Thiamine Nutritional Status and Depressive Symptoms Are Inversely Associated among Older Chinese Adults^{1–3}

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Abstract

Thiamine has been hypothesized to play an important role in mental health; however, few studies have investigated the association between thiamine nutritional status and depression in the general population. Concentrations of free thiamine and its phosphate esters [thiamine monophosphate (TMP) and thiamine diphosphate (TDP)] in erythrocytes were measured by HPLC among 1587 Chinese men and women aged 50–70 y. The presence of depressive symptoms was defined as a Center for Epidemiological Studies Depression Scale score of ≥ 16 . The median erythrocyte concentration (nmol/L) was 3.73 for free thiamine, 3.74 for TMP, and 169 for TDP. The overall prevalence of depressive symptoms was 11.3%. Lower concentrations of all 3 erythrocyte thiamine biomarkers were monotonically associated with a higher prevalence of depressive symptoms: the multivariable adjusted ORs comparing the lowest with the highest quartiles were 2.97 (95% CI = 1.87, 4.72; P -trend < 0.001) for free thiamine, 3.46 (95% CI = 1.99, 6.02; P -trend < 0.001) for TMP, and 1.98 (95% CI = 1.22, 3.21; P -trend = 0.002) for TDP. In conclusion, poorer thiamine nutritional status and higher odds of depressive symptoms were associated among older Chinese adults. This finding should be further investigated in prospective or interventional studies. *J. Nutr.* 143: 53–58, 2013.

Introduction

Depression is one of the most common psychiatric disorders among the elderly, with a prevalence of 40% in hospitalized and nursing home patients and 8–15% in community residents (1,2). Depression adversely affects daily functioning (3), decreases quality of life (4), and increases mortality (5). According to the Global Burden of Disease project, major depression will be the second leading cause of disability worldwide by 2030 (6).

The life expectancy in China has dramatically increased in the past 2 decades with a fast-growing aging population (7). Accordingly, depression has also become a major public health issue among Chinese elderly. A meta-analysis of 10 cross-

sectional studies (total sample size >8000) estimated a prevalence of 3.9% for depression and 14.8% for depressive mood among Chinese adults aged ≥ 60 y (8).

Meanwhile, China has also experienced a rapid dietary transition from a plant-based diet to higher consumption of fat and animal foods (9). The shift has changed the nutritional status for macronutrients as well as micronutrients such as thiamine. According to the Report of China Health and Nutrition Survey 2002, 79% of Chinese adults had a thiamine intake less than the Recommended Nutrient Intake (1.3 mg/d for adults aged 50 y and older) (9). Inadequate thiamine intake may lead to physical and mental consequences. For example, thiamine diphosphate (TDP)⁶, the most bioactive form of thiamine, is a coenzyme in glucose metabolism crucial for the secretion of serotonin (10) and plays an important role in nerve conduction (11). In the elderly, thiamine deficiency (TD) is common (12–14) and could induce mitochondrial dysfunction and chronic oxidative stress (15), which may contribute to depression (16,17). Moreover, thiamine supplementation was associated with mood improvements in previous studies (18,19). However, few epidemiological studies have investigated the relationship between TD and depression in an elderly population

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³ Supplemental Table 1 is available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online table of contents at <http://jn.nutrition.org>.

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⁶ Abbreviations used: CES-D, Center for Epidemiological Studies Depression Scale; TD, thiamine deficiency; TDP, thiamine diphosphate; TMP, thiamine monophosphate.

(20,21). Available studies were hospital-based, case-control studies and often used indirect methods to assess thiamine nutritional status (e.g., a transketolase activity assay) (22). We therefore conducted a population-based analysis to investigate the association of thiamine status and depressive symptoms in an elderly Chinese population with directly measured erythrocyte concentrations of free thiamine, thiamine monophosphate (TMP), and TDP.

Methods

Subjects. In 2005, we conducted a community-based survey in Beijing and Shanghai that sampled participants from one rural county and 2 urban districts in each city. Based on the residential registration records, 800 participants were randomly selected from each rural county and 400 from each urban district. The survey recruited a total of 3289 noninstitutionalized residents aged 50–70 y (23). Participants were ineligible if they had any of the following: a physical disability, a severe psychological disorder, cancer or Alzheimer's disease, or active tuberculosis, AIDS, or any other communicable disease. Fasting peripheral venous blood (~7 mL) was drawn from each study participant using an EDTA-treated tube, centrifuged to separate plasma, buffy coat, and erythrocytes, and then stored at -80°C . After excluding 1702 participants with insufficient erythrocytes, a total of 1587 eligible participants were included in the current analysis. Participants in the current analysis did not significantly differ from the overall sample in major population characteristics (Supplemental Table 1). The study was approved by the Institutional Review Board of the Institute for Nutritional Sciences and each study participant provided informed consent.

