Association of vitamin B-6 status with inflammation, oxidative stress, and chronic inflammatory conditions: the Boston Puerto Rican Health Study1–3

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ABSTRACT

Background: Low vitamin B-6 status has been linked to an increased risk of cardiovascular diseases. The cardioprotective effects of vitamin B-6 independent of homocysteine suggest that additional mechanisms may be involved.

Objective: Our objective was to examine the cross-sectional association of vitamin B-6 status with markers of inflammation and oxidative stress.

Design: We measured plasma pyridoxal-5'-phosphate (PLP), C-reactive protein (CRP), and an oxidative DNA damage marker, urinary 8-hydroxydeoxyguanosine (8-OHdG), in Puerto Rican adults who were living in Massachusetts (n = 1205, aged 45–75 y).

Results: There was a strong dose-response relation of plasma PLP concentration with plasma CRP. Increasing quartiles of PLP were significantly associated with lower CRP concentrations (geometric means: 4.7, 3.6, 3.1, and 2.5 mg/L; \( P \) for trend < 0.0001) and with lower urinary 8-OHdG concentrations (geometric means: 124, 124, 117, and 108 ng/mg creatinine; \( P \) for trend: 0.025) after multivariate adjustment. These negative associations persisted after plasma homocysteine was controlled for. Plasma PLP concentrations were significantly correlated with plasma fasting glucose (\( r = -0.1, P = 0.0006 \)), glycated hemoglobin (\( r = -0.08, P = 0.006 \)), and homeostasis model assessment of \( \beta \) cell function (\( r = 0.082, P = 0.005 \)). Metabolic syndrome, obesity, and diabetes were also significantly associated with low plasma PLP concentrations (\( P = 0.011, 0.0007, \) and 0.004, respectively).

Conclusions: Low vitamin B-6 concentrations are associated with inflammation, higher oxidative stress, and metabolic conditions in older Puerto Rican adults. Our data suggest that vitamin B-6 may influence cardiovascular disease risk through mechanisms other than homocysteine and support the notion that nutritional status may influence the health disparities present in this population. Am J Clin Nutr doi: 10.3945/ajcn.2009.28571.

INTRODUCTION

Vitamin B-6 includes pyridoxal, pyridoxine, and pyridoxamine, which function as essential cofactors for enzymes involved in various metabolic activities, which include amino acid, fat, and glucose metabolism (1). The phosphate ester derivative pyridoxal 5'-phosphate (PLP) is the biologically active form of this vitamin (2) and reflects long-term body storage (3). Studies have shown that low plasma PLP concentrations are associated with increased risk of cardiovascular disease (CVD) (4, 5). The potential mechanism has been proposed to act through PLP regulation of homocysteine metabolism, itself an independent risk factor for CVD and stroke (6).

The observation of protective effects of vitamin B-6 on CVD independent of homocysteine (4) suggests that additional mechanisms may be involved. Biochemical studies have revealed some underlying mechanisms of the cardioprotective effect, such as the regulation of cholesterol metabolism (7) and the inhibition of platelet aggregation (8) and endothelial cell proliferation (9). Recent data have shown that plasma PLP was adversely associated with inflammatory markers, which include C-reactive protein (CRP), fibrinogen, and blood cell count (4, 10–12). Additionally, low vitamin B-6 concentrations are commonly present in diseases with a strong inflammatory basis, such as diabetes (13), rheumatoid arthritis (14), and inflammatory bowel disease (15). Current evidence highlights the notion that inflammation may represent another link between vitamin B-6 and CVD. However, the relation of vitamin B-6 status with inflammation and other CVD risk factors has not been investigated extensively in a population at high risk of CVD.

Puerto Ricans who live in the United States represent one of the largest Hispanic ethnic groups. Health disparities have been well documented in this minority population. We have reported previously that Puerto Rican elders who live in Massachusetts have a high prevalence of depressive symptoms, cognitive impairment, type 2 diabetes, obesity, and hypertension compared with non-Hispanic whites and other Hispanic subgroups (16–19). It is therefore important to explore and identify factors that contribute to those disparities. Nutritional status may influence those disadvantageous health outcomes (18). In the present study, we aimed to examine the association of vitamin B-6 status with markers of inflammation and oxidative stress as well as metabolic

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2 Supported by the National Institutes of Health, National Institute on Aging grant 01AG023394-02 and National Heart, Lung, and Blood Institute grant HL54776; and the US Department of Agriculture, Agricultural Research Service contracts 53-K06-5-10 and 58-1950-9-001.

