



# Preliminary study of the association between plasma vitamin B<sub>12</sub>, folate levels and chronic kidney disease in a Taiwanese population.

Yu-Mei Hsueh<sup>1,2</sup>; Yuh-Feng Lin<sup>3,4</sup>; Horng-Sheng Shiue,<sup>5</sup>; Hsi-Hsien Chen,<sup>6,7</sup>; Ying-Chin Lin<sup>1,8,9</sup> Wen-Chi Chu<sup>10</sup>, Ya-Li Huang<sup>2,10</sup>

- <sup>1</sup> Department of Family Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan.  
<sup>2</sup> Department of Public Health, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan.  
<sup>3</sup> Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan.  
<sup>4</sup> Division of Nephrology, Department of Internal Medicine, Shuang Ho Hospital, Taipei Medical University, Taipei, Taiwan.  
<sup>5</sup> Department of Chinese Medicine, Chang Gung University College of Medicine, Taoyuan, Taiwan.  
<sup>6</sup> Division of Nephrology, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan.  
<sup>7</sup> Division of Nephrology, Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan.  
<sup>8</sup> Department of Family Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan.  
<sup>9</sup> Department of Geriatric Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan.  
<sup>10</sup> Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taipei, Taiwan

## Objective:

This study aimed to explore the association between plasma folate, vitamin B<sub>12</sub> levels and chronic kidney disease (CKD).

## Material and methods:

We performed a hospital-based case-control study including 220 CKD cases and 438 age- and sex-matched controls recruited from the Taipei Medical University Hospital, Taipei Municipal Wan Fang Hospital and the between July 2007 and September 2011. Subjects who had an eGFR of less than 60 mL/min/1.73m<sup>2</sup> that continued for 3 months were defined as having stages 3–5 CKD. Matched controls with no evidence of CKD were recruited. Plasma folate and vitamin B<sub>12</sub> levels were measured using a Simul-TRAC-SNB radioassay. Red blood cell cadmium and lead concentrations were measured by ICP-MS. Urinary arsenic species were determined by HPLC-HG-AAS.

## Results:

The distribution of educational level, alcohol, coffee, tea consumption, analgesic use frequency, diabetes and hypertension status were different significantly between CKD cases and controls. The OR of CKD was significantly lower in subjects with higher education levels or alcohol, coffee and tea consumption than that in patients with lower education levels or non-drinkers. The OR for CKD in patients with diabetes or hypertension was significantly higher than that in patients without diabetes or were normotensive. We found that the B<sub>12</sub> levels and the red blood cell lead, cadmium levels and total urinary arsenic concentration (μg/g creatinine) were significantly correlated with the increased OR for CKD. Subjects with high B<sub>12</sub> levels (> 9.54 pg/mL) had a significantly higher odds ratio (OR) and 95% confidence interval (CI) (2.04, 1.16–3.58) for CKD compared to those with low B<sub>12</sub> levels (≤ 6.27 pg/mL). Plasma B<sub>12</sub> levels was significantly negatively correlated to eGFR. We conducted a stratified analysis for plasma vitamin B<sub>12</sub>. It was found that the ORs of blood lead concentration on CKD in the low-plasma vitamin B<sub>12</sub> layer seemed to be higher than that in the high-plasma vitamin B<sub>12</sub> layer.

**Conclusion:** These findings may suggest that the plasma B<sub>12</sub> levels will decline the eGFR then increase the OR of CKD. And vitamin B<sub>12</sub> may alter the OR of CKD related to total blood lead. The potential mechanisms need further studies to be illustrated.

Keywords: Vitamin B<sub>12</sub>, folate, cadmium, lead, arsenic, chronic kidney disease

**Table 1. Sociodemographic characteristics, lifestyle, and disease histories between CKD cases and controls.**

Variables	CKD cases (N = 220)	Controls (N = 438)	P value Chi square or Fisher
Age	64.21 ± 0.60	65.14 ± 0.91	0.3796
Gender			
Male	135	270	0.9444
Female	85	168	
eGFR	31.57 ± 0.98	84.34 ± 0.75	<0.0001
Educational level			
Illiterate/elementary school	92 (41.82)	100 (22.83)	<0.0001
Junior/senior high school	72 (32.73)	152 (34.70)	
College and above	56 (25.45)	186 (42.47)	
Cigarette smoking			
Non-smoker	162 (73.64)	319 (72.83)	0.7197
Former smoker	33 (15.00)	75 (17.12)	
Current smoker	25 (11.36)	44 (10.05)	
Alcohol consumption			
Never	181 (82.27)	279 (63.70)	<0.0001
Occasional or frequently	39 (17.73)	159 (36.30)	
Coffee consumption			
Never	171 (77.73)	225 (51.37)	<0.0001
Occasional or frequently	49 (22.27)	213 (48.63)	
Tea consumption			
Never	124 (56.36)	157 (35.84)	<0.0001
Occasional or frequently	96 (43.64)	281 (64.16)	
Analgesic usage			
No/yes as-needed basis	192 (87.27)	419 (95.66)	<0.0001
Yes, routinely	28 (12.73)	19 (4.34)	
Diabetes			
No	134 (60.91)	393 (89.73)	<0.0001
Yes	86 (39.09)	45 (10.27)	
Hypertension			
No	96 (43.64)	306 (69.86)	<0.0001
Yes	124 (56.36)	132 (30.14)	