Assessment of depressive symptoms. Depressive symptoms were evaluated using the Center for Epidemiological Studies Depression Scale (CES-D) (24), which was previously validated among Chinese (25). The scale contains 20 questions that assess 6 major symptoms of depression over the past week, including depressed mood, thoughts of guilt or worthlessness, feelings of helplessness or hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance. Each question is scored on a scale from 0 (no symptoms) to 3 (most or all of the time) adding to a total score ranging from 0 to 60, with a higher score representing more severe depressive symptoms. We defined the presence of depressive symptoms as a CES-D score of ≥ 16 , as recommended by Radloff (24).

Covariates. Details of the data collection were previously published (26). In brief, information on demographics, diet, lifestyle, medical history, and health status was collected during a face-to-face home interview. Physical activity was assessed using the short, previous 7-d International Physical Activity Questionnaire (27). We defined low physical activity as <77.5 metabolic equivalent h/wk, moderate as 77.5–137.8, and high as at least 137.9. Diabetes mellitus was defined as a fasting glucose level ≥ 7.0 mmol/L, self-reported clinical diagnosis of type 2 diabetes, or current use of oral antidiabetic medications or insulin. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Dietary habit was assessed with a 74-item food FFQ modified from the one developed for the China Health and Nutrition Survey (9). Intakes of individual nutrients were calculated based on the intake frequency and the Chinese Food Composition Table (28). All nutrient intakes were adjusted for total energy intake using the residual method (29).

Measurements of free thiamine, TMP, and TDP in erythrocytes. Concentrations of free thiamine, TMP, and TDP in erythrocytes were determined by HPLC as described by Mancinelli et al. (30). Because ~80% of total circulating thiamine is found in erythrocytes, these biomarkers are considered to reliably reflect the nutritional status of thiamine (30). In this assay, erythrocyte samples were first mixed with 10% trichloroacetic acid. After vortexing and centrifuging, the liquid phase was extracted by water-saturated methyl tert-butyl ether. Subsequently, the extract was further recovered and filtered. To make a 25- μL

extracted and filtered sample, 3 μL 0.5% potassium hexacyanoferrate and 3 μL 5% sodium hydroxide were added; the sample was then ready for HPLC analysis (Agilent Eclipse XDB C₁₈ 4.6 $\times$ 150 mm, 5 μm). The isocratic mobile phase for chromatography was 25 mmol/L sodium dihydrogen phosphate buffer containing methanol delivered at a flow rate of 1.0 mL/min. Fluorescence detection was operated at 365 nm excitation and 435 nm emission. The within-run CV was 2.7% for free thiamine, 2.5% for TMP, and 0.3% for TDP. The corresponding between-run CVs were 2.8, 2.2, and 0.4%, respectively. TD was defined as erythrocyte TDP <150 nmol/L (11) as well as the derived cutoff value from a regression analysis of erythrocyte TDP concentration with in vitro activation of erythrocyte transketolase by TDP, i.e., TDP effect ($r = 0.79$; $P < 0.001$) (31).

Statistical analyses. We used unpaired Student's t tests or Wilcoxon's Signed Rank tests for continuous variables and chi-squared tests for categorical variables to compare population characteristics between participants with and without depressive symptoms. ANCOVA was utilized to investigate factors associated with TDP concentrations. We used the Tukey-Kramer method to adjust for multiple comparisons. The correlation coefficient between TDP and dietary thiamine intake was calculated by partial correlation analysis on ranks (Spearman correlation). Indicators of thiamine nutrition were all defined as quartiles, with the highest category as the reference; their relations with the presence of depressive symptoms were evaluated using multivariable logistic regression. We first adjusted for age, sex, city (Beijing/Shanghai), and rural or urban residence and then also for years of education (0–6, 7–9, or ≥ 10 y in school), annual household income [$<10,000$, 10,000–19,999, 20,000–29,999 or $\geq 30,000$ renmibi (RMB)], living status (living alone or not), smoking status (current or not), alcohol consumption (never, frequency <1 , 1–4, or 5–7 d/wk), physical activity level (low, moderate, or high), BMI, history of diabetes or cardiovascular or cerebrovascular diseases, and total energy intake. Because few study participants ($<2.5\%$) used supplements of vitamin B complex, folate, or vitamin B-12, these variables were not included. All statistical analyses were performed with Stata (version 9.2) with a 2-tailed α of 0.05.

