

Original Article

Trends in folate status in the Taiwanese population aged 19 years and older from the Nutrition and Health Survey in Taiwan 1993-1996 to 2005-2008

Kuan-Ju Chen PhD¹, Wen-Harn Pan PhD^{2,3,4}, Yi-Chin Lin PhD⁵, Bi-Fong Lin PhD²

¹Department of Hospitality Management, Chung-Hwa University of Medical Technology, Tainan, Taiwan, ROC

²Department of Biochemical Science and Technology, National Taiwan University, Taipei, Taiwan, ROC

³Institute of Biomedical Science, Academia Sinica, Taipei, Taiwan, ROC

⁴Nutrition Medicine Research Program, Division of Preventive Medicine and Health Services Research, Institute of Population Health Sciences, National Health Research Institutes, Miaoli, Taiwan, ROC

⁵Department of Nutrition, Chung Shan Medical University, Taichung, Taiwan, ROC

To investigate ten year trends in folate status in Taiwanese aged ≥ 19 yrs by three Nutrition and Health Survey in Taiwan (NAHSIT) in 1993-1996, 1999-2000 and 2005-2008. Women had higher blood folate levels than men in all three surveys. The prevalence of folate deficiency (5.2% < 3 ng/mL) and insufficiency (34.1% ≤ 6 ng/mL) in men was highest in 2005-2008. Adults aged 19-30 yrs had the lowest blood levels and the highest prevalence of deficiency (8.1% in men; 3.5% in women) and insufficiency (48.6% in men; 25% in women) as compared to other age groups in 2005-2008. Folate insufficiency rate in those aged 31-44 yrs was twice as high in men and three times as high in women in 2005-2008 compared to 1993-1996. In the elderly, folate insufficiency rate (28%) in 2005-2008 was not higher than that of 1993-1996, although it was higher than that found in 1999-2000 (18.4%). Men aged ≥ 80 yrs had the poorest folate status in 2005-2008, and men were twice as likely to have inadequate status as women. Plasma homocysteine (Hcy) levels were higher in older men than older women in both surveys. The elderly had significantly higher plasma tHcy in 2005-2008 compared to the 1999-2000 survey. Dark green vegetables and fruit intake frequency in young adults (19-30 yrs) was the lowest among all age groups. This study suggests that folate status in Taiwan has not improved during the past fifteen years, and has worsened in the young population.

Key Words: folate status, NAHSIT, nutrition survey, homocysteine, hyperhomocysteinemia

INTRODUCTION

Folate is essential for optimal growth and development, and for chronic disease prevention and health maintenance throughout all stages of life. Adequate folate status has received increased emphasis in recent years because of the association between low folate status and certain types of cancer, cardiovascular disease,^{1,2} and developmental defects (e.g. neural tube defects, and neurological or psychiatric disorders).³⁻⁵ Folate is also the major nutritional determinant of homocysteine (Hcy) levels.⁶ In humans, inadequate folate intake leads to elevated Hcy concentrations, which have been associated with an increased risk of cardiovascular disease.⁷⁻⁹ Based on these links between folate status and health, many countries have carried out folate fortification to ensure adequate folate intake by the general population.

Recent data indicates that folate fortification in the US population has significantly improved circulating folate and red blood cell folate concentrations and has lowered circulating tHcy concentrations.^{10,11} Previous Taiwanese surveys, the Nutrition and Health Survey in Taiwan (NAHSIT) 1993-1996, and Elderly NAHSIT 1999-2000, found that adults aged ≥ 19 yrs and older people had a

high prevalence of folate insufficiency. In addition, it was found that older Taiwanese men had a high prevalence of hyperhomocysteinemia.^{12,13} However, both surveys were conducted more than ten years ago, and therefore another survey was needed to determine whether blood folate and tHcy levels have continued to rise or have improved in Taiwanese people in the past decade.

In this report, we present trends in folate status in Taiwanese adults and older persons using data from several

Corresponding Author: Dr Kuan-Ju Chen, Department of Hospitality Management, Chung-Hwa University of Medical Technology, No 89, Wen-Hwa 1st St, Jen-Te Hsiang, Tainan 717, Taiwan, ROC.

Tel: +886-6-267-4567 ext 759; Fax: +886-6-2903181

Email: d89623701@ntu.edu.tw

Or Professor Bi-Fong Lin, Department of Biochemical Science and Technology, National Taiwan University, No 1, Section 4, Roosevelt Road, Taipei 106, Taiwan, ROC.

Tel: +886-2-3366-4451; Fax: +886-2-2362-1301

Email: bifong@ntu.edu.tw

Manuscript received 26 April 2011. Revision accepted 27 April 2011.

NAHSIT surveys. Blood folate was measured in NAHSIT 1993-1996, Elderly NAHSIT 1999-2000, and NAHSIT 2005-2008, which has enabled the evaluation of trends in blood folate concentration from 1993 to 2008. Plasma tHcy levels were measured in the Elderly NAHSIT 1999-2000 and NAHSIT 2005-2008 enabling evaluation of trends in plasma tHcy concentrations from 1999 to 2008.