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Received August 24, 2009. Accepted for publication November 6, 2009. doi: 10.3945/ajcn.2009.28571.
conditions in older Puerto Rican adults who were living in Massachusetts.

SUBJECTS AND METHODS

Subjects
The present study consisted of 1222 self-identified Puerto Ricans aged 45–75 y who were living in Boston, Massachusetts (361 men and 861 women; mean ± SD age: 52 ± 7 y) and were participating in the Boston Puerto Rican Health Study, a longitudinal study on stress, nutrition, health, and aging (18, 20). The design and methodology of the study have been described previously (20). Detailed materials and methods can be found under “Supplemental data” in the online issue. Dietary intake was assessed with the use of a semiquantitative food-frequency questionnaire with 126 items, which was adapted and validated for this population (21). This food-frequency questionnaire has been validated against plasma carotenoids (22), vitamin E (23), and vitamin B-12 (24) in Hispanics aged ≥60 y. A total of 1205 participants with complete data for demographic and biochemical characteristics and dietary intake (600 kcal < energy intake < 4000 kcal) were included in the final analyses. The metabolic syndrome (MetS) was defined in accordance with the 2001 National Cholesterol Education Program Adult Treatment Panel III guidelines modified to reflect glucose recommendations from the American Diabetes Association (25). Type 2 diabetes was determined with the use of American Diabetes Association criteria (fasting glucose ≥ 7 mmol/L or 126 mg/dL) (26) and/or use of diabetes medications. Participants were classified as obese if their body mass index (BMI; in kg/m²) was ≥30. Vitamin B-6 inadequacy was defined as plasma PLP < 20 nmol/L, the concentration used to set the current Recommended Dietary Allowance (RDA) (27).

The protocol for this study was approved by the Human Studies Committee of the Institutional Review Board at Tufts Medical Center. Written informed consent was obtained from all participants.

Biochemical measurements
Plasma PLP was determined enzymatically with the use of tyrosine decarboxylase, based on the principles described by Shin-Buehring et al (28). Serum folate was measured by using Immulite chemiluminescent kits according to the manufacturer’s instructions (Diagnostic Products Corporation/Siemens, Los Angeles, CA). Plasma homocysteine was determined by reverse-phase HPLC analysis. Plasma CRP was measured by the Immulite 1000 High Sensitive CRP Kit (LKCRP1) on the Immulite 1000 (Siemens Medical Solutions Diagnostics, Los Angeles, CA). Urinary 8-hydroxydeoxyguanosine (8-OHdG) was measured by a monoclonal antibody enzyme-linked immunosorbent assay kit (EKS-350; Assay Designs, Ann Arbor, MI). Briefly, ~10 µL of urine collected from each participant after a 12-h overnight period was thawed after storage at −80°C and diluted 20-fold before analysis. Diluted urine samples were measured in duplicate with a standard provided by the vendor in a 96-well plate format. Concentrations of urinary 8-OHdG were calculated by the multiplication of the measured concentration by the total volume of 12-h urine, and then normalized by urinary creatinine concentrations.

Statistical analysis
Statistical analyses were performed with the use of SAS for Windows, version 9.0 (SAS Institute, Cary, NC). A logarithmic transformation was applied to plasma concentrations of CRP, PLP, urinary 8-OHdG, and triglycerides to normalize the distribution of data. Partial Pearson’s correlation was applied to examine the relation between plasma PLP and clinical and biochemical measurements. Analysis of covariance was used to compare mean differences across quartiles of plasma PLP with Tukey adjustment for multiple comparisons. Covariates included age, sex, BMI, smoking (current smoker, never smoked, or past smoker), alcohol consumption (current drinker, never drank, or past drinker), medication use (treatment of hypertension, dia-betes, hyperlipidemia, and use of hormone therapy by women), physical activity, urinary creatinine, serum homocysteine, vitamin B-6 and folate intake (diet and supplements), protein, and total energy intake. A 2-tailed P value of <0.05 was considered statistically significant.

