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Association between plasma Vitamin B5 levels and all-cause mortality: A nested case-control study

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Abstract

We aimed to evaluate the prospective association of vitamin B5 with all-cause mortality and explore its potential modifiers in Chinese adults with hypertension. A nested, case-control study was conducted in the China Stroke Primary Prevention Trial, including 505 deaths of all causes and 505 matched controls. The median follow-up duration was 4.5 years. The primary outcome measure in this investigation was all-cause mortality, which encompassed deaths for any reason. The mean plasma vitamin B5 concentration for cases (43.7 ng/mL) was higher than that in controls (40.9 ng/mL) (p = .001). When vitamin B5 was further assessed as quintiles, compared with the reference group (Q1: < 33.0 ng/mL), the risk of all-cause mortality increased by 29% (OR = 1.29, 95% CI: 0.83-2.01) in Q2, 22% (OR = 1.22, 95% CI: 0.77-1.94) in Q3, 62% (OR = 1.62, 95% CI: 1.00-2.62) in Q4, and 77% (OR = 1.77, 95% CI: 1.06-2.95) in Q5.

The trend test was significant (p = .022). When Q4-Q5 were combined, a significant 41% increment (OR = 1.41, 95% CI: 1.03-1.95) in all-cause death risk was found compared with Q1-Q3. The adverse effects were more pronounced in those with normal folate levels (p-interaction = .019) and older people (p-interaction = .037). This study suggests that higher baseline levels of plasma vitamin B5 are a risk factor for all-cause mortality among Chinese patients with hypertension, especially among older adults and those with adequate folate levels. The findings, if confirmed, may inform novel clinical and nutritional guidelines and interventions to optimize vitamin B5 levels.

KEYWORDS
all-cause mortality, folate, hypertension, pantothenic acid, vitamin B5

1 | INTRODUCTION

Vitamin B5, also known as pantothenic acid, is a water-soluble vitamin found in various plant- and animal-based foods.[1] Vitamin B5 can be measured in human blood and urine and is vital for maintaining health as it is a precursor to coenzyme A (CoA),[2] which is required for metabolic reactions in humans such as the Krebs cycle, fatty acid metabolism, and oxidation.

The importance of vitamin B5 as a precursor of CoA in cellular metabolism is unquestionable.[3] However, epidemiological research on vitamin B5, specifically on the connection between vitamin B5 and death, is scant. Vitamin B5 has been associated with lipid metabolism,[4] inflammation,[5] insulin resistance (IR),[6] cognitive dysfunction,[7] and cancer,[8] although the mechanisms behind these associations remain unknown. According to the available research, vitamin B5 may be a double-edged sword. Numerous studies have demonstrated a linkage between vitamin B5 and C reactive protein (CRP) levels[9] and an inverse correlation between low density lipo-protein cholesterol (LDL-C) and triglyceride (TG) levels,[10] although the underlying mechanisms remain unexplained. On the other hand, vitamin B5 characterizes chronic inflammatory processes. Recent studies have shown that Vanin-1 cleaves pantetheine into vitamin B5 and cysteamine, the latter of which increases inflammation.[5] A case-control study also noted that serum vitamin B5 levels were significantly higher in type 2 diabetes mellitus (T2DM) patients with higher body mass index (BMI), which may be associated with IR.[11,12] In addition, in neurodegenerative disease, studies have indicated that circulating levels of vitamin B5 were higher among those participants who had greater odds of cognitive decline over a 12-year follow-up.[7] Vitamin B5 intake may be associated with increased cerebral amyloid-b peptide (Aβ) burden in patients with cognitive impairment.[13] Additionally, a 12-month prospective study found a significant association between increased levels of vitamin B5 intake and increased rates of genome damage,[14] a biomarker for higher cancer risk. Thus, available evidence suggests that vitamin B5 may be detrimental or beneficial depending on the disease and the pathophysiological processes involved, emphasizing the critical importance of determining the optimal range of vitamin B5 levels among patients of varying conditions in order to maximize its health benefits while minimizing undue harm.

Hypertension is a severe public health problem with significant health consequences, including morbidity and mortality.[15] However, no studies have examined the relationship between vitamin B5 and all-cause mortality in hypertensive individuals. To bridge this research gap, we sought to evaluate the association of baseline vitamin B5 with all-cause mortality, and to explore its potential modifiers. To maximize cost effectiveness, this study used a nested case-control design, identifying mortality cases and matched controls using data from the China Stroke Primary Prevention Trial (CSPPT).[16]

2 | METHODS

2.1 | Study population

A nested, case-control study, derived from the CSPPT was conducted. The original design, protocol, and principal findings of the CSPPT have been previously reported in detail [17]. Briefly, the CSPPT was a randomized, double-blind, controlled trial that took place between May 19, 2008, and August 24, 2013, in 32 communities in China. Eligible participants were men and women aged 45–75 years with hypertension, defined as seated, resting systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mmHg at both the screening and recruitment visit, or who had recently taken antihypertensive medication. The key exclusion criteria included a history of stroke, myocardial infarction (MI), heart failure, postcoronary revascularization, and/or congenital heart disease as determined by a physician.

The CSPPT was registered at ClinicalTrials.gov, with the identifier NCT00794885. Both the parent CSPPT study and this study were approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China (Federal wide Assurance Number: FWA00001263). All participants provided written, informed consent.