MATERIALS AND METHODS

Subjects

The present study uses data from three surveys mentioned above. All three surveys adopted a multistage, stratified sampling design. A detailed description of the sampling design can be found in Pan *et al's* report.¹⁴ Blood folate was measured in participants aged ≥ 19 yrs in NAHSIT 2005-2008, in the first year of NAHSIT 1993-1996, and in the Elderly NAHSIT 1999-2000. Plasma tHcy was measured in participants aged ≥ 65 yrs in Elderly NAHSIT 1999-2000 and NAHSIT 2005-2008. For the purpose of data analysis, age was classified into the groups: 19-30, 31-44, 45-64, and ≥ 65 yrs for adults, and 65-69, 70-74, 75-79, ≥ 80 yrs for older persons. We excluded participants with missing values for blood folate or tHcy concentration.

Biochemical analyses

Plasma or serum was separated directly after sampling and frozen at -80°C until analysis. Plasma or serum folate was measured by a combined system of competitive immunoassay and chemiluminescence (IMMULITE 2000 analyzer, Diagnostic Products Corporation, LA, USA). This procedure involved the use of monoclonal antibodies, para-magnetic particles, and a chemiluminescence substrate. The light emitted was inversely proportional to the concentration of folic acid. Plasma tHcy was measured by a fluorescence polarization immunoassay (AxSym Homocysteine, Abbott). A series of quality control tests were performed to evaluate the precision of this assay, and confirmed both the between- and within-run consistency of this method. The Coefficient of Variation (CV) for the folate assay was 6.0% in NAHSIT 1993-1996, 11% in Elderly NAHSIT 1999-2000, and 6.9% in NAHSIT 2005-2008; and the CV was 7.1% in NAHSIT 1999-2000, and 2.0% in NAHSIT 2005-2008 for the tHcy assay. Folate deficiency and insufficiency were defined as a plasma or serum folate < 6.8 nmol/L (3 ng/mL) and ≤ 13.5 nmol/L (6 ng/mL), respectively.¹⁵ Hyperhomocysteinemia was defined as a plasma tHcy > 15 $\mu\text{mol/L}$.¹⁶⁻¹⁸

Dietary assessment

Folate-rich food intake frequency was estimated using a food frequency questionnaire (FFQ) in NAHSIT 2005-2008. The FFQ assessed intake of folate-rich foods in the past month with three possible frequency choices (times/month, times/week, and times/day), the selected frequency was then converted to a weekly intake.

Statistical analyses

Statistical analyses were carried out in SAS (SAS/STAT Version 9.0, SAS Institute, Cary, NC). As NAHSIT 1993-1996, Elderly NAHSIT 1999-2000, and NAHSIT 2005-

2008 all used a stratified, multistage probability design, SUDAAN software was used to adjust for this design effect. Folate data from the three surveys (NAHSIT 1993-1996, Elderly NAHSIT 1999-2000 and NAHSIT 2005-2008) and tHcy data from two surveys (Elderly NAHSIT 1999-2000 and NAHSIT 2005-2008) were analyzed by gender, and stratified by age. The prevalence of folate insufficiency and hyperhomocysteinemia were estimated. The student's t test was used for analysis of continuous variables, and the chi-squared test was used for analysis of categorical variables. Trends across age groups were evaluated using linear regression. Analysis of folate-rich food intake frequency by age group was carried out using ANOVA. Differences were considered statistically significant if $p < 0.05$.

RESULTS

Blood folate levels and the prevalence of folate insufficiency in Taiwanese adults aged ≥ 19 yrs in NAHSIT 1993-1996 and NAHSIT 2005-2008 are shown in Table 1. The results showed that women in all age groups had significantly higher blood folate levels than men in both surveys. A significant age trend in blood folate level was only found in NAHSIT 2005-2008 (p for trend < 0.0001 in men and women). Using a serum/plasma folate less than 6 ng/ml (13.5 nmol/L) to define folate insufficiency,¹⁵ we found that the prevalence of folate insufficiency decreased with age in both sexes in the latest survey, NAHSIT 2005-2008 (p for trend < 0.0001). However, this trend of decreasing prevalence with age was not found in NAHSIT 1993-1996.

The greatest increases in the prevalence of folate insufficiency from NAHSIT 1993-1996 to NAHSIT 2005-2008 were observed in men aged 31-44 yrs (change in prevalence of 24.5% to 45.6%), women aged 19-30 yrs (9.9% to 25.1%) and women aged 31-44 yrs (8.8% to 22.8%). Moreover, men and women aged 19-30 yrs in NAHSIT 2005-2008 had the lowest serum folate levels and the highest prevalence of folate deficiency and insufficiency compared to other age groups. Overall, our results showed similar blood folate levels in both surveys, however, the prevalence of folate deficiency increased in Taiwanese men from 2.6% to 5.2%. Women maintained a similar folate status between surveys, apart from younger women aged < 44 yrs (Table 1).

