Association between blood cadmium and vitamin D levels in the Yangtze Plain of China in the context of rapid urbanization

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Abstract

Background: China has experienced rapid urbanization in the past 30 years. We aimed to report blood cadmium level (BCL) in the rapidly urbanized Yangtze Plain of China, and explore the association between BCL and 25-hydroxyvitamin D (25(OH)D).

Methods: Our data source was the Survey on Prevalence in East China for Metabolic Diseases and Risk Factors (SPECT-China) cross-sectional study (ChiCTR-ECS-14005052, www.chictr.org). We enrolled 3234 subjects from 12 villages in the Yangtze Plain. BCLs were measured by atomic absorption spectrometry. 25(OH)D was measured with a chemiluminescence assay.

Results: A total of 2560 (79.2%) subjects were diagnosed with vitamin D deficiency. The median (interquartile range) BCL was 1.80 μg/L (0.60–3.42) for men and 1.40 μg/L (0.52–3.10) for women. In women, mean 25(OH)D concentrations were inversely associated with BCL (0.401, 95% confidence interval: –0.697 to –0.105 nmol/L lower with each doubling of the BCL) after adjustment for age, educational status, current smoking, body mass index, diabetes, and season. However, there was no significant difference in 25(OH)D across the BCL tertiles for men.

Conclusions: BCL in Chinese residents in the Yangtze Plain were much higher than that in developed countries. An inverse association between BCL and 25(OH)D was found in general Chinese women after multivariable adjustment. Future prospective cohort and animal studies are warranted to resolve the direction and temporality of these relationships, and to elucidate the exact mechanisms involved.

Keywords: Cadmium; Chinese; 25-hydroxyvitamin D; Urbanization

Introduction

Vitamin D is a steroid hormone that can either be produced in the skin by ultraviolet B radiation or ingested from certain foods. Vitamin D is hydroxylated in the liver to 25-hydroxyvitamin D (25(OH)D), the primary form measured to determine vitamin D nutritional status, and can be further hydroxylated in the kidney to its active form, 1,25-dihydroxyvitamin D (1,25$(OH)_2$D).[1] In addition to adverse bone health, vitamin D deficiency may play a role in susceptibility to cardiovascular diseases,[2] non-alcoholic fatty liver disease,[3] hypogonadism,[4] and certain cancers.[5] Vitamin D status is affected by many factors, including geographic latitude, sunlight exposure, skin pigmentation, genetics, dietary supplements, and certain foods.[6] There is also interest in identifying environmental risk factors that may influence vitamin D status.

Recent evidence has gradually shown that environmental exposure to endocrine-disrupting toxicants may influence vitamin D status. Data from the 2005 to 2010 National Health and Nutrition Examination Survey suggested that bisphenol A and di(2-ethylhexyl) phthalate were inversely associated with 25(OH)D in US general population.[7] Another epidemiologic study also showed that lead exposure was negatively associated with 25(OH)D.[8]

Cadmium, a ubiquitous environmental pollutant, is present in soils, sediments, air, and water.[9] Cadmium exposure affects human population worldwide. In addition to cigarette smoke, contamination of the food chain by natural and anthropogenic sources is the primary route of cadmium exposure.[10] It has been shown that chronic cadmium exposure can lead to a decrease in serum 25(OH)D concentrations.[11] Epidemiologic studies exploring the association between blood cadmium level (BCL) and vitamin D are scarce and inconclusive. Nogawa *et al*[12] found that cadmium exposure was inversely associated with 1,25$(OH)_2$D in Japanese subjects, whereas data from a Mexican study showed that cadmium

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001068

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Chinese Medical Journal 2021;134(1)

Received: 28-02-2020 **Edited by:** Li-Shao Guo

exposure was not associated with vitamin D.[13] To date, no study has explored the association between BCL and 25(OH)D in the general population of Chinese adults.