Note: Values expressed as the mean ± SE or the number of cases (percent).  
 Abbreviations: CKD chronic kidney disease

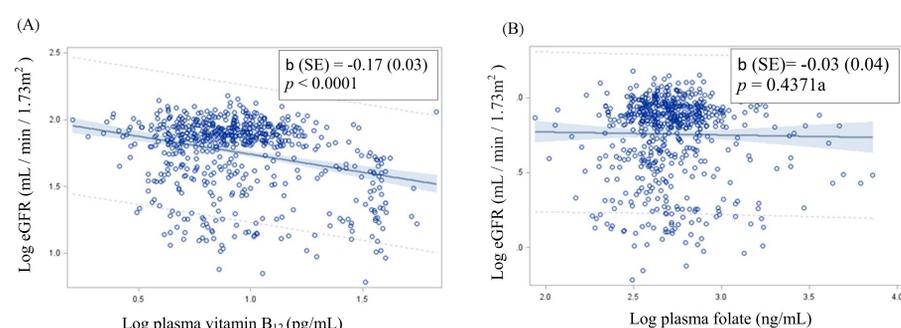


Figure 1. The correlation between eGFR and plasma vitamin B<sub>12</sub> (A) and plasma folate (B)  
 b (SE): adjusted for age, gender, educational level, alcohol, coffee, and tea consumption, analgesic usage, diabetes, hypertension, red blood cell lead and cadmium levels and total arsenic urinary (μg/g creatinine)

**Table 2. The association between levels of total urinary arsenic, blood cadmium and lead, and plasma vitamin B<sub>12</sub> and folate and CKD.**

Variables	CKD cases (N = 220)	Controls (N = 438)	Age-sex adjusted OR (95% CI)	Multivariate adjusted OR (95% CI)
Total urinary arsenic (μg/g creatinine)	27.34 ± 1.46	19.86 ± 0.66 <sup>#</sup>		
≤ 12.07	36 (16.36)	146 (33.33)	1.00 <sup>§</sup>	1.00 <sup>§a</sup>
>12.07 – 21.90	70 (31.82)	146 (33.33)	1.95 (1.23–3.11)**	1.76(0.96 – 3.24)
> 21.90	114 (51.82)	146 (33.33)	3.22 (2.06–5.05)**	2.66 (1.46 – 4.85)**
Red blood cell lead (μg/L)	69.00 ± 2.62	41.83 ± 1.09 <sup>#</sup>		
≤ 27.94	19 (8.64)	146 (33.33)	1.00 <sup>§</sup>	1.00 <sup>§b</sup>
>27.94 - 46.36	51 (23.18)	147 (33.56)	2.72 (1.53 - 4.85)**	2.55 (1.20 – 5.34)*
>46.36	150 (68.18)	145 (33.11)	8.17 (4.78 - 13.99)**	5.17 (2.54 – 10.56)**
Red blood cell cadmium (μg/L)	2.43 ± 0.23	1.22 ± 0.04 <sup>#</sup>		
≤ 0.80	20 (9.09)	149 (34.02)	1.00 <sup>§</sup>	1.00 <sup>§b</sup>
>0.80 – 1.30	47 (21.36)	147 (33.56)	2.57 (1.44 - 4.60)**	2.28 (1.05 – 4.93)*
> 1.30	153 (69.55)	142 (32.42)	8.77 (5.13 – 14.98)**	6.37 (2.97 – 13.65)**
Plasma vitamin B <sub>12</sub> (pg/mL)	15.59 ± 0.89	8.66 ± 0.25 <sup>#</sup>		
≤ 6.27	68 (30.91)	158 (36.07)	1.00 <sup>§</sup>	1.00 <sup>§c</sup>
>6.27– 9.54	52 (23.64)	140 (31.96)	0.87 (0.56 – 1.34)	0.87 (0.48 – 1.57)
> 9.54	100 (45.45)	140 (31.96)	1.66 (1.12 – 2.45)*	2.04 (1.16 – 3.58)*
Plasma folate (ng/mL)	856.03 ± 57.71	590.67 ± 22.12		
≤ 422	89 (40.45)	157 (35.84)	1.00	1.00 <sup>c</sup>
>422 - 589	60 (27.27)	142 (32.42)	0.74 (0.50 – 1.11)	1.05 (0.59 – 1.85)
>589	71 (32.27)	139 (31.74)	0.89 (0.60 – 1.32)	1.02 (0.59 – 1.78)