Results

Population characteristics. At the time of our survey, the mean age of the study population was 58.2 ± 6.1 y, and 45.6% were male. Approximately 11% of the study participants had depressive symptoms defined as a CES-D score ≥ 16 . Compared with those without depressive symptoms, participants with depressive symptoms were more likely to be women, from Beijing, living alone, have a history of chronic conditions, and have lower carbohydrate intake (Table 1). Erythrocyte free thiamine and TMP were significantly lower among individuals with depressive symptoms than among those without. In contrast, thiamine and total energy intakes did not differ.

Factors associated with concentrations of TDP in erythrocytes. The median concentration in erythrocytes was 3.73 nmol/L for free thiamine, 3.74 nmol/L for TMP, and 169 nmol/L for TDP. Using a cutoff value of TDP <150 nmol/L, 28.2% of study participants had TD. Because TDP is the most abundant and bioactive thiamine in vivo, we evaluated covariates in relation to the TDP concentration in erythrocytes. Participants from Beijing or urban areas had higher erythrocyte TDP concentrations than those from Shanghai or rural areas (Table 2). In addition, higher total energy intake was marginally associated with a lower concentration of erythrocyte TDP ($P = 0.05$). Higher thiamine intake was not related to a higher erythrocyte TDP concentration; the difference between the extreme quartiles of thiamine intake was not significant ($P = 0.32$). When analyzed as a

TABLE 1 Characteristics of study participants with and without depressive symptoms¹

Characteristic	Depressive symptoms (<i>n</i> = 180)	No depressive symptoms (<i>n</i> = 1407)	<i>P</i> ²
Age, y	58.0 ± 6.2	58.2 ± 6.1	0.58
BMI, kg/m ²	24.7 ± 3.9	24.5 ± 3.6	0.44
Male, <i>n</i> (%)	62 (34.4)	661 (47.0)	0.002
Beijing residents, <i>n</i> (%)	138 (76.7)	669 (47.6)	<0.001
Urban residents, <i>n</i> (%)	83 (46.1)	574 (40.8)	0.17
Living alone, <i>n</i> (%)	21 (11.7)	67 (4.8)	<0.001
Current smoker, <i>n</i> (%)	48 (26.7)	426 (30.3)	0.32
Frequency of alcoholic beverage consumption, <i>n</i> (%)			
Never	995 (70.7)	124 (8.9)	0.10
<1 d/wk	107 (7.6)	23 (1.8)	
1–4 d/wk	92 (6.5)	9 (0.6)	
5–7 d/wk	213 (15.1)	24 (1.7)	
Physical activity level, ³ <i>n</i> (%)			
Low	23 (12.8)	108 (7.7)	0.05
Moderate	71 (39.4)	546 (38.8)	
High	86 (47.8)	753 (53.5)	
Years of education, <i>n</i> (%)			
0–6	80 (44.4)	629 (44.7)	0.92
7–9	65 (36.1)	521 (37.0)	
≥10	35 (19.4)	257 (18.3)	
Household income, <i>n</i> (%)			
<10,000 RMB	61 (33.9)	425 (30.2)	0.05
10,000–19,999 RMB	51 (28.3)	303 (21.5)	
20,000–29,999 RMB	27 (15.0)	271 (19.3)	
≥30,000 RMB	41 (22.8)	408 (29.0)	
History of chronic conditions, ⁴ <i>n</i> (%)	57 (31.7)	269 (19.1)	<0.001
Total energy intake, MJ/d	9.7 ± 3.7	10.0 ± 3.5	0.32
Carbohydrate intake, ⁵ g/d	340 ± 68.9	358 ± 64.8	<0.001
Thiamine intake, ⁵ mg/d	1.16 ± 0.64	1.09 ± 0.57	0.18
RBC free thiamine, nmol/L	2.78 (1.77–4.45)	3.86 (2.52–6.31)	<0.001
RBC TMP, nmol/L	2.92 (2.03–4.17)	3.86 (2.65–5.26)	<0.001
RBC TDP, nmol/L	162 (146–189)	170 (147–200)	0.06

¹ Data are mean ± SD, *n* (%), or median (IQR). RMB, renminbi; TDP, thiamine diphosphate; TMP, thiamine monophosphate.