2.2 | Intervention and follow-up in the CSPPT

Based on their MTHFR C677 genotype (CC, CT, or TT), a total of 20,702 eligible participants were randomly assigned to a daily, double-blind treatment of either enalapril 10 mg with folate 0.8 mg or enalapril 10 mg alone. Every three months, participants were asked to participate in a follow-up visit. Follow-up visits were conducted by qualified researchers and physicians where vital signs, study drug adherence, concurrent medication use, adverse events, and possible end point occurrences, such as stroke and death, were recorded.

2.3 | Study outcomes

The primary outcome in this analysis was all-cause mortality, a prespecified endpoint of the CSPPT. All-cause mortality consisted of any death (cancer, stroke, etc). Additional evidence for mortality was found in the form of death certificates provided by hospitals, or through the investigator's findings after completion of a follow-up visit. The members of the Endpoint Adjudication Committee were not informed of participant study-group designations when evaluating and ruling on the research outcomes.

2.4 | Nested case-control study

The enalapril-folic acid group had 302 all-cause fatalities (2.9 %) compared to 320 (3.1 %) in the enalapril group (HR = 0.94; 95% CI: 0.81-1.10; $p = .47$) with a median treatment duration of 4.5 years.

A nested, case-control study with 622 deaths and 622 matched controls was developed using data from the CSPPT. All participants from the CSPPT pool of baseline participants who were still living at the end of the follow-up period were identified as eligible controls. Eligible controls were then matched with mortality cases by age (±1 year), sex, treatment group, and test center. In cases where more than one matched control was detected, only one control was randomly selected using a random table, maintaining a 1:1 matched case-control ratio. Exclusions included 114 participants with missing vitamin B5 data, 12 participants with extreme values and 108 unpaired participants. For the current analyses, 505 mortality cases and 505 matched controls were included (Figure 1).

2.5 | Laboratory assays

Baseline morning serum samples were collected from all patients, following an overnight fast. Serum folate and vitamin B12 were measured by a commercial laboratory with the use of a chemiluminescent immunoassay (New Industrial). Serum trimethylamine-N-oxide (TMAO) was quantified by stable isotope dilution liquid chromatography tandem mass spectrometry (6460 Series Triple Quadrupole LC/MS; Agilent, CA, USA). Serum total homocysteine (tHcy), fasting lipids, and glucose concentrations were measured with automatic clinical analyzers (Beckman Coulter) at the core laboratory of the National Clinical Research Center for Kidney Disease, Nanfang Hospital, Guangzhou, China. Plasma vitamin B5 was measured by liquid chromatography–tandem mass spectrometry (LC-MS/MS) in the central laboratory (Shenzhen). Estimated glomerular filtration rate (eGFR) was calculated using the equation according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).

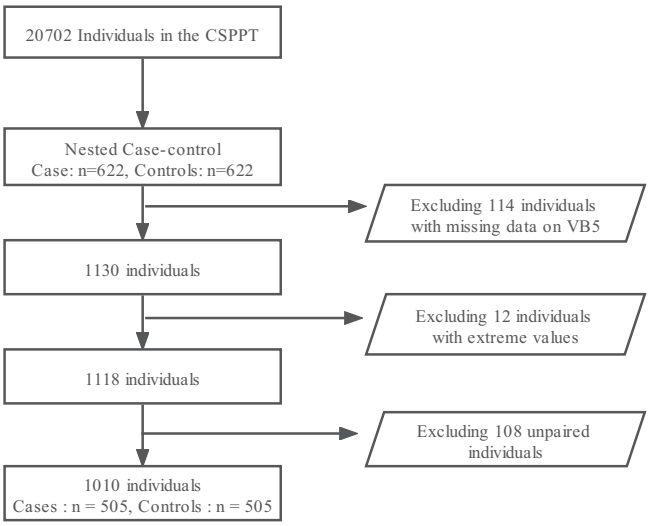

FIGURE 1 Flow chart of the study participants: a nested case-control design based on the CSPPT

2.6 | Statistical analysis

Baseline characteristics were presented as means ± standard deviations (SDs) or medians (interquartile ranges, IQRs) for continuous variables and as proportions for categorical variables. Differences in baseline characteristics between cases and controls were compared by chi-square tests for categorical variables and generalized paired t-tests or ANOVA tests for continuous variables.

Conditional logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for all-cause mortality in relation to plasma vitamin B5. Based on its distribution, plasma vitamin B5 concentrations were divided into tertiles and quintiles. Models were adjusted for age, sex, BMI, treatment group, center, methylenetetrahydrofolate reductase (MTHFR) C677 genotypes, SBP, DBP, fasting blood glucose, smoking and alcohol drinking status, total cholesterol (TC), TG, high-density lipo-protein cholesterol (HDL-C), folate, tHcy, and vitamin B12 levels, eGFR, TMAO at baseline, as well as mean SBP and DBP during the treatment period.

