the lack of cut-off point for the acceptable or toxic reference range of trace elements in a diverse specimen (e.g., blood, serum or plasma, nail, hair, and urine). Furthermore, a sensitive method, such as the ICP-MS, is required to accurately quantitate the concentrations of trace elements. The advantages of the ICP-MS method over the conventional methods include its accuracy, reliability, speed, and simplicity. However, the ICP-MS is expensive and required trained technicians to operate the machine. The lack of exposure data is also one of the limitations. It is believed that diet represents the most relevant exposure source of trace elements in general population. Future study is needed to clarify the role of diet in the relationship between essential trace elements and risk of MetS.

We also observed an inverse relationship between plasma Mo and the visceral fat mass ($\beta = -1.622$ ($-3.23, -0.017$), $p < 0.05$). This result supports the findings of Wang et al., who showed that urinary Mo levels were correlated with favorable profiles of adipokines (e.g., leptin, adiponectin, and soluble leptin receptor), while exposure to non-essential metals (Cd and Pb) was associated with adverse adipokine profiles in 1228 US women [30].

A possible relationship between exposure to Mo and B and a risk of hyperglycemia was found in this study. Our result agrees with findings of Flores et al., which showed that compared to non-diabetic healthy controls, diabetic patients had higher levels of serum Mo, and serum Mo concentrations further increased in patients with more-severe diabetic complications [31]. Mo is an essential trace element and has numerous biological functions, including purine synthesis, detoxification of aldehyde, and ATP synthesis. However, Mo is also a potent inhibitor of Cu, and high plasma Mo levels may disrupt enzymatic activity of Cu-containing enzymes (e.g., superoxide dismutase and ceruloplasmin). It was postulated that Mo overload may lead to a Cu deficiency resulting in disruption of Cu-carbohydrate interactions. Nonetheless, the exact mechanism linking Mo and hyperglycemia remains to be elucidated. Another interesting observation was a positive relationship between plasma B exposure and the risk of diabetes (OR = 3.92 (0.66, 7.18)). Currently, mechanisms linking B exposure to glucose homeostasis are not fully understood. B, a probably essential metal, is present in the human body and plants (as boric acid or borate forms as food preservatives). It was suggested that B in nutritional amounts may have beneficial health effects on bone metabolism and metabolic function [32]. The recommended daily intake of B is 0.16 mg/kg body weight according to the European Food Safety Agency, and daily intake of 500 mg boric acid (87 mg B) may cause appetite and digestive discomfort [32].

As the increasing widespread use of Li-containing batteries in electric cars and mobile devices continues, Li has emerged as an environmental contaminant. Li is also one of the well-known medicines for bipolar disorder, with potential hypoglycemic effects [33]. However, a meta-analysis showed that Li is associated with increased risks of a reduced glomerular filtration rate, hypothyroidism, and hyperparathyroidism [34]. In addition, patients receiving Li medication had a 1.89-fold (OR = 1.89, 1.27, 2.82, $p = 0{\cdot}002$) higher risk of weight gain compared to those who did not [34]. This result agrees with the findings of the current study, in which a significant positive relationship between plasma Li levels and body fat mass was observed. Furthermore, we also observed positive relationships of plasma Li levels with fasting plasma glucose and dyslipidemia. Although an animal study showed that low doses of Li enhance glucose utilization [33], excess Li exposure can trigger chronic inflammaton and oxidative stress and may lead to endocrine disruption. Indeed, bipolar disorder patients who received Li medication had increased serum atherogenic lipid profiles including TC, TGs, and LDL-C [35].

There are several limitations to this study which should be taken into account to avoid over-interpreting the results. First, this study was a cross-sectional study, and there was a small sample size ($n = 150$) which limited our ability to determine causal relationships between metal exposure and obesity risks. Nonetheless, Niehoff and colleagues investigated the causal relationship of the BMI and metal exposure in US women in a 5.2-year follow-up period, and those authors concluded that metal exposure at the baseline predicted a risk of obesity [14]. Although we adjusted for the smoking history as a potential confounding factor, other residual confounding effects known to affect the BMI or metal exposure could not be fully controlled for in this study, such as total calories, food intake, sources of environmental pollutants, and exercise or physical activity. Another limitation includes a one-time measurement of plasma metal exposure and not cumulative levels. Although plasma metal concentrations indicate the fraction of circulating metals in the body, they reflect short-term exposure, rather than long-term external exposure to metals.