Over the past 30 years, the Chinese government has implemented the largest-scale urbanization in human history. The middle and lower reaches of the Yangtze River Economic Belt, also called the Yangtze Plain, is an important grain, oil, and cotton production center.[14] During the past three decades, this region has experienced a remarkable period of population growth and accelerated urbanization and is now the most rapidly urbanized region in China. However, rapid urbanization may also pose a great threat to environmental protection, posing challenges to sustainable development in this region.[15,16] Based on the investigation conducted by the Ministry of Land and Resources of China in 2014, approximately 19.4% of the agricultural soils exceeded the national standard limits of cadmium, nickel, copper, arsenic, mercury and lead as the main pollutants, and among them the Yangtze Plain was no exception.[17]

The 2014 Survey on Prevalence in East China for Metabolic Diseases and Risk Factors (SPECT-China, 2014) measured the BCL in a Chinese population. Using these data, we aimed to investigate the current BCL in the rapidly urbanized Yangtze Plain, and further investigate the association between BCL and vitamin D.

Methods

Ethical approval

The study protocol was approved by the Ethics Committee of the Shanghai Ninth People's Hospital, Shanghai Jiaotong University School of Medicine. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2008. All participants provided informed written consent before participation.

SPECT-China is a population-based cross-sectional survey on the prevalence of metabolic diseases and risk factors in East China from February to June 2014 (ChiCTR-ECS-14005052, www.chictr.org),[18-20] in which twelve villages of the Yangtze Plain were randomly chosen. Three villages were randomly chosen from the Fengcheng community, which is located in southern Shanghai, 40 km away from the downtown; another three villages were randomly chosen from the Xiaoyue community, which is located in eastern Shaoxing city (Zhejiang) adjacent to Hangzhou Bay, 45 km away from downtown; The other six villages were randomly chosen from the Changdong community, which is located in eastern Nanchang, the capital city of Jiangxi Province, 12 km away from downtown. With the rapid urbanization of the Yangtze Plain, residents living in these areas have undergone a rapid shift from peasant to citizen. Citizens ≥18 years old who had lived in their current area for at least 6 months were selected and invited to participate in the study. Those with severe communication problems, acute illness or those who were unwilling to participate were excluded from the study. The overall response rate was 90.8%.[18] A total of 4073 subjects were enrolled from three villages in Shanghai, three villages in Zhejiang Province, and six villages in Jiangxi Province. Individuals with missing values for 25(OH)D ($n = 3$) or BCL ($n = 836$) were excluded. After these exclusions, the study included a total number of 3234 subjects with a mean ± standard deviation age of 58 ± 13 years. An overview of the participants included in and excluded from this analysis can be found in the flowchart [Figure 1].

Anthropometric and laboratory measurements

At every study site, the same trained staff collected information on socioeconomic characteristics, medical history, and lifestyle-related risk factors using a pretested questionnaire. Education was defined using two categories: less than a high school education, high school graduate, and above. Current smoking was defined as having smoked at least 100 cigarettes in one's lifetime and currently smoking cigarettes.[21] Standing height and body weight were measured with light clothing and no shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared.

Venous blood samples were drawn from all subjects after an overnight fast of at least 8 h. The blood samples for the fasting plasma glucose (FPG) assessment were centrifuged at the site of collection within 1 h of collection. Other blood samples were shipped in dry ice within 2 to 4 h of collection to a central laboratory, which was certified by the College of American Pathologists. BCL was determined by graphite-furnace atomic absorption spectrometry (GFAAS, BH2200S, China).[22] Standard curves were established with $r > 0.9950$, and quality control materials were measured before the samples were tested. Two

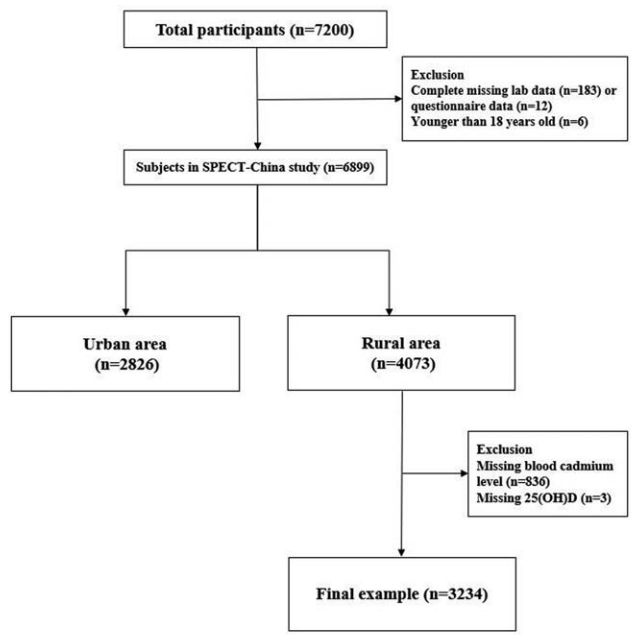

Figure 1: Flowchart of participants from 12 villages in the Yangtze Plain who meet inclusion and exclusion criteria.