² Means were compared by Student's *t* tests, proportions by chi-squared tests, and medians by Wilcoxon's Signed Rank tests.

³ The cutoff points for low, moderate, and high levels of physical activity were ≤77.4, 77.5–137.8, and ≥137.9 metabolic equivalent h/wk, respectively.

⁴ History of chronic conditions was defined as having any of the following diseases: diabetes, self-reported cardiovascular diseases, or cerebrovascular diseases.

⁵ Nutrient intakes are energy-adjusted using residual regression method.

continuous variable, thiamine intake was only weakly associated with erythrocyte TDP ($r = 0.12$; $P < 0.001$). The correlation was no longer significant after adjusting for age, sex, city, and residence ($r = 0.04$; $P = 0.11$).

Thiamine nutritional status in relation to depressive symptoms. After adjustment for age, sex, city, and residence, lower concentrations of free thiamine, TMP, or TDP were associated with higher odds of being depressed (all *P*-trend < 0.01) (Table 3, model 1). Further controlling for other potential confounders did not materially change the results (Table 3, model 2). When analyzed as a continuous variable, the OR of depressive symptoms for a 1-SD decrease in the free thiamine concentration was 1.21 (95% CI = 1.00, 1.46) and the corresponding OR was 1.57 (95% CI = 1.30, 1.89) for TMP and 1.30 (95% CI = 1.09, 1.56) for TDP. However, we observed no association between dietary thiamine intake and depressive symptoms in multivariable models (Table 3).

We further examined the potential effect modification by sex, geographic location, physical activity, household income, BMI,

and history of chronic conditions and found no significant interactions (data not shown).

Discussion

In this study, we found a relatively high prevalence of subclinical TD in older Chinese adults. More importantly, we found that lower concentrations of erythrocyte free thiamine and its phosphate esters were monotonically associated with higher odds of having depressive symptoms independent of other potential risk factors for depression.

In the current study, we found that 28.2% of these Chinese adults aged 50–70 y had subclinical TD, and erythrocyte TDP concentrations did not differ across age groups. Although there are few data on TD in China, this prevalence is consistent with findings from several studies conducted in other countries. In a British study, 46% of the elderly (age range 67–92 y) in a nursing home had erythrocyte thiamine concentrations below the detection limit (20 μg/L, i.e., 66 nmol/L) compared with only 13% of younger participants (age range 19–37 y) (12). Another

TABLE 2 Erythrocyte TDP concentrations of older Chinese adults grouped by the covariates tested¹

Covariate	<i>n</i>	TDP	<i>P</i> ²
		nmol/L	
Age group, ³ y			
50–54	548	175 ± 1.75	Ref
55–59	395	174 ± 2.07	0.99
60–64	314	176 ± 2.30	0.99
65–70	330	176 ± 2.24	0.99
Sex ⁴			0.20
Male	723	174 ± 1.53	
Female	864	177 ± 1.39	
City ⁵			<0.001
Beijing	807	179 ± 1.45	
Shanghai	780	171 ± 1.47	
Residence ⁶			<0.001
Urban	657	179 ± 1.59	
Rural	930	172 ± 1.33	
Current smoker ⁷			0.34
Yes	474	174 ± 2.14	
No	1113	176 ± 1.35	
Frequency of alcoholic beverage consumption ⁷			
Never	1119	175 ± 1.32	Ref
<1 d/wk	130	175 ± 3.64	1.00
1–4 d/wk	101	179 ± 4.11	0.75
5–7 d/wk	237	175 ± 2.84	1.00
Physical activity level ^{7,8}			
Low	131	179 ± 3.58	Ref
Moderate	617	177 ± 1.67	0.93
High	839	173 ± 1.50	0.30
Education, ⁷ y			
0–6	709	170 ± 1.90	Ref
7–9	586	180 ± 1.74	<0.001
≥10	292	177 ± 2.58	0.15
Household income, ⁷ RMB			
<10,000	486	173 ± 2.09	Ref
10,000–19,999	354	178 ± 2.21	0.32
20,000–29,999	298	177 ± 2.37	0.58
≥30,000	449	174 ± 1.97	0.98
Total energy intake, ⁷ MJ/d			
<7.5	396	181 ± 2.20	Ref
7.5–9.2	397	174 ± 2.07	0.09
9.3–11.5	397	174 ± 2.05	0.08
≥11.6	397	173 ± 2.21	0.05
Carbohydrate intake, ⁷ g/d			
<323.3	396	176 ± 2.10	Ref
323.3–356.3	397	175 ± 2.07	0.99
356.4–393.1	397	176 ± 2.06	1.00
≥393.2	397	173 ± 2.24	0.75
Thiamine intake, mg/d ⁷			
<0.93	396	168 ± 2.44	Ref
0.93–1.08	397	178 ± 2.09	0.01
1.09–1.22	397	180 ± 2.11	0.004
≥1.23	397	175 ± 2.27	0.32