We performed subgroup analyses of essential population characteristics and adjustment variables to assess potential modifiers on the association between plasma vitamin B5 and all-cause mortality, including sex, age (< 66.4 compared with ≥ 66.4 y), BMI (< 23.3 compared with ≥ 23.3 kg/m^2), test center (Anqing compared with Lianyungang), treatment group (enalapril compared with enalapril +

folic acid), SBP (< 164.7 compared with ≥164.7 mmHg), tHcy (< 13.8 compared with ≥ 13.8 μmol/L), TC (< 5.2 compared with ≥ 5.2 mmol/L), folate (< 6.0 compared with ≥ 6.0 ng/mL), fasting glucose (< 5.3 compared with ≥ 5.3 mmol/L or history of diabetes), eGFR (< 90.0 compared with ≥ 90.0 mL/(min·1.73 m^2), TMAO (< 0.2 compared with ≥ 0.2 μmol/L) at baseline, using the median for cutoff points. Folate deficiency was defined as a folate level < 6 ng/mL, and normal folate was defined as a folate level ≥6 ng/mL.[17]

A two-tailed $p < .05$ was considered to be statistically significant in all analyses. Empower Stats (http://www.empowerstats.com) and R software, version 4.0.0 (http://www.R-project.org/) were used for all statistical analyses.

3 | RESULTS

3.1 | Characteristics of study participants

As illustrated in the flow chart (Figure 1), the current study included 505 cases and 505 matched controls from the CSPPT cohort. Among the 505 cases, 79 (15.6%) died of cancer, 77(15.2%) from cardiovascular disease (CVD) and 26 (5.1%) from stroke. In total, 598 (59.2%) males and 412 (40.8%) females were included in the analyses. The mean age of all participants was 64.8 ± 7.2 years. There were 476 participants (47.1%) in the enalapril—folic acid group; the remaining participants were in the enalapril—only group (52.9%). Vitamin B5 had a median plasma concentration of 41.9 ng/mL (IQR, 34.8-52.0). Baseline characteristics of the study participants are shown in Table 1 by case-control status. There was a statistically significant difference ($p = .001$) between mortality cases (43.7 ng/mL [IQR, 36.1-53.9]) and controls (40.9 ng/mL [IQR, 33.9-50.3]) in plasma vitamin B5 levels.

Moreover, mortality cases also had higher TMAO and tHcy at baseline, and higher SBP and DBP values during the study period than controls.

Additionally, plasma vitamin B5 concentrations were positively associated with TC, and TG at baseline (Supplemental Table 2), whereas they were negatively associated with baseline eGFR (Supplemental Table 3). Furthermore, there was no significant correlation between plasma vitamin B5 and SBP and DBP at baseline, or with time-averaged SBP and DBP during the treatment period or with changes in BP during follow-up (Supplemental Table 4).

3.2 | Association of plasma vitamin B5 with the risk of all-cause mortality

The median treatment duration was 4.5 years (IQR, 4.2-4.6 years). The smoothing curve between vitamin B5 concentrations and all-cause mortality risk is shown in Figure 2. All-cause mortality risk increased with the increase in plasma vitamin B5 concentrations. When plasma vitamin B5 levels were classified into quintiles, compared with the reference group (Q1: < 33.0 ng/mL), the risk of all-cause mortality increased by 29% (OR = 1.29, 95% CI: 0.83-2.01) in Q2, 22% (OR = 1.22, 95% CI: 0.77-1.94) in Q3, 62% (OR = 1.62, 95% CI: 1.00-2.62) in Q4, and 77% (OR = 1.77, 95% CI: 1.06-2.95) in Q5. The trend test was significant ($p = .022$). When Q4-Q5 were combined, a significant 41% increment (OR = 1.41, 95% CI: 1.03-1.95) in all-cause death risk was found compared with Q1-Q3 (Table 2). The relationship between vitamin B5 and different mortality subtypes was also analyzed. The relation of plasma vitamin B5 levels with stroke-related mortality was U-shaped (Supplemental Figure 1), while the smoothing curve of vitamin B5 and CVD-related mortality showed an increasing trend with increasing vitamin B5 concentrations (Supplemental Figure 2). The results for cancer-related mortality are detailed in Supplemental Figure 3.

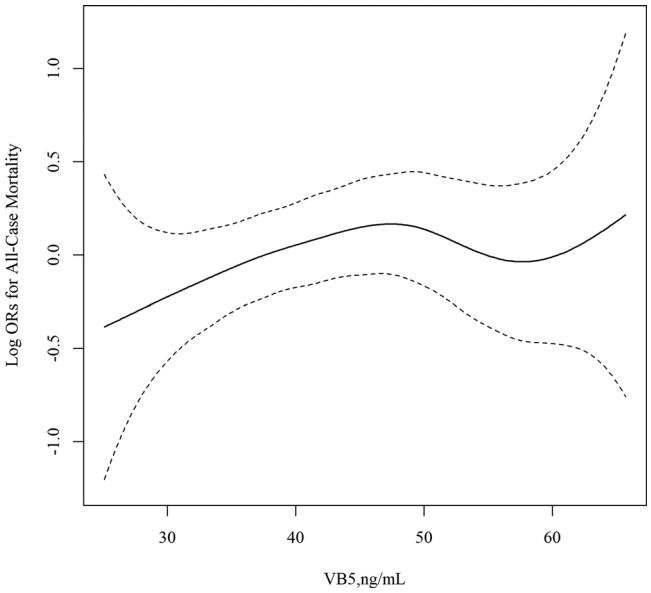

FIGURE 2 Association between vitamin B5 and the risk of all-cause mortality. Note: Adjusted for age, sex, body mass index, treatment group, center, MTHFR C677T, smoking status, alcohol drinking status, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol, triglycerides, high density-lipoprotein cholesterol, eGFR, TMAO, total homocysteine, total folate, vitamin B12 at baseline, and treatment BP