quality control personnels participated in the control process. Outliers were detected by duplicate runs. The detection limit for blood cadmium was 0.01 μg/L. None of the samples exhibited values below the detection limits of blood cadmium. The inter-assay coefficient of variation for cadmium was 10%. 25(OH)D was measured with a chemiluminescence assay (Siemens Advia Centaur XP, Munich, Germany). The intra- and inter-assay coefficients of variation for 25(OH)D were 6.25% and 8.33%, respectively. Glycated hemoglobin (HbA1c) was measured using high-performance liquid chromatography (MQ-2000PT, Medconn, Shanghai, China). FPG was measured by a Beckman Coulter AU 680 (Brea, CA, USA).

In accordance with the American Diabetes Association 2014 criteria, diabetes was defined as a previous diagnosis by healthcare professionals, FPG ≥7.0 mmol/L, or HbA1c ≥6.5%. According to the World Health Organization, the threshold limit for BCL in the general non-occupational population was less than 5 μg/L. February to March was defined as the winter season. April to June was defined as the spring season.

Statistical analysis

All data management and analyses were performed with IBM SPSS Statistics, Version 24 (IBM Corporation, Armonk, NY, USA). Two-sided P value <0.05 was considered significant. Continuous variables were shown as mean ± standard deviation or median (interquartile range) based on their distribution style, and categorical variables were described as a percentage. Normality was evaluated by Kolmogorov-Smirnov test. Characteristics of the study sample were compared by analysis of variance for continuous variables with a normal distribution, the Kruskal-Wallis test or Mann-Whitney U test for continuous variables with a skewed distribution, and the Pearson Chi-squared test for categorical variables.

Multiple linear regression analysis was performed to determine the association of 25(OH)D (outcome) with BCL modeled either as $\log_2$-transformed continuous variables or as tertiles (predictors). BCL was log base$_2$-tranformed because of skewed distribution. The data were expressed as unstandardized coefficient (B) and 95% confidence intervals (CIs). We ran three models with progressive adjustment factors. First, we ran a model unadjusted. Then, we ran a second model adjusted for age (continuous), educational status, current smoking, BMI (continuous), and diabetes (yes or no). The third model was further adjusted for season (February to March, April to June). In the models using tertiles, P for trend was calculated by modeling the tertiles, coded as 1, 2, and 3, as a continuous variable.

Results

Among the 3234 adult participants, there were 1245 (38.5%) men and 1989 (61.5%) women. Overall, the prevalence of vitamin D deficiency (25(OH)D <50 nmol/L) was 79.2% in this study population (69.9% in men and 85.0% in women). The medians (interquartile range) of BCL were 1.80 μg/L (0.60–3.42) for men and 1.40 μg/L (0.52–3.10) for women. The abnormal rates of men and women were 9.7% and 8.5%, respectively. BCLs differed significantly by population characteristics [Table 1]. BCLs were significantly higher in males than in females, in participants sampled in winter months than in individuals sampled in spring months, and in those who were current smokers.

The characteristics of the study population according to the tertiles of BCL are presented in Table 2. Compared with those in the low tertile, males in the high tertile were more likely to be current smokers. In women, with increasing BCL tertiles, women had a significantly higher FPG. In women, serum 25(OH)D concentrations showed a decreasing trend across the three BCL tertiles (P for trend = 0.001), with 25(OH)D concentrations in the low, middle, and high tertiles of 40.52 ± 10.62, 39.93 ± 10.65, and 38.64 ± 9.79 nmol/L, respectively. However, there was no significant difference in 25(OH)D across the BCL tertiles in men.