¹ Data are least squares means ± SEM. Ref, reference group; RMB, renminbi; TDP, thiamine diphosphate.

² *P* values were calculated with Tukey-Kramer adjustment for multiple comparisons.

³ *P* values were adjusted for sex, city (Beijing/Shanghai), and residence (urban/rural).

⁴ *P* values were adjusted for age, city (Beijing/Shanghai), and residence (urban/rural).

⁵ *P* values were adjusted for age, sex, and residence (urban/rural).

⁶ *P* values were adjusted for age, sex, and city (Beijing/Shanghai).

⁷ *P* values were adjusted for age, sex, city (Beijing/Shanghai), and residence (urban/rural).

⁸ The cutoff points for low, moderate, and high levels of physical activity were ≤77.4, 77.5–137.8, and ≥137.9 metabolic equivalent h/wk, respectively.

study in New Zealand found that ~43% of free-living participants aged 65 y and older had erythrocyte TDP <140 nmol/L (13). Moreover, a high prevalence of TD (36.6%) evaluated by transketolase activation assay was documented in a cross-sectional survey among 204 urban Indonesian elderly (14). It remains unclear why older adults tend to have TD, although lower dietary intake, reduced absorption, and increased urinary excretion have been suspected (32,33).

TD in humans may lead to irreversible neurological consequences such as Wernicke's encephalopathy and peripheral neuropathy (11). Moreover, low TDP concentrations and impaired thiamine-dependent enzymatic activities have been detected in the brains of patients with Alzheimer's, Parkinson's, and other neurodegenerative diseases (34–36). On the other hand, benfotiamine, a lipophilic thiamine derivative, was found to ameliorate cognitive decline in a mouse model for Alzheimer's disease (37).

However, epidemiological data on TD and depression are scarce. To the best of our knowledge, this is the first large-scale, community-based study that has shown inverse associations of erythrocyte thiamine biomarkers and depressive symptoms among older adults. Our results expand previous findings from small, hospital-based studies that indicated a potential association between thiamine and depression. In a study of 74 patients with a history of malnutrition admitted to a general hospital psychiatric unit, Carney et al. (20) found an association between low thiamine and clinical signs of endogenous depression. A similar observation was made in another study of elderly patients admitted to acute geriatric wards in Belgium (21). Although there are no published clinical trials specifically designed to examine the effect of thiamine on depressive symptoms, 2 small trials suggested that thiamine supplementation might be beneficial for mental health. In a randomized trial among 80 Irish elderly, thiamine supplementation (10 mg/d for 6 wk) resulted in better feelings of well-being and less fatigue (18). In another trial of 120 young British women, thiamine intervention (50 mg/d for 2 mo) led to more self-reports of being clearheaded, composed, and energetic compared with controls (19).

Our data provide preliminary evidence for a beneficial effect of thiamine on depression in community-dwelling older adults. However, the mechanisms for this potential benefit remain elusive. TDP is an essential coenzyme in glucose metabolism and the biosynthesis of many neurotransmitters, such as acetylcholine, γ-aminobutyrate, glutamate, aspartate, and serotonin (38–41). Norepinephrine, serotonin, and glutamate as well as their receptors are major or potential targets for antidepressive therapies (42,43). Another plausible interpretation may relate to TD-induced oxidative stress (44), which was linked to neuronal damage and decreased hippocampal volume in patients with major depression (17). The relevance of these potential mechanisms needs to be further evaluated.