3.3 | Subgroup analyses

To explore whether other relevant factors had a modifying effect on the relationship between plasma vitamin B5 (Q4-Q5 vs Q1-Q3) and the risk of all-cause mortality, subgroup analyses were conducted (Table 3). Plasma vitamin B5 had a significantly stronger positive association with the risk of all-cause mortality in participants aged ≥ 66.4 years (Q4-Q5 vs Q1-Q3: OR = 1.86, 95% CI: 1.23-2.82) than in those aged < 66.4 years (Q4-Q5 vs Q1-Q3: OR = 0.92, 95% CI: 0.61-1.38; *p*-interaction = .037). Furthermore, participants with folate ≥ 6.0 ng/mL (Q4-Q5 versus Q1-Q3: OR = 1.64, 95% CI: 1.15-2.32) had a substantially greater, positive connection with the risk of all-cause death than those with folate < 6.0 ng/mL (Q4-Q5 vs Q1-Q3: OR = 0.67, 95%

TABLE 1 Baseline characteristics of the study participants stratified by case-control status

Characteristics	Total (no. = 1010)	Controls (no. = 505)	Cases (no. = 505)	*p*
Age, y	64.8 (7.2)	64.8 (7.2)	64.8 (7.2)	.986
Male, no. (%)	598 (59.2)	299 (59.2)	299 (59.2)	1.000
BMI, kg/m^2	23.6 (3.7)	23.8 (3.6)	23.4 (3.8)	.053
Treatment group, no. (%)				1.000
Enalapril	534 (52.9)	267 (52.9)	267 (52.9)	
Enalapril-folic acid	476 (47.1)	238 (47.1)	238 (47.1)	
Test center, no. (%)				1.000
Anqing	430 (42.6)	215 (42.6)	215 (42.6)	
Lianyungang	580 (57.4)	290 (57.4)	290 (57.4)	
BP, mmHg				
Systolic BP at baseline	167.9 (21.1)	166.7 (20.3)	169.0 (21.9)	.088
Diastolic BP at baseline	92.0 (12.6)	91.7 (12.2)	92.3 (13.0)	.485
Time-averaged systolic BP	142.3 (13.4)	140.0 (11.0)	144.6 (15.1)	<.001
Time-averaged diastolic BP	82.0 (8.9)	80.9 (7.8)	83.1 (9.8)	<.001
Laboratory results				
Fasting glucose, mmol/L[b]	5.3 (4.8, 6.0)	5.3 (4.8, 6.0)	5.3 (4.8, 6.0)	.824
Total cholesterol, mmol/L[b]	5.2 (4.5, 6.0)	5.3 (4.6, 6.0)	5.1 (4.4, 6.0)	.106
Triglycerides, mmol/L[b]	1.3 (1.0, 1.8)	1.3 (1.0, 1.8)	1.3 (1.0, 1.8)	.926
HDL cholesterol, mmol/L[b]	1.3 (1.1, 1.6)	1.3 (1.1, 1.5)	1.3 (1.1, 1.6)	.635
tHcy, μmol/L[b]	13.8 (11.4, 17.5)	13.6 (11.2, 16.9)	14.1 (11.7, 18.2)	.049
Folate, ng/mL[b]	8.1 (5.5, 10.8)	8.1 (5.5, 10.9)	8.1 (5.4, 10.7)	.931
Vitamin B12, pmol/L[b]	385.8 (314.7, 482.4)	385.0 (312.5, 491.7)	386.1 (319.9, 475.4)	.672
eGFR, mL/min per 1.73 m^2	87.7 (15.8)	88.7 (13.3)	86.7 (18.0)	.051
TMAO, μmol/L[b]	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)	.034
Vitamin B5, ng/mL[b]	41.9 (34.8, 52.0)	40.9 (33.9, 50.3)	43.7 (36.1, 53.9)	.001
MTHFR genotype, no. (%)				.425
CC	297 (29.4)	155 (30.7)	142 (28.1)	
CT	485 (48.0)	244 (48.3)	241 (47.7)	
TT	228 (22.6)	106 (21.0)	122 (24.2)	
Smoking, no. (%)				.796
Never	546 (54.1)	274 (54.3)	272 (53.9)	
Former	333 (33.0)	169 (33.5)	164 (32.5)	
Current	131 (13.0)	62 (12.3)	69 (13.7)	
Drinking, no. (%)				.299
Never	569 (56.3)	279 (55.2)	290 (57.4)	
Former	319 (31.6)	170 (33.7)	149 (29.5)	
Current	122 (12.1)	56 (11.1)	66 (13.1)	

Abbreviations: BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; MTHFR, methylenetetrahydrofolate reductase, TMAO, serum trimethylamine-N-oxide.; tHcy, serum total homocysteine.

[a]Continuous variables are presented as mean ± SD.

[b]Variables are presented as median (interquartile range).