RESULTS
Baseline characteristics for 1205 participants across quartiles of plasma PLP concentrations are presented in Table 1. Because no significant modification by sex was observed, men and women were analyzed together. There were significant associations between plasma PLP concentration and BMI and waist circumference: participants in the highest quartile of PLP had a lower BMI and waist circumference than those in lower quartiles of PLP, after adjustment for age and sex (P < 0.001). Higher plasma PLP concentrations were associated with higher intake of vitamin B-6 (P < 0.001), folate (P < 0.001), and vitamin B-12 (P < 0.001); higher antioxidants, which included vitamin C (P < 0.001), β-carotene (P = 0.006), and vitamin E (P < 0.001); and higher intake of vegetables (P = 0.012). High plasma PLP concentrations were also associated with a higher physical activity score (P < 0.001), higher current drinking status (P = 0.018), and lower current smoking status (P < 0.001).

There were significant correlations between plasma PLP and plasma fasting glucose (P = 0.0006), glycated hemoglobin (Hb A1c) (P = 0.0058), and homeostasis model assessment (HOMA) of β cell function (P = 0.005), but no significant associations with insulin or HOMA of insulin resistance (Table 2). Participants in the highest quartile of plasma PLP had lower plasma fasting glucose and Hb A1c concentrations than those in the lower quartiles. Higher plasma PLP was significantly correlated with higher HDL cholesterol (P = 0.039). No significant associations were observed for other lipid measures or for blood pressure. Plasma homocysteine was negatively correlated with plasma PLP (P < 0.0001).

There was a strong dose-response relation of plasma PLP with plasma CRP (Figure 1) after adjustment for age, sex, BMI, smoking status, alcohol intake, physical activity, diabetes status, hormone use among women, and dietary intakes of vitamin B-6, folate, protein, and total energy. Participants in higher quartiles of plasma PLP had lower plasma CRP concentrations than those
Variables | Q1 (5.5–28.3 nmol/L) | Q2 (28.4–42.4 nmol/L) | Q3 (42.5–65.2 nmol/L) | Q4 (65.3–737 nmol/L) | P for trend
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n | 301 | 305 | 299 | 300 | —
Mean PLP (nmol/L) | 20.4 ± 5.3 | 34.8 ± 4.1 | 52.0 ± 6.4 | 128.2 ± 92.1 | —
Age (y) | 57.4 ± 7.5 | 56.9 ± 7.3 | 57.1 ± 7.6 | 58.3 ± 7.8 | 0.27
Female [%] | 235 (71) | 234 (72) | 231 (72) | 225 (69) | 0.36
BMI (kg/m²) | 32.9 ± 7.7 | 32.3 ± 6.6 | 31.7 ± 6.5 | 30.7 ± 5.6 | <0.001
Current smoker [%] | 104 (32) | 103 ± 16 | 101 (3) | 103 ± 14 | 0.36
Current drinker [%] | 109 (33) | 129 (40) | 73 (23) | 49 (15) | <0.001
Total energy intake (kcal/d) | 2315 ± 1170 | 2380 ± 1218 | 2360 ± 1198 | 2282 ± 1274 | 0.78
Vitamin B‐6 intake (mg/d) | 2.49 ± 1.31 | 2.54 ± 1.19 | 2.76 ± 1.31 | 2.99 ± 1.59 | <0.001
Folate intake (μg/d) | 495 ± 241 | 512 ± 236 | 548 ± 268 | 610 ± 317 | <0.001
Vitamin B12 intake (μg/d) | 9.8 ± 8.9 | 9.8 ± 8.8 | 10.3 ± 8.0 | 11 ± 10 | 0.006
Vitamin C intake (mg/d) | 143 ± 104 | 135 ± 89 | 151 ± 114 | 169 ± 109 | <0.001
β‐Carotene intake (mg/d) | 3228 ± 3464 | 3026 ± 2824 | 3524 ± 4193 | 3634 ± 3117 | 0.006
Vitamin E intake (mg/d) | 13.4 ± 11.3 | 15.4 ± 11.9 | 17.7 ± 14.4 | 22.5 ± 16.2 | <0.001
Fruit intake (servings/d) | 2.0 ± 1.9 | 2.0 ± 1.7 | 2.1 ± 1.8 | 2.2 ± 1.9 | 0.13
Vegetable intake (servings/d) | 3.6 ± 3.2 | 3.6 ± 2.8 | 3.7 ± 2.7 | 4.3 ± 3.5 | 0.012
Physical activity | 30.6 ± 3.8 | 31.7 ± 5.3 | 31.6 ± 4.5 | 32.1 ± 5.0 | <0.001

1 Values were adjusted for age and sex, except where otherwise indicated, by using a general linear model.  
2 Mean ± SD (all such values).  
3 Adjusted for sex.  
4 Adjusted for age.  
5 Additionally adjusted for energy intake.