Table 3 summarizes the results of the linear regression models studying the association of BCL with 25(OH)D. In women, in the unadjusted model, mean serum 25(OH)D concentrations were 0.542 nmol/L lower (95% CI, –0.832, –0.251; $P < 0.001$] with each doubling of the BCL. Adjusting for age, educational status, current smoking, BMI, and diabetes did not weaken the association. When season was added to the model predicting 25(OH)D as a covariate, the association was slightly attenuated but remained statistically significant. The mean 25(OH)D concentrations were 0.401 nmol/L lower [95% CI –0.697, –0.105; $P = 0.008$] with each doubling of the BCL [Table 3, model 3]. Using the lowest BCL tertile as the

Table 1: Blood cadmium levels of 3234 subjects from 12 villages in the Yangtze Plain by participants' characteristics.

Groups	Percent	BCL (μg/L), median (IQR)
Age (years)		
Youth (18–44) [Ref]	20.9	1.60 (0.56–3.30)
Middle (45–59)	34.7	1.50 (0.53–3.17)
Old (60–93)	44.4	1.50 (0.56–3.30)
Gender		
Male [Ref]	38.5	1.80 (0.60–3.42)
Female	61.5	1.40 (0.52–3.10)*
BMI (kg/m^2)		
Normal (<24.9) [Ref]	62.7	1.62 (0.60–3.30)
Overweight (25.0–29.9)	31.7	1.34 (0.51–3.20)*
Obesity (≥30.0)	5.6	1.61 (0.60–3.39)
Sampling season		
Winter months [Ref]	84.6	1.60 (0.60–3.30)
Spring months	15.4	1.10 (0.40–3.10)*
Education level		
<High school [Ref]	86.0	1.50 (0.56–3.20)
≥High school	14.0	1.59 (0.50–3.43)
Current smoking status		
Yes [Ref]	23.5	1.90 (0.65–3.60)
No	76.5	1.43 (0.54–3.15)*
Diabetes		
Yes [Ref]	12.6	1.43 (0.55–3.34)
No	87.4	1.50 (0.56–3.21)

* $P < 0.05$ for a significant difference in BCL in the category compared to reference (first category listed) using Mann-Whitney U test. BCL: Blood cadmium level; BMI: Body mass index; IQR: Interquartile range; Ref: Reference.

Table 2: General characteristics of the study population by blood cadmium tertiles.

Characteristics	Tertile 1	Tertile 2	Tetile 3	*P* for trend
Men				
BCL (μg/L)	≤0.86	0.87–2.88	≥2.89	
N	415	414	416	
Age (years)	60 (50–66)	58 (47–66)	58 (46–66)	0.170
Education (%)				0.379
<High school	83.0	82.5	80.5	
≥High school	17.0	17.5	19.5	
Current smoker (%)	51.3	56.7	58.5	0.046
BMI (kg/m^2)	23.9 (21.7–26.8)	23.9 (21.5–26.1)	23.6 (21.4–25.9)	0.073
FPG (mmol/L)	5.50 (5.10–6.00)	5.50 (5.10–6.11)	5.50 (5.10–6.00)	0.445
HbA1c (%)	5.30 (5.00–5.70)	5.30 (5.00–5.70)	5.40 (5.10–5.80)	0.072
Diabetes (%)	13.3	12.8	14.9	0.488
25(OH)D (nmol/L)	46.12 ± 12.94	44.19 ± 13.47	45.53 ± 13.57	0.524
Women				
BCL (μg/L)	≤0.69	0.70–2.44	≥2.45	
N	632	693	664	
Age (years)	57 (47–64)	57 (47–65)	57 (46–65)	0.283
Education (%)		0.326		
<High school	86.8	89.5	88.8	
≥High school	13.2	10.5	11.2	
Current smoker (%)	3.1	3.3	3.4	0.756
BMI (kg/m^2)	23.8 (21.4–26.1)	23.8 (21.4–26.1)	23.8 (21.6–26.4)	0.476
FPG (mmol/L)	5.40 (5.10–6.00)	5.60 (5.10–6.05)	5.70 (5.20–6.20)	0.015
HbA1c (%)	5.30 (4.90–5.60)	5.20 (4.90–5.60)	5.30 (5.00–5.60)	0.507
Diabetes (%)	12.7	10.2	13.0	0.851
25(OH)D (nmol/L)	40.52 ± 10.62	39.93 ± 10.65	38.64 ± 9.79	0.001

Data are summarized as median with interquartile range for continuous variables or as number with proportion for categorical variables. BCL: Blood cadmium level; BMI: Body mass index; FPG: Fasting plasma glucose; HbA1c: Glycated hemoglobin; 25(OH)D: 25-Hydroxyvitamin D.