Conclusions

In summary, the current study demonstrated significant relationships between essential metals and body composition but not common anthropometric indices (e.g., BMI or W/H

ratio). Our findings provide evidence that exposure to essential metals may also exert effects on abdominal obesity, dyslipidemia, and hyperglycemia, which might be mechanisms by which metal exposure leads to MetS risks. Future studies are needed to confirm these relationships and elucidate the mechanisms underlying the link between exposure to essential metals and MetS risk.

Acknowledgements Authors would like to thank the technique assistances of Trace Element Research Center, Tri-Service General Hospital, Taipei, Taiwan, and Dr. Skalny Laboratory Asia-Pacific promotion center.

Author Contribution Conceptualization, J.S.C., A.V.S., and A.A.T.; methodology, Y.K.C., C.F.C., and C.S.T.; validation, A.V.S. and A.A.T.; formal analysis, Y.J.N.; investigation, Y.J.N.; resources, Y.K.C. and C.F.C.; data curation, C.F.C.; writing—original draft preparation, J.S.C.; writing—review and editing, Y.K.C. and C.F.C.; supervision, C.S.T., A.V.S., and A.A.T.; project administration, C.S.T.; funding acquisition, J.S.C. and A.V.S. All authors have read and agreed to the published version of the manuscript.

Funding This work was supported by grants from the Ministry of Science and Technology,Taiwan (MOST 109–2923-B-038–001-MY3) and the Russian Foundation for Basic Research (No. 20–515-S52003). Dr. JS Chang was also supported by the grants from the Taipei Medical University Hospital (110TMU-TMUH-109) and the Ministry of Science and Technology (MOST 109–2923-B-038–001-MY3, MOST 110–2320-B-038–046). Российский Фонд Фундаментальных Исследований (РФФИ),No. 20–515-S52003,Anatoly V. Skalny,Ministry of Science and Technology,Taiwan,MOST 110–2320-B-038–046,Jung-Su Chang,MOST109-2923-B-038–001-MY3,Jung-Su Chang,Taipei Medical University Hospital,110TMU-TMUH-109,Jung-Su Chang

Declarations

Institutional Review Board Statement The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Taipei Medical University Hospital (201,502,018).

Informed Consent Statement Informed consent was obtained from all subjects involved in the study.

Conflict of Interest The authors declare no competing interests.

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Authors and Affiliations

Yi Jing Ngu[1] · Anatoly V. Skalny[2,3] · Alexey A. Tinkov[2,4] · Chien-Sung Tsai[5,6] · Chun-Chao Chang[7,8] · Yung-Kun Chuang[9] · Vladimir N. Nikolenko[2] · Dmitry A. Zotkin[2] · Ching-Feng Chiu[1] · Jung-Su Chang[1,10,11,12]

Yi Jing Ngu
ma48109008@tmu.edu.tw

Anatoly V. Skalny
skalnylab@gmail.com

Alexey A. Tinkov
tinkov.a.a@gmail.com

Chien-Sung Tsai
sung1500@mail.ndmctsgh.edu.tw

Chun-Chao Chang
chunchao@tmu.edu.tw

Yung-Kun Chuang
ykchuang@tmu.edu.tw

Ching-Feng Chiu
chodino1106@gmail.com

[1] Graduate Institute of Metabolism and Obesity Sciences, College of Nutrition, Taipei Medical University, Taipei, Taiwan

[2] IM Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia

[3] KG Razumovsky Moscow State University of Technologies and Management, 109004 Moscow, Russia

[4] Yaroslavl State University, Yaroslavl, Russia

[5] Division of Cardiovascular Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

[6] Department and Graduate Institute of Pharmacology, National Defense Medical Center, Taipei, Taiwan

[7] Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan

[8] Division of Gastroenterology and Hepatology, Department of Internal Medicine, School of Medicine, Collage of Medicine, Taipei Medical University, Taipei, Taiwan

[9] College of Nutrition, Master Program in Food Safety, Taipei Medical University, Taipei, Taiwan

[10] School of Nutrition and Health Sciences, College of Nutrition, Taipei Medical University, Taipei, Taiwan

[11] Nutrition Research Center, Taipei Medical University Hospital, Taipei, Taiwan

[12] Chinese Taipei Society for the Study of Obesity (CTSSO), Taipei, Taiwan