The presence of chronic conditions, such as MetS, obesity, and type 2 diabetes, was strongly associated with lower plasma PLP concentrations (P = 0.011, 0.0007, and 0.004, respectively) (Figure 2). The prevalence of vitamin B-6 inadequacy among participants with MetS was higher than in those without this condition (12% compared with 7%, P = 0.0016). Similarly, 13% of participants with type 2 diabetes were vitamin B-6 inadequate compared with 9% of those without diabetes (P = 0.014). Obese

| Pearson correlation (r) | Q1 (5.5–28.3 nmol/L) | Q2 (28.4–42.4 nmol/L) | Q3 (42.5–65.2 nmol/L) | Q4 (65.3–737 nmol/L) | P for trend
--- | --- | --- | --- | --- | ---
Glucose (mg/dL) | — | −0.10² | 137 ± 4 | 120 ± 3 | 119 ± 3 | 113 ± 3
Hb A1c (%) | — | −0.08² | 7.5 ± 0.1 | 7.0 ± 0.1 | 6.9 ± 0.1 | 6.8 ± 0.1
Insulin (uIU/mL) | — | 0.010 | 21.0 ± 1.7 | 18.2 ± 1.2 | 17.0 ± 0.9 | 16.4 ± 0.9
HOMA‐IR | — | −0.03 | 8.8 ± 1.7 | 6.0 ± 0.6 | 5.5 ± 0.5 | 4.7 ± 0.3
HOMA‐β cell function | — | 0.08³ | 141 ± 11 | 158 ± 12 | 153 ± 17 | 166 ± 16
Triglycerides (mg/dL) | — | 0.02 | 156 ± 6 | 159 ± 7 | 172 ± 9 | 168 ± 6
Total cholesterol (mg/dL) | — | 0.01 | 177 ± 2 | 185 ± 2 | 186 ± 2 | 187 ± 3
LDL‐C (mg/dL) | — | 0.01 | 103 ± 2 | 109 ± 2 | 109 ± 2 | 108 ± 2
HDL‐C (mg/dL) | — | 0.06³ | 43.0 ± 0.7 | 44.4 ± 0.6 | 45.6 ± 0.7 | 46.6 ± 0.8
Homocysteine (μmol/L) | — | −0.11² | 9.9 ± 0.3 | 9.5 ± 0.3 | 8.9 ± 0.3 | 8.3 ± 0.2
Diastolic BP (mm Hg) | — | −0.04 | 81.2 ± 0.6 | 81.7 ± 0.6 | 81.0 ± 0.6 | 80.0 ± 0.6
Systolic BP (mm Hg) | — | −0.02 | 137 ± 1.2 | 135 ± 1 | 136 ± 1 | 136 ± 1

¹ Hb A1c, glycated hemoglobin; HOMA‐IR, homeostasis model assessment of insulin resistance; HOMA‐β cell function, homeostasis model assessment of β cell function; LDL‐C, LDL cholesterol; HDL‐C, HDL cholesterol; BP, blood pressure. Partial Pearson’s correlation coefficient was adjusted for age, sex, BMI, smoking status, alcohol intake, physical activity, and intake of dietary vitamin B-6 and total energy.
² P < 0.001.
³ Mean ± SEM (all such values).
⁴ P < 0.01.
⁵ P < 0.05.
participants tended to show more vitamin B-6 inadequacy compared with nonobese participants, but this association was not statistically significant (11% compared with 9%, \( P = 0.14 \)).