Table 3: Change in 25(OH)D concentrations (nmol/L) by doubling of exposure or quartile of exposure.

Cadmium	Log$_2$-transformed	*P* value	Quartile 1	Quartile 2	Quartile 3	*P* for trend
Men						
Model 1	−0.160 (−0.644, 0.323)	0.515	Ref.	−1.927 (−3.744, −0.110)	−0.591 (−2.406, 1.224)	0.524
Model 2	−0.022 (−0.529, 0.486)	0.934	Ref.	−1.241 (−3.097, 0.614)	−0.162 (−2.034, 1.709)	0.885
Model 3	−0.037 (−0.525, 0.451)	0.883	Ref.	−0.737 (−2.530, 1.056)	−0.117 (−1.922, 1.689)	0.912
Women						
Model 1	−0.542 (−0.832, −0.251)	<0.001	Ref.	−0.586 (−1.704, 0.532)	−1.881 (−3.010, −0.751)	0.001
Model 2	−0.548 (−0.857, −0.239)	0.001	Ref.	−0.509 (−1.695, 0.676)	−1.780 (−2.978, −0.582)	0.003
Model 3	−0.401 (−0.697, −0.105)	0.008	Ref.	−0.025 (−1.157, 1.108)	−1.306 (−2.449, −0.162)	0.024

Data are presented as B coefficients and 95% confidence interval. Model 1 was unadjusted. Model 2 was adjusted for age, educational status, current smoking, body mass index, and diabetes (yes or no). Model 3 was additionally adjusted for season (February to March, April to June). 25(OH)D: 25-Hydroxyvitamin D; Ref: Reference.

referent group (assuming zero change in serum 25(OH)D concentrations), significant negative trends were observed for BCL with 25(OH)D in women from the base model to the fully adjusted model [Table 3, models 1–3]. By contrast, there was no association of BCL with 25 (OH)D in men, either using log$_2$-transformed concentrations as continuous variables or categorized in tertiles [Table 3, models 1–3].

Discussion

To the best of our knowledge, this study reported BCLs in the largest sample of the general Chinese population living in the rapidly urbanized Yangtze Plain. This study is also the first to find an inverse association between BCL and vitamin D in the general population of Chinese adults. This association was independent of age, educational level, current smoking, BMI, diabetes, and season.

China has been experiencing urbanization at an unparalleled pace since the 1990s. The Yangtze Plain, the study area of the present paper, boasts a faster rate of urbanization than the national average rate (China City Statistical Yearbook, 2014). Rapid urbanization leads to changes in the lifestyles of the residents.[23] An increasing number of people have become reliant on automobiles and can afford computers; and high levels of car and computer use decrease physical activity and increase sedentariness, thus reducing the chance of being exposed to sunlight. Meanwhile, high-calorie fast food enjoys increasing popularity as the numbers of time-poor but income-wealthier urban populations grow, which contributes to the risk of obesity. Less exposure to sunlight and obesity are known risk factors for vitamin D deficiency.[6,24]

Urbanization not only induces lifestyle changes but also causes changes in the urban environment, including air pollution caused by construction and transportation, arable lands contaminated by heavy metals and irrigation of some paddy fields by industrial wastewaters.[25,26] Based on the investigation conducted by the Ministry of Land and Resources of China in 2014, approximately 19.4% of the agricultural soils have exceeded the national standards, with cadmium among the most serious pollutants, and the Yangtze Plain is one of the most seriously polluted areas.[17] Since rice has long been a major staple food for Chinese residents, the consumption of contaminated crops has become a primary route of cadmium exposure for the general non-occupational population in China.[27,28] Emerging evidence has shown that in addition to conventional risk factors, various environmental factors termed endocrine-disrupting chemicals can also exert a broad range of actions on the vitamin D endocrine system.[29]

Scarce epidemiologic studies have explored the association between cadmium exposure and vitamin D. Our study was consistent with a previous study conducted in Japanese adults who lived near a zinc mine or had itai-itai disease.[12] In this study, cadmium exposure was inversely associated with $1,25(OH)_2D$. However, Zamoiski *et al*[13] found that cadmium exposure may not affect vitamin D metabolism. However, this study recruited adolescents from a smelter town in Mexico, and the data may, therefore, not be generalizable to other ages or to populations in areas with different levels of environmental exposure. In addition, this study used urine cadmium, which is believed to represent the body burden of cadmium. Instead, we expand on prior research by using BCL, a marker of recent exposure.