On the other hand, dietary thiamine intake was related to neither TDP concentration in erythrocytes nor to depressive symptoms in our study population. Measurement error in dietary assessment might have contributed to this discrepancy, because the Chinese food composition database was mostly based on the raw weight of foods and substantial loss of water-soluble vitamins is inevitable in food preparation. Other factors, such as diabetes, altered hormone profiles, and ethanol exposure might also affect the bioavailability and intestinal absorption of thiamine (11). In addition, the degradation rate of TDP bound to its dependent enzymes is directly proportional to the amount of its main substrate, carbohydrate (45). Indeed, intakes of

TABLE 3 Adjusted ORs and 95% CIs for depression according to quartiles of erythrocyte concentrations of free thiamine and its phosphate esters in older Chinese adults¹

	Q4	Q3	Q2	Q1	P-trend ²
Free thiamine, nmol/L	≥6.19	3.74–6.18	2.41–3.73	≤2.40	
Cases/n	32/398	26/394	46/397	76/398	
Model 1	1.00	0.91 (0.53, 1.57)	1.71 (1.05, 2.77)	2.96 (1.89, 4.64)	<0.001
Model 2	1.00	0.92 (0.53, 1.61)	1.81 (1.10, 2.97)	2.97 (1.87, 4.72)	<0.001
TMP, nmol/L	≥5.16	3.75–5.15	2.52–3.74	≤2.51	
Cases/n	20/399	36/394	55/399	69/395	
Model 1	1.00	1.90 (1.07, 3.36)	2.68 (1.56, 4.61)	3.19 (1.87, 5.44)	<0.001
Model 2	1.00	1.98 (1.10, 3.57)	2.94 (1.69, 5.12)	3.46 (1.99, 6.02)	<0.001
TDP, nmol/L	≥199	169–199	146–169	≤146	
Cases/n	35/397	40/396	55/398	50/396	
Model 1	1.00	1.20 (0.74, 1.94)	1.70 (1.08, 2.69)	1.81 (1.13, 2.89)	0.006
Model 2	1.00	1.27 (0.77, 2.10)	1.90 (1.18, 3.04)	1.98 (1.22, 3.21)	0.002
Thiamine intake, mg/d	≥1.23	1.09–1.22	0.93–1.08	≤0.92	
Cases/n	60/397	54/396	39/398	27/396	
Model 1	1.00	1.04 (0.69, 1.58)	1.16 (0.72, 1.86)	1.36 (0.76, 2.46)	0.31
Model 2	1.00	0.97 (0.63, 1.50)	1.19 (0.73, 1.93)	1.49 (0.81, 2.75)	0.22

¹ Model 1: adjusted by age, sex, city (Beijing or Shanghai), and residence (rural or urban). Model 2: further adjusted by smoking (current smoker or not) and alcohol drinking (current drinker or not), physical activity (tertile), years of education (0–6, 7–9, or ≥10), living status (living alone or not), household income, history of chronic conditions, total energy intake (quartile), and BMI. TDP, thiamine diphosphate; TMP, thiamine monophosphate.

² The significance of linear trends across quartiles was tested by assigning the median value within quartiles to each participant and modeling this value as a continuous variable.

thiamine and carbohydrate were correlated in our study participants ($r = 0.67$; $P < 0.001$), which might also contribute to the null findings on thiamine intake.

The major strengths of our study include its population-based design, relatively large sample size, and objective assay of thiamine using HPLC. The direct measurement of thiamine status is considered to be superior to functional assays (i.e., transketolase activity assay or transketolase activation assay) (46–48). Our study also has several notable limitations. The study is cross-sectional in nature and therefore does not allow direct causal inference. Further, we defined depressive symptoms based on a conventional definition (CES-D score) rather than a full psychiatric evaluation. However, CES-D has been widely used in large epidemiological studies in various populations and has been found to be highly sensitive and specific in detecting major depression (24). Finally, because Chinese diets are complex, we could not exclude the possibility of residual confounding from dietary or nondietary factors other than thiamine.

In conclusion, this population-based analysis suggests an association between thiamine malnutrition and depressive symptoms among older Chinese adults. This finding warrants further investigation in prospective studies.