Note: Values are expressed as the mean ± standard error, or the number (percent)

Abbreviation: CKD: chronic kidney disease; CI: confidence interval

\*  $p < 0.05$ , #  $p < 0.05$  for the Wilcoxon rank sum test, §  $p < 0.05$  for the trend test

<sup>a</sup> Adjusted for gender, age, educational level, alcohol, coffee, and tea consumption, analgesic usage, diabetes, hypertension, and red blood cell lead and cadmium levels and plasma vitamin B<sub>12</sub>.

<sup>b</sup> Adjusted for gender, age, educational level, alcohol, coffee, and tea consumption, analgesic usage, diabetes, hypertension, and urinary creatinine, total urinary arsenic (μg/L), other metal (red blood cell lead or cadmium) and plasma vitamin B<sub>12</sub>.

<sup>c</sup> Adjusted for gender, age, educational level, alcohol, coffee, and tea consumption, analgesic usage, diabetes, hypertension, urinary creatinine, total urinary arsenic (μg/L) red blood cell lead and cadmium

**Table 3 The association between levels of total urinary arsenic, blood cadmium and lead and CKD stratified by B<sub>12</sub> levels**

Variables	Plasma vitamin B <sub>12</sub> level ≤ 7.76 pg/mL			Plasma vitamin B <sub>12</sub> level >7.76 pg/mL		
	Case/Control	Age-sex adjusted ORs (95% CI)	Multivariate adjusted OR (95% CI)	Case/Control	Age-sex adjusted ORs (95% CI)	Multivariate adjusted OR (95%CI)
Total urinary arsenic (μg/g creatinine)				Total urinary arsenic (μg/g creatinine)		
≤ 11.91	17/75	1.00 <sup>§</sup>	1.00 <sup>a</sup>	≤ 12.07	53/76	1.00
11.91 – 21.80	27/77	1.55 (0.77 – 3.09)	1.03 (0.41 – 2.58)	12.07 – 23.01	36/66	0.78 (0.45 – 1.33)
> 21.80	54/76	3.13 (1.63 – 6.00)**	1.94 (0.81 – 4.69)	> 23.01	33/68	0.68 (0.39 – 1.18)
Red blood cell lead (μg/L)				Red blood cell lead (μg/L)		
≤ 28.06	8/75	1.00 <sup>§</sup>	1.00 <sup>b,§</sup>	≤ 27.76	12/70	1.00 <sup>§</sup>
28.06 – 49.08	24/77	3.05(1.28 – 7.27)*	3.01 (0.99 – 9.19)	27.76 – 44.34	26/71	2.25(1.04 – 4.84)*
>49.08	66/76	8.75 (3.85 – 19.86)**	7.12 (2.44 – 20.75)**	>44.34	84/69	7.69 (3.79 – 15.61)**
Red blood cell cadmium (μg/L)				Red blood cell cadmium (μg/L)		
≤ 0.82	7/78	1.00 <sup>§</sup>	1.00 <sup>b,§</sup>	≤ 0.74	10/70	1.00 <sup>§</sup>
0.82 – 1.32	24/76	3.75 (1.50 – 9.34)**	3.13 (0.98 – 10.00)	0.74 – 1.26	27/72	2.98 (1.32 – 6.73)**
>1.32	67/74	10.88 (4.58 – 25.83)**	9.28 (2.87 – 29.96)**	>1.26	85/68	10.47 (4.88 – 22.47)**

Abbreviation: CKD, chronic kidney disease; CI: confidence interval

<sup>a</sup> Adjusted for gender, age, educational level, alcohol, coffee, and tea consumption, analgesic usage, diabetes, hypertension, and red blood cell lead and cadmium levels.

<sup>b</sup> Adjusted for gender, age, educational level, alcohol, coffee, and tea consumption, analgesic usage, diabetes, hypertension, and urinary creatinine, total urinary arsenic (μg/L), and other metal (red blood cell lead or cadmium).

\*  $0.05 \leq P < 0.1$ , \*\*  $P < 0.05$ , \*\*\*  $P < 0.01$ , and §  $P < 0.05$  for the trend test.