TABLE 2 The association of vitamin B5 concentrations and the risk of all-cause mortality

	No.	Cases (%)	Crude model		[a]Adjusted model	
			OR (95%CI)	*p*	OR (95%CI)	*p*
Vitamin B5, ng/mL (Per SD)	1010	505(50.0)	1.31(0.99,1.74)	.060	1.21(0.96,1.52)	.114
Tertiles						
T1 (< 37.1)	337	147(43.6)	ref		ref	
T2 (37.1- < 8.4)	336	171(50.9)	1.39(1.03,1.87)	.032	1.37(0.98,1.92)	.068
T3 (≥ 48.4)	337	187(55.5)	1.80(1.28,2.54)	<.001	1.58(1.05,2.38)	.027
P for trend				<.001		.024
Quintiles						
Q1 (< 33.0)	202	87(43.1)	ref		ref	
Q2 (32.9 - < 38.9)	202	95(47.0)	1.22(0.82,1.79)	.324	1.29(0.83,2.01)	.257
Q3 (38.9 - < 45.7)	202	98(48.5)	1.33(0.89,1.97)	.162	1.22(0.77,1.94)	.395
Q4 (45.7- < 55.0)	202	107(53.0)	1.63(1.07,2.48)	.023	1.62(1.00,2.62)	.051
Q5 (≥ 55.0)	202	118(58.4)	2.06(1.34,3.15)	<.001	1.77(1.06,2.95)	.03
p for trend				<.001		.022
Categories						
Q1 - Q3 (< 45.7)	606	280(46.2)	ref		ref	
Q4 - Q5 (≥ 45.7)	404	225(55.70)	1.53(1.17,2.00)	.002	1.41(1.03,1.95)	.034

[a]Adjusted for age, sex, body mass index, treatment group, center, MTHFR C677T, smoking status, alcohol drinking status, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol, triglycerides, HDL-C, eGFR, TMAO, total homocysteine at baseline, total folate at baseline, vitamin B12 at baseline, and treatment BP.

CI: 0.38-1.18; *p*-interaction = .019).The relationships between vitamin B5 and the risk of mortality in various age subgroups and treatment groups are presented in Supplementary Tables 5 and 6.

None of the other stratified variables examined, including sex, BMI, treatment group test center, SBP at baseline, TC, fasting glucose, eGFR, TMAO, or tHcy, significantly modified the relation of plasma vitamin B5 with all-cause mortality in participants (*p*-interaction > .05 for all variables).

4 | DISCUSSION

To date, there is very limited evidence from epidemiological studies on the role of vitamin B5 on mortality, especially from prospective studies. This is the first study to show that higher baseline plasma vitamin B5 levels (≥ 45.7 ng/mL) were linked to an increased risk of all-cause death in Chinese adults with hypertension during an average 4.5 years of follow-up, compared to those with low plasma vitamin B5 (< 45.7 ng/mL). Furthermore, the significant relationship between plasma vitamin B5 and all-cause mortality was stronger among persons aged ≥ 66.4y and with folate levels ≥ 6.0 ng/mL.

Earlier research indicates that the effect of vitamin B5 on disease may be indirect. Vitamin B5 is associated with the maintenance of inflammatory homeostasis.[18] Recent research employing mice deficient in the vanin-1 gene (pantetheinase gene) indicates that pantothenase increases oxidative stress through the production of cysteamine, thereby exposing tissues to damage from reactive oxygen species,[5] and that vitamin B5, produced simultaneously during this process, may function as a biomarker of inflammation. Many common disorders, such as CVD, cancer, obesity, and Alzheimer's disease (AD), are now understood to be influenced by chronic inflammation. In addition, several prospective studies have shown that participants with higher circulating vitamin B5 have greater odds of cognitive decline[7] and, similarly, that dietary intake of vitamin B5 is linearly associated with Aβ load in several regions of the brain.[13] In addition, some studies have shown that hypertension increases the risk of AD.[19] In our study, participants were a cohort of middle-aged and elderly adults with hypertension. We hypothesize that hypertensive populations with higher circulating vitamin B5 levels may have a higher risk of AD-related mortality, but this hypothesis needs to be further tested by more studies due to the lack of data related to AD in this study.

It is well known that cancer and CVD are the leading causes of death and morbidity worldwide. During follow-up, the percentage of cases who died of cancer, CVD, and stroke in our study were 15.6%, 15.2% and 5.1%, respectively. Notably, the risk of CVD-related mortality increased with rising vitamin B5 concentrations in our study, and there was a U-shaped connection with stroke-related mortality. In contrast to previous studies,[20] Vitamin B5 levels were found to be positively connected with TC and TG levels, and individuals who had both high vitamin B5 and TC levels had a higher risk of mortality. However, the mechanisms around these relationships are unclear and need further validation. Plasma lipid concentrations are critical in the development and progression of atherosclerosis. Vitamin B5, as a precursor to CoA, has a beneficial effect on TG synthesis and

TABLE 3 The association between vitamin B5 and the risk of mortality in various subgroups*