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Literature Cited

- Chang-Quan H, Xue-Mei Z, Bi-Rong D, Zhen-Chan L, Ji-Rong Y, Qing-Xiu L. Health status and risk for depression among the elderly: a meta-analysis of published literature. *Age Ageing*. 2010;39:23–30.
- Leon FG, Ashton AK, D'Mello DA, Dantz B, Hefner J, Matson GA, Montano CB, Pradko JF, Sussman N, Winsberg B. Depression and comorbid medical illness: therapeutic and diagnostic challenges. *J Fam Pract*. 2003; Suppl:S19–33.
- Guico-Pabia CJ, Fayyad RS, Soares CN. Assessing the relationship between functional impairment/recovery and depression severity: a pooled analysis. *Int Clin Psychopharmacol*. 2012;27:1–7.
- Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, Whooley MA. Depressive symptoms and health-related quality of life: the Heart and Soul Study. *JAMA*. 2003;290:215–21.
- Pan A, Lucas M, Sun Q, van Dam RM, Franco OH, Willett WC, Manson JE, Rexrode KM, Ascherio A, Hu FB. Increased mortality risk in women with depression and diabetes mellitus. *Arch Gen Psychiatry*. 2011;68:42–50.
- Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med*. 2006;3:e442.
- WHO. Global health observatory. China. Internet [cited 2012 Jun 25]. Available from: <http://www.who.int/gho/countries/chn/en/>.
- Chen R, Copeland JR, Wei L. A meta-analysis of epidemiological studies in depression of older people in the People's Republic of China. *Int J Geriatr Psychiatry*. 1999;14:821–30.
- Zhai F, Yang X. Report of China Nationwide Nutrition and Health Survey 2002 (2): diet and nutrient intake status. Beijing: People's Medical Publishing House; 2006.
- Wurtman RJ, Wurtman JJ. Brain serotonin, carbohydrate-craving, obesity and depression. *Obes Res*. 1995;3 Suppl 4:S477–80.
- Zemleni J, Rucker RB, McCormick DB, Suttie JW. Handbook of vitamins. 4th ed. Boca Raton (FL): CRC Press; 2007. p. 253–87.