DISCUSSION

In the present study, we observed strong inverse associations between vitamin B-6 status, measured as plasma PLP concentration, and the systematic inflammatory marker CRP in a cohort of older Puerto Ricans who were living in Massachusetts, a group which has been identified previously to be at higher risk of several age-related diseases (18). Furthermore, chronic inflammatory conditions, such as MetS, diabetes, and obesity, were significantly associated with lower plasma PLP, and participants with those conditions were more likely to have vitamin B-6 inadequacy. Additionally, lower PLP was associated with oxidative stress, as reflected by a higher concentration of the urinary DNA damage marker, 8-OHdG.

Our data confirm previous reports from both healthy subjects and patients with various inflammatory conditions such as CVD (11, 15, 29) that showed that plasma CRP concentrations are associated with lower plasma PLP. CRP is an important downstream inflammatory marker that integrates the action of several activated cytokines. Plasma CRP not only predicts future CVD events (30) but also actively participates in the pathogenesis of atherosclerosis (31). On the other hand, low vitamin B-6 has been shown to increase CVD risk (4, 5). The observed inverse association between plasma CRP and PLP supports the notion that inflammation may represent the common link between low vitamin B-6 status and CVD risk. Although the causal factor remains to be clarified, inflammation has been suggested as facilitating redistribution of PLP from circulation to tissues with high demand. This compartmentalization of PLP could be an important adaptive response under certain circumstances (32). Because of the integral involvement of vitamin B-6 in the synthesis of nucleic acids and consequently in mRNA and protein synthesis, the production of cytokines and inflammatory mediators during the inflammatory response might increase the use of PLP (11).

More than 40% of our study population had type 2 diabetes and more than one-half were obese or had MetS. This confirms the findings of a previous report that Puerto Ricans who live in the United States have a high prevalence of CVD risk factors (18). Furthermore, participants with those metabolic conditions had lower plasma PLP compared with those without the conditions. This observation is in agreement with recent studies that suggested that MetS, obesity, and diabetes are negatively associated with the status of vitamins C, B-6, and E, and carotenoids (13, 33, 34). However, the mechanisms responsible for altered vitamin B-6 among subjects with those conditions are unclear. Given that those disorders were significantly associated with elevated CRP, chronic inflammation could be an underlying cause of low vitamin B-6 status. Although the majority of participants had intakes of vitamin B-6 above the current RDA, with a mean (\( \pm \)SD) intake of 3.0 \( \pm \) 1.5 mg for men and 2.5 \( \pm \) 1.3 mg for women, the prevalence of vitamin B-6 inadequacy in participants with MetS, obesity, or diabetes was substantial and significantly higher than that in participants without those conditions. Our results, thus, support the notion that the current RDA for vitamin B-6 may not guarantee adequate vitamin B-6 status in certain subgroups (3). In this regard, improved dietary

![FIGURE 1. Geometric means (with 95% CIs) of plasma C-reactive protein (CRP) (A) and urinary 8-hydroxydeoxyguanosine (8-OHdG) concentrations (B) by quartiles (Q) of plasma pyridoxal 5’-phosphate (PLP). \( P \) values for trend, in general linear models, were adjusted for age, sex, smoking status, alcohol intake, physical activity, hormone use among women, dietary vitamin B-6, folate intake, protein and total energy intake, and plasma homocysteine. \( * \), \( ** \)Significantly different from the lowest quartile: \( * P < 0.05, ** P < 0.001 \).](image)

![FIGURE 2. Mean (\( \pm \)SE) association of plasma pyridoxal 5’-phosphate (PLP) concentration and chronic disease status. \( P \) values for mean differences between groups with and without a condition were adjusted for age, sex, smoking status, alcohol intake, physical activity, hormone use among women, dietary vitamin B-6, and folate, protein, and total energy intake in a general linear model. Black bars represent the percentage of vitamin B-6 inadequacy (PLP < 20 nmol/L). MetS, metabolic syndrome.](image)
intake or nutritional supplementation may benefit older Puerto Rican adults and other subgroups with a high prevalence of chronic conditions, by helping them maintain normal function of various metabolic processes and lower risk of future disease, such as CVD.