	VB5, ng/mL					
	Q1-Q3 (< 45.7)		Q4 - Q5 (≥ 45.7)			
Subgroups	No.	Case (%)	No.	Case (%)	OR (95%CI)	*p* for interaction
Age, y						.037
< 66.4	327	161(49.2)	178	92(51.7)	0.92(0.61,1.38)	
≥ 66.4	279	119(42.7)	226	133(58.8)	1.86(1.23,2.82)	
Sex						.361
Female	351	167(47.6)	247	132(53.4)	1.24(0.85,1.79)	
Male	255	113(44.3)	157	93(59.2)	1.46(0.91,2.35)	
Test center						.731
Anqing	230	108(47.0)	200	107(53.5)	1.16(0.73,1.82)	
Lianyungang	376	172(45.7)	204	118(57.8)	1.38(0.93,2.05)	
Treatment group						.564
Enalapril	323	150(46.4)	211	117(55.5)	1.20(0.80,1.79)	
Enalapril-folic acid	283	130(45.9)	193	108(56.0)	1.47(0.97,2.22)	
BMI, kg/m^2						.085
< 23.3	296	136(45.9)	209	125(59.8)	1.56(1.04,2.34)	
≥ 23.3	310	144(46.5)	195	100(51.3)	1.05(0.70,1.59)	
Systolic BP at baseline, mmHg						.420
< 164.7	301	126(41.9)	199	105(52.8)	1.48(0.98,2.24)	
≥ 164.7	305	154(50.5)	205	120(58.5)	1.16(0.77,1.76)	
Total cholesterol, mmol/L						.140
< 5.2	286	144(50.3)	210	115(54.8)	1.12(0.75,1.69)	
≥ 5.2	310	130(41.9)	189	105(55.6)	1.60(1.05,2.44)	
Glucose, mmol/L						.116
< 5.3	287	135(47.0)	210	108(51.4)	0.99(0.66,1.50)	
≥ 5.3	309	139(45.0)	189	112(59.3)	1.75(1.16,2.65)	
eGFR, mL/(min·1.73 m^2)						.066
< 90.4	253	110(43.5)	244	142(58.2)	1.85(1.24,2.76)	
≥ 90.4	343	164(47.8)	155	78(50.3)	1.00(0.66,1.52)	
Folate, ng/mL						.019
< 6.0	194	101(52.1)	113	59(52.2)	0.67(0.38,1.18)	
≥ 6.0	404	173(42.8)	285	162(56.8)	1.64(1.15,2.32)	
tHcy, μmol/L						.819
< 13.8	323	142(44.0)	175	92(52.6)	1.37(0.90,2.08)	
≥ 13.8	275	134(48.7)	224	128(57.1)	1.38(0.91,2.10)	
TMAO, μmol/L						.819
< 0.2	324	142(43.8)	174	92(52.9)	1.33(0.87,2.01)	
≥ 0.2	278	137(49.3)	226	131(58.0)	1.24(0.82,1.87)	

*Each subgroup analysis adjusted, if not stratified for, age, sex, body mass index, treatment group, center, MTHFR C677T, smoking status, alcohol drinking, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol, triglycerides, HDL-C, eGFR, total homocysteine, TMAO, folate, vitamin B12 at baseline, and treatment BP.

lipoprotein metabolism, promoting the initiation and progression of subclinical atherosclerosis.[4] At the same time, some studies have also pointed out that higher plasma vitamin B5 concentrations have been linked to an adverse cardiometabolic risk-factor profile, including higher BMI[11] and IR.[6] Therefore, it is reasonable to assume that CVD risks amplify the relationship between vitamin B5 and all-cause mortality. More interestingly, in our study, lower eGFR levels were observed in participants with high vitamin B5 levels. One study found vitamin B5 to be a possible predictor of the development of albuminuria in 118 patients with hypertension.[21] Apart from that, another study noted that vitamin B5 was significantly downregulated in the urine of patients with diabetic nephropathy (DKD) and that vitamin B5 synthesis and vitamin B5-related metabolism in DKD individuals were disturbed.[22] However, the direct contribution of vitamin B5 to the pathogenesis of DKD remains a mystery. Although we lacked relative data on death due to kidney injury in our investigation, we discovered a clear inverse relationship between plasma vitamin B5 and eGFR in patients with hypertension. Future studies on the health effects of vitamin B5-related substances on renal illness are needed.

Interestingly, we observed a stronger link between plasma vitamin B5 concentrations and the risk of all-cause mortality in those aged ≥ 66.4 years and with folate levels ≥ 6.0 ng/mL. First, while it has been reported that many people regularly consume vitamin and mineral supplements or choose vitamin-fortified foods with the aim of improving their health status,[23,24] the efficacy and the safety climate of this habit, remains controversial. This is of particular concern for elderly people with reduced bioavailability. According to one study, older adults had higher circulating vitamin B5 levels than younger adults following vitamin B5 supplementation, and less vitamin B5 was eliminated in the urine.[23] High vitamin B5 levels may have unanticipated consequences on CoA pathways, protein synthesis, and carbohydrate synthesis. There is reason to suspect that increased vitamin B5 may exacerbate some of the physical damage caused by reduced metabolism in the elderly. Taken together, increased age may amplify the positive association of plasma vitamin B5 concentrations with the risk of all-cause mortality. Second, folate (vitamin B9) is a water-soluble B vitamin that is mostly derived from dark, leafy green vegetables. It is converted in the body to tetrahydrofolate (THF), which is involved in a wide variety of metabolic events in vivo.[16] Vital steps in the growth and survival of proliferating cells are supported by folate-mediated one-carbon metabolism (FOCM). FOCM has been linked to redox homeostasis and cancer epigenetics in a recent study.[25] However, this study did not exclude patients with existing tumors, and the promoting effect of folic acid on the occurrence and development of existing tumors is a crucial factor to consider when examining the relationship between vitamin B5 and all-cause death. Additionally, some studies have shown that unmetabolized folate in the plasma was associated with a decrease in natural killer (NK) cell toxicity,[26] suggesting that excessive folate may be related to immunological dysfunction. However, there is a complex interaction between folate and vitamin B5 in patients with hypertension, but the underlying mechanism is unknown. Further research is required to corroborate our findings and hypotheses.