Although mechanistic studies are lacking, it is plausible that cadmium exposure may act either directly or indirectly on the vitamin D endocrine system. First, the liver plays an important role in vitamin D metabolism, since the first hydroxylation occurs in the liver, where cutaneous vitamin D is converted to 25(OH)D, the circulating biomarker of vitamin D status.[1] It is well known that the liver is the main target organ for cadmium toxicity.[30] Hence, it is reasonable to deduce that hepatotoxicity of cadmium may play a role in vitamin D deficiency. In addition, animal and *in vitro* studies have shown that cadmium can alter the expression of cytochrome P450 enzymes,[31,32] which are involved in the hydroxylation steps in vitamin D metabolism.[33] Why did BCL have sex-specific association with 25(OH)D in our analysis? Reproductive hormones may be involved. It is already known that reproductive hormones are closely related to vitamin D status in men and women.[34] Some investigations have also studied the association between BCL and 25(OH)D, although they are limited and inconclusive. Lee *et al*[35] reported that in men cadmium exposure was not associated with follicle-stimulating hormone. However, in women BCL showed a significant negative association with estradiol.[36] Knowledge of this sex-specific association is still very limited and warrants further investigation.

A growing body of evidence has suggested that there is no safe threshold for cadmium intake.[37] Our research provides further evidence that links vitamin D deficiency with blood cadmium at levels that are within the normal range according to the Centers for Disease Control and Prevention of USA (<5 μg/L). Although most of BCLs in our subjects were in the normal range, the medians of BCL (1.50 μg/L) in Chinese residents in the rapidly urbanized Yangtze Plain were still much higher than Americans (0.31 μg/L) based on the National Health and Nutrition Examination Survey (NHANES) 2007 to 2012 data.[38] Given that China's urbanization rate continues to move forward, our findings have implications from a public health perspective. It is now time to pay attention to the quality rather than the pace of urbanization and to take actions to reduce adult cadmium exposure. Large numbers of people are experiencing remarkable lifestyle and environmental changes during the transition of urbanization. These individuals are in urgent need of health education programs to adopt healthy lifestyles. More importantly, these populations should be encouraged to actively engage in environmental monitoring and management.

The strengths of our study included our relatively large sample size and the use of community-dwelling population-based data that allowed for the detection of subtle effects between our exposures and outcome of interest. Despite these strengths, our investigation was potentially limited by its cross-sectional design that precluded any conclusions regarding cause-effect relationships.

Conclusion

Our results provide suggestive evidence that environmental exposure to cadmium may alter serum 25(OH)D concentrations in the general population of Chinese women. Future prospective cohort and animal studies are warranted to resolve the direction and temporality of the observed associations, and to elucidate the exact mechanisms through which cadmium may act to disrupt the vitamin D endocrine system.

Funding

This study was supported by grants from the National Natural Science Foundation of China (No. 81600609); Science and Technology Commission of Shanghai Municipality (No. 18410722300); Municipal Human Resources

Development Program for Outstanding Young Talents in Medical and Health Sciences in Shanghai (No. 2017YQ053); Fundamental Research Program Funding of Ninth People's Hospital affiliated to Shanghai Jiao Tong University School of Medicine (No. JYZZ099); and Shanghai Sailing Program (No. 20YF1423500).

Conflicts of interest

None.

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How to cite this article: Chen C, Zhang HJ, Zhai HL, Chen Y, Han B, Li Q, Xia FZ, Wang NJ, Lu YL. Association between blood cadmium and vitamin D levels in the Yangtze Plain of China in the context of rapid urbanization. Chin Med J 2021;134:53–59. doi: 10.1097/CM9.0000000000001068