Our results suggest that low plasma PLP was associated with higher fasting glucose and Hb A1c, whereas higher plasma PLP was significantly correlated with improved HOMA index for β cell function. Vitamin B-6 deficiency has been shown to cause degenerative changes in β cells in the islets of Langerhans and to decrease both pancreatic and circulating insulin (35, 36). Likewise, pyridoxamine treatment of streptozotocin-induced diabetic hamsters improves glucose tolerance and restores β cell function (37). Moreover, supplementation with pyridoxine lowers blood glucose and decreases Hb A1c in diabetic patients (38, 39). We also observed a positive correlation between plasma PLP and HDL-cholesterol concentrations in this population, which is consistent with a report in European subjects (40). We postulate that, as a coenzyme of δ6-desaturase (7), The effect of PLP on HDL may be mediated through its effect on the metabolism of polyunsaturated fatty acids, which regulates the expression of genes involved in lipid metabolism (41).

In this study, low plasma PLP was significantly associated with higher urinary 8-OHdG, which suggests that low vitamin B-6 status may contribute to oxidative DNA damage. 8-OHdG is a product of the oxidative modification of the DNA base deoxyguanosine, and elevation of 8-OHdG may reflect oxidative damage induced by reactive oxygen species (42). Urinary 8-OHdG has been shown to be associated with atherosclerosis-related risk factors (43) and diabetes (44). A vitamin B-6–deficient diet increases plasma lipid peroxidation and decreases plasma vitamins E and C concentrations in rats (45). Experimental models have further shown that supplementation with vitamin B-6 suppresses the colonic concentrations of 8-OHdG induced by colonic carcinogen (46) and decreases plasma 8-OHdG and malonaldehyde in hyperglycemia-induced oxidative stress (37). Vitamin B-6 compounds can prevent the oxygen radical generation and lipid peroxidation caused by hydrogen peroxide in U937 monocytes as well (47). In this study the association between plasma PLP and the DNA damage marker persisted even after plasma homocysteine was controlled for, which indicates that higher oxidative stress was not mediated through homocysteine. Because PLP serves as a coenzyme for cystathionine β-synthase and cystathionine γ-lyase, both of which are required for the synthesis of cysteine, which is the precursor of glutathione (6, 48), inadequate vitamin B-6 status may decrease the production of glutathione and thus impair the antioxidant defense system (49). Oxidative stress, therefore, may represent a mechanistic pathway through which low vitamin B-6 may lead to CVD.

Several limitations of this study need to be addressed. First, the cross-sectional associations cannot be translated into a clear cause–effect relation. Prospective studies and randomized trials are needed. Second, as with any observational study, there may be unknown residual confounding. Third, despite the fact that CRP and 8-OHdG are widely used markers, results with only one marker of inflammation and one marker of oxidative stress may not satisfactorily reflect the full complexity of these associations. Future studies with multiple measurements may substantiate our findings. Finally, in this particular high-risk population, low plasma PLP concentrations could be due to the redistribution of PLP from circulation to tissues in response to inflammation, and may not necessarily indicate deficiency. Therefore, measurement of PLP concentrations in intracellular depots, such as red blood cells, may be a useful measure of vitamin B-6 status in populations with inflammatory conditions (50).

In conclusion, there was a strong inverse association between plasma PLP and the inflammatory marker CRP in older Puerto Ricans who were living in Massachusetts. Moreover, participants with metabolic conditions—namely MetS, diabetes, or obesity—had a lower vitamin B-6 status and a higher prevalence of vitamin B-6 inadequacy than those without these conditions. Low plasma PLP was also associated with oxidative stress. Our results suggest a potential link between vitamin B-6 and CVD, independent of the homocysteine-mediated pathway. In addition, our findings support the notion that nutritional status, particularly vitamin B-6 status, may influence the association between life stress, physiologic responses, and chronic diseases in this population. This information may help develop more effective dietary recommendations and future dietary interventions to help improve the health of, and decrease health disparities among, Puerto Ricans.

We thank Laurence D Parnell for manuscript editing and Jimmy W Crott for valuable discussions.

The authors’ responsibilities were as follows—JS, JMO, and KLT: study concept and design; CQL and KLT: acquisition of data; JS, JM, JMO, and KLT: analysis and interpretation of data; JS: drafting of the manuscript; JS, CQL, JM, JMO, and KLT: critical revision of the manuscript for intellectual content; JS: statistical analysis; and KLT and JMO: obtaining of funding, and supervision. None of the authors had a conflict of interest.

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