Our current study is innovative because it is the first to identify an association between plasma vitamin B5 levels (a precursor to CoA) and the risk of all-cause mortality in adult patients with hypertension. It is important for patients with hypertension to have their plasma vitamin B5 levels checked regularly, especially older patients or those who have normal folate levels. The large prospective cohort study used in this nested, case-control study reduced recollection bias to a bare minimum. Using blood samples taken prior to death, we were able to rule out the potential of reverse causation. Finally, in contrast to previous studies based on dietary intake and urine samples, this study was based on circulating vitamin B5 levels. Blood samples are more reflective and representative of systemic conditions, and they are also more conducive to dynamic monitoring.

A number of potential limitations to our studies must be considered. Firstly, a paucity of data precluded a thorough examination of more specific causes of death. This study examined 5-year mortality, and a second phase of the CSPPT is currently underway, including a more extended follow-up period. Second, previous research has demonstrated that there are sex-, age-, and season-related differences in levels of water-soluble vitamins[27]; the plasma vitamin B5 concentrations used in our study were determined only at baseline. Measurements of plasma vitamin B5 on a more frequent basis would have provided more relevant details. Third, because this study included middle-aged or older Chinese individuals with hypertension, extrapolating our findings to other groups with different features should be done with caution. Finally, residual confounding cannot be ruled out even though main covariables were taken into account in this study. As a result, additional research, including intervention trials, is necessary to corroborate our findings and to further investigate the association between vitamin B5 and cause-specific mortality, in order to gain deeper insight into causes and mechanisms of the effect of vitamin B5 on mortality.

5 | CONCLUSIONS

This study found that higher vitamin B5 levels were associated with increased risk of all-cause mortality among Chinese patients with hypertension. This association was more pronounced among older adults and those with adequate folate levels. If confirmed, our findings may inform novel clinical and nutritional guidelines for lowering the risk of all-cause mortality in patients with hypertension, including the biomonitoring and managing of plasma vitamin B5 levels as a potentially modifiable risk factor of all-cause mortality, particularly in the elderly or those with adequate folate levels.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Yuan Hong contributed to writing—original draft preparation; Ziyi Zhou, Nan Zhang, Qiangqiang He were involved in methodology; Lishun Liu, Yaping Wei, Yun Song, Ping Chen, Qiuyue Xu, Ya Li contributed to conceptualization; Ziyi Zhou, Nan Zhang; Zhangyou Guo, Binyan Wang, Xianhui Qin, Xiping Xu, Yong Duan contributed to writing—review and editing.