12. O'Rourke NP, Bunker VW, Thomas AJ, Finglas PM, Bailey AL, Clayton BE. Thiamine status of healthy and institutionalized elderly subjects: analysis of dietary intake and biochemical indices. *Age Ageing*. 1990;19:325-9.
13. Wilkinson TJ, Hanger HC, George PM, Sainsbury R. Is thiamine deficiency in elderly people related to age or co-morbidity? *Age Ageing*. 2000;29:111-6.
14. Andrade Juguan J, Lukito W, Schultink W. Thiamine deficiency is prevalent in a selected group of urban Indonesian elderly people. *J Nutr*. 1999;129:366-71.
15. Ke Z-J, Gibson GE. Selective response of various brain cell types during neurodegeneration induced by mild impairment of oxidative metabolism. *Neurochem Int*. 2004;45:361-9.
16. Kato T, Kato N. Mitochondrial dysfunction in bipolar disorder. *Bipolar Disord*. 2000;2:180-90.
17. Sapolsky RM. The possibility of neurotoxicity in the hippocampus in major depression: a primer on neuron death. *Biol Psychiatry*. 2000;48:755-65.
18. Smidt LJ, Cremin FM, Grivetti LE, Clifford AJ. Influence of thiamin supplementation on the health and general well-being of an elderly Irish population with marginal thiamin deficiency. *J Gerontol*. 1991;46:M16-22.
19. Benton D, Griffiths R, Haller J. Thiamine supplementation mood and cognitive functioning. *Psychopharmacology (Berl)*. 1997;129:66-71.
20. Carney MW, Williams DG, Sheffield BF. Thiamine and pyridoxine lack newly-admitted psychiatric patients. *Br J Psychiatry*. 1979;135:249-54.
21. Peppersack T, Garbusinski J, Robberecht J, Beyer I, Willems D, Fuss M. Clinical relevance of thiamine status amongst hospitalized elderly patients. *Gerontology*. 1999;45:96-101.
22. Talwar D, Davidson H, Cooney J, St JO'Reilly D. Vitamin B1 status assessed by direct measurement of thiamin pyrophosphate in erythrocytes or whole blood by HPLC: comparison with erythrocyte transketolase activation assay. *Clin Chem*. 2000;46:704-10.
23. Pan A, Franco OH, Wang YF, Yu ZJ, Ye XW, Lin X. Prevalence and geographic disparity of depressive symptoms among middle-aged and elderly in China. *J Affect Disord*. 2008;105:167-75.
24. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1:385-401.
25. Zhang J, Norvilitis JM. Measuring Chinese psychological well-being with Western developed instruments. *J Pers Assess*. 2002;79:492-511.
26. Ye X, Yu Z, Li H, Franco OH, Liu Y, Lin X. Distributions of C-reactive protein and its association with metabolic syndrome in middle-aged and older Chinese people. *J Am Coll Cardiol*. 2007;49:1798-805.
27. Craig CL, Marshall AL, Sjoström M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35:1381-95.
28. Yang Y. Chinese Food Composition Table 2004. Beijing: Peking University Medical Press; 2005.
29. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol*. 1986;124:17-27.
30. Mancinelli R, Ceccanti M, Guiducci MS, Sasso GF, Sebastiani G, Attilia ML, Allen JP. Simultaneous liquid chromatographic assessment of thiamine, thiamine monophosphate and thiamine diphosphate in human erythrocytes: a study on alcoholics. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2003;789:355-63.
31. Herve C, Beyne P, Letteron P, Delacoux E. Comparison of erythrocyte transketolase activity with thiamine and thiamine phosphate ester levels in chronic alcoholic patients. *Clin Chim Acta*. 1995;234:91-100.
32. Baum RA, Iber FL. Thiamin: the interaction of aging, alcoholism, and malabsorption in various populations. *World Rev Nutr Diet*. 1984;44:85-116.
33. Suter PM, Vetter W. Diuretics and vitamin B1: are diuretics a risk factor for thiamin malnutrition? *Nutr Rev*. 2000;58:319-23.
34. Héroux M, Raghavendra Rao VL, Lavoie J, Richardson JS, Butterworth RF. Alterations of thiamine phosphorylation and of thiamine-dependent enzymes in Alzheimer's disease. *Metab Brain Dis*. 1996;11:81-8.
35. Mastrogiacoma F, Bettendorff L, Grisar T, Kish SJ. Brain thiamine, its phosphate esters, and its metabolizing enzymes in Alzheimer's disease. *Ann Neurol*. 1996;39:585-91.
36. Gibson GE, Zhang H. Interactions of oxidative stress with thiamine homeostasis promote neurodegeneration. *Neurochem Int*. 2002;40:493-504.
37. Pan X, Gong N, Zhao J, Yu Z, Gu F, Chen J, Sun X, Zhao L, Yu M, Xu Z, et al. Powerful beneficial effects of benfotiamine on cognitive impairment and β -amyloid deposition in amyloid precursor protein/presenilin-1 transgenic mice. *Brain*. 2010;133:1342-51.
38. Butterworth RF. Neurotransmitter function in thiamine-deficiency encephalopathy. *Neurochem Int*. 1982;4:449-64.
39. Plaitakis A, Hwang EC, Woert MH, Szilagyi PE, Berl S. Effect of thiamin deficiency on brain neurotransmitter systems. *Ann N Y Acad Sci*. 1982;378:367-81.
40. Vigil FA, Oliveira-Silva Ide F, Ferreira LF, Pereira SR, Ribeiro AM. Spatial memory deficits and thalamic serotonergic metabolite change in thiamine deficient rats. *Behav Brain Res*. 2010;210:140-2.
41. Botez MI, Young SN. Biogenic amine metabolites and thiamine in cerebrospinal fluid in heredo-degenerative ataxias. *Can J Neurol Sci*. 2001;28:134-40.
42. Delgado PL, Moreno FA. Role of norepinephrine in depression. *J Clin Psychiatry*. 2000;61 Suppl 1:5-12.
43. Paul IA, Skolnick P. Glutamate and depression: clinical and preclinical studies. *Ann N Y Acad Sci*. 2003;1003:250-72.
44. Singleton CK, Martin PR. Molecular mechanisms of thiamine utilization. *Curr Mol Med*. 2001;1:197-207.
45. McCourt JA, Nixon PF, Duggleby RG. Thiamin nutrition and catalysis-induced instability of thiamin diphosphate. *Br J Nutr*. 2006;96:636-8.
46. Fennelly J, Frank O, Baker H, Leevy CM. Red blood cell-transketolase activity in malnourished alcoholics with cirrhosis. *Am J Clin Nutr*. 1967;20:946-9.
47. Kaczmarek MJ, Nixon PF. Variants of transketolase from human erythrocytes. *Clin Chim Acta*. 1983;130:349-56.
48. Puxty JA, Haskew AE, Ratcliffe JG, McMurray J. Changes in erythrocyte transketolase activity and the thiamine pyrophosphate effect during storage of blood. *Ann Clin Biochem*. 1985;22:423-7.