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REFERENCES

1. Huang YC, Lee MS, Wahlqvist ML. Prediction of all-cause mortality by B group vitamin status in the elderly. *Clin Nutr*. 2012; 31(2): 191–198. https://doi.org/10.1016/j.clnu.2011.10.010
2. Bourgin M, Kepp O, Kroemer G. Immunostimulatory effects of vitamin B5 improve anticancer immunotherapy. *Oncoimmunology*. 2022; 11(1): 2031500. https://doi.org/10.1080/2162402X.2022.2031500
3. Yasuda K, Hiraoka M. [Pantothenic acid]. *Nihon Rinsho*. 2004; 62(S2): 198–202.
4. Mitu O, Cirneala IA, Lupsan AI, et al. The effect of vitamin supplementation on subclinical atherosclerosis in patients without manifest cardiovascular diseases: never-ending hope or underestimated effect?. *Molecules*. 2020; 25(7): 1717. https://doi.org/10.3390/molecules25071717
5. Nitto T, Onodera K. Linkage between coenzyme a metabolism and inflammation: roles of pantetheinase. *J Pharmacol Sci*. 2013; 123(1): 1–8. https://doi.org/10.1254/jphs.13r01cp
6. Li LO, Hu YF, Wang L, Mitchell M, Berger A, Coleman RA. Early hepatic insulin resistance in mice: a metabolomics analysis. *Mol Endocrinol*. 2010; 24(3): 657–666. https://doi.org/10.1210/me.2009-0152
7. Gonzalez-Dominguez R, Castellano-Escuder P, Lefevre-Arbogast S, et al. Apolipoprotein E and sex modulate fatty acid metabolism in a prospective observational study of cognitive decline. *Alzheimers Res Ther*. 2022; 14(1): 1. https://doi.org/10.1186/s13195-021-00948-8
8. Mazzilli KM, McClain KM, Lipworth L, et al. Identification of 102 correlations between serum metabolites and habitual diet in a metabolomics study of the prostate, lung, colorectal, and ovarian cancer trial. *J Nutr*. 2020; 150(4): 694–703. https://doi.org/10.1093/jn/nxz300
9. Scheurig AC, Thorand B, Fischer B, Heier M, Koenig W. Association between the intake of vitamins and trace elements from supplements and C-reactive protein: results of the MONICA/KORA Augsburg study. *Eur J Clin Nutr*. 2008; 62(1): 127–137. https://doi.org/10.1038/sj.ejcn.1602687
10. Jung S, Kim MK, Choi BY. The long-term relationship between dietary pantothenic acid (vitamin B5) intake and C-reactive protein concentration in adults aged 40 years and older. *Nutr Metab Cardiovasc Dis*. 2017; 27(9): 806–816. https://doi.org/10.1016/j.numecd.2017.05.008
11. Gogna N, Krishna M, Oommen AM, Dorai K. Investigating correlations in the altered metabolic profiles of obese and diabetic subjects in a South Indian Asian population using an NMR-based metabolomic approach. *Mol Biosyst*. 2015; 11(2): 595–606. https://doi.org/10.1039/c4mb00507d
12. van Diepen JA, Jansen PA, Ballak DB, et al. Genetic and pharmacological inhibition of vanin-1 activity in animal models of type 2 diabetes. *Sci Rep*. 2016; 6: 21906. https://doi.org/10.1038/srep21906
13. Lee JH, Ahn SY, Lee HA, et al. Dietary intake of pantothenic acid is associated with cerebral amyloid burden in patients with cognitive impairment. *Food Nutr Res*. 2018; 62: 1415. 10.29219/fnr.v62.1415
14. Fenech M, Baghurst P, Luderer W, et al. Low intake of calcium, folate, nicotinic acid, vitamin E, retinol, beta-carotene and high intake of pantothenic acid, biotin and riboflavin are significantly associated with increased genome instability–results from a dietary intake and micronucleus index survey in South Australia. *Carcinogenesis*. 2005; 26(5): 991–999. https://doi.org/10.1093/carcin/bgi042
15. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet*. 2021;398(10304):957–980. https://doi.org/10.1016/s0140-6736(21)01330-1
16. Huo Y, Li J, Qin X, et al. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. *JAMA*. 2015; 313(13): 1325–1335. https://doi.org/10.1001/jama.2015.2274
17. Zhou Z, Li J, Yu Y, et al. Effect of smoking and folate levels on the efficacy of folic acid therapy in prevention of stroke in hypertensive men. *Stroke*. 2018; 49(1): 114–120. https://doi.org/10.1161/STROKEAHA.117.018273
18. Caffaratti C, Plazy C, Mery G, et al. What we know so far about the metabolite-mediated microbiota-intestinal immunity dialogue and how to hear the sound of this crosstalk. *Metabolites*. 2021; 11(6): 406. https://doi.org/10.3390/metabo11060406
19. Lennon MJ, Koncz R, Sachdev PS. Hypertension and Alzheimer's disease: is the picture any clearer?. *Curr Opin Psychiatry*. 2021; 34(2): 142–148. https://doi.org/10.1097/YCO.0000000000000684
20. Evans M, Rumberger JA, Azumano I, Napolitano JJ, Citrolo D, Kamiya T. Pantethine, a derivative of vitamin B5, favorably alters total, LDL and non-HDL cholesterol in low to moderate cardiovascular risk subjects eligible for statin therapy: a triple-blinded placebo and diet-controlled investigation. *Vasc Health Risk Manag*. 2014; 10: 89–100. https://doi.org/10.2147/VHRM.S57116

21. Gonzalez-Calero L, Martin-Lorenzo M, Martinez PJ, et al. Hypertensive patients exhibit an altered metabolism. A specific metabolite signature in urine is able to predict albuminuria progression. *Transl Res*. 2016; 178: 25–37 e7. https://doi.org/10.1016/j.trsl.2016.07.003
22. Ma T, Liu T, Xie P, et al. UPLC-MS-based urine nontargeted metabolic profiling identifies dysregulation of pantothenate and CoA biosynthesis pathway in diabetic kidney disease. *Life Sci*. 2020; 258: 118160. https://doi.org/10.1016/j.lfs.2020.118160
23. Sharma P, Han SM, Gillies N, et al. Circulatory and urinary B-vitamin responses to multivitamin supplement ingestion differ between older and younger adults. *Nutrients*. 2020; 12(11): 3529. https://doi.org/10.3390/nu12113529
24. Sebastian RS, Cleveland LE, Goldman JD, Moshfegh AJ. Older adults who use vitamin/mineral supplements differ from nonusers in nutrient intake adequacy and dietary attitudes. *J Am Diet Assoc*. 2007; 107(8): 1322–1332. https://doi.org/10.1016/j.jada.2007.05.010
25. Yang C, Zhang J, Liao M, et al. Folate-mediated one-carbon metabolism: a targeting strategy in cancer therapy. *Drug Discov Today*. 2021; 26(3): 817–825. https://doi.org/10.1016/j.drudis.2020.12.006
26. Troen AM, Mitchell B, Sorensen B, et al. Unmetabolized folic acid in plasma is associated with reduced natural killer cell cytotoxicity among postmenopausal women. *J Nutr*. 2006; 136(1): 189–194. https://doi.org/10.1093/jn/136.1.189
27. Tong WW, Tong GH, Yang MH, Qin XS. Age and seasonal variation and establishment of reference intervals for water-soluble vitamins determined by liquid chromatography tandem mass spectrometry. *Nutrition*. 2022; 95: 111490. https://doi.org/10.1016/j.nut.2021.111490

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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