Trends in folate status in older Taiwanese persons from Elderly NAHSIT 1999-2000 and NAHSIT 2005-2008 are shown in Table 2. Older women in all age groups had significantly higher blood folate levels than older men aged ≥ 65 yrs. The higher prevalence of folate deficiency and insufficiency in NAHSIT 2005-2008 was observed in all age groups apart from women aged 65-69 yrs. In older persons, the prevalence of folate deficiency and insufficiency increased with age for both sexes in NAHSIT 2005-2008 (p for trend < 0.0001), but only in women in Elderly NAHSIT 1999-2000 (p for trend = 0.0223). The prevalence of folate insufficiency between Elderly NAHSIT 1999-2000 and NAHSIT 2005-2008, increased from 16.2% to 31.7% in men aged 75-79 yrs, from 16.0% to 40.0% in men aged ≥ 80 yrs, and from 12.3% to 26.0% in women aged 75-79 yrs. In other words,

Table 1. Blood folate levels, folate deficiency and insufficiency in Taiwanese population age ≥ 19 yrs from NAHSIT 1993-1996 to NAHSIT 2005-2008[†]

Age (yrs)	NAHSIT 1993-1996				NAHSIT 2005-2008			
	n	Plasma folate (ng/mL)	Folate status (%) [‡]		n	Serum folate (ng/mL)	Folate status (%) [‡]	
			<3 ngl/mL	≤ 6 ng/mL			<3 ngl/mL	≤ 6 ng/mL
Male								
19-30	59	6.9 \pm 0.3	3.4	41.5	99	6.5 \pm 0.5	8.1	48.6
31-44	102	8.1 \pm 0.4	2.9	24.5	137	7.1 \pm 0.4	6.6	45.6**
45-64	210	8.7 \pm 0.8	1.9	26.7	266	9.3 \pm 0.7	3.8	27.5
≥ 65	89	8.3 \pm 0.4	3.4	33.7	293	10.0 \pm 0.5	4.8	28.4
<i>p</i> trend		0.2047	0.808			<0.0001	<0.0001	
Total	460	8.3 \pm 0.3	2.6	30.0	795	8.2 \pm 0.4	5.2	34.1
Female								
19-30	81	10.2 \pm 0.3*	0	9.9	116	8.9 \pm 0.7*	3.5	25.1**
31-44	136	11.5 \pm 0.2*	0	8.8	145	9.7 \pm 0.5*,**	0.7	22.8**
45-64	212	11.6 \pm 0.5*	0.9	9.4	295	12.8 \pm 0.8*	0	7.8
≥ 65	85	10.8 \pm 0.8*	0	18.8	269	12.2 \pm 1.0*	1.1	13.7
<i>p</i> trend		0.766	0.084			<0.0001	<0.0001	
Total	514	11.2 \pm 0.4*	0.4	10.9	825	10.9 \pm 0.6*	1.0	14.8

[†]All values are shown as mean \pm SE or percentage of participants analyzed by SUDAAN.

[‡]Plasma or serum folate concentrations <3 ng/mL (6.8 nmol/L) indicate folate deficiency; ≤ 6 ng/mL (13.5 nmol/L) indicate folate insufficiency.

*Significantly different from the male value of the same age group and the corresponding period of time. ($p < 0.0001$).

**Significantly different from the NAHSIT 1993-1996 value of the corresponding age ($p < 0.05$).

Table 2. Blood folate levels, folate deficiency and insufficiency in Taiwanese population age ≥ 65 yrs from Elderly NAHSIT 1999-2000 to NAHSIT 2005-2008[†]

Age (yrs)	Elderly NAHSIT 1999-2000				NAHSIT 2005-2008			
	n	Plasma folate (ng/mL)	Folate status (%) [‡]		n	Serum folate (ng/mL)	Folate status (%) [‡]	
			<3 ng/mL	≤ 6 ng/mL			<3 ng/mL	≤ 6 ng/mL
Male								
65-69	453	9.9 \pm 0.5	0	19.3	103	9.9 \pm 0.8	1.9	20.3
70-74	421	10.2 \pm 0.5	0	19.6	85	9.5 \pm 1.1	4.7	29.4
75-79	422	10.6 \pm 0.5	0	16.2	60	10.0 \pm 1.2	6.7	31.7**
≥ 80	117	11.4 \pm 1.6	0	16.0	45	9.5 \pm 0.9**	8.9	40.0**
<i>p</i> trend		0.551	0.550			0.405	<0.0001	
Total	1213	10.4 \pm 0.6	0	18.4	293	9.8 \pm 0.8	4.8	28.4
Female								
65-69	478	12.5 \pm 0.6*	0	11.2	110	13.1 \pm 1.1*	0.9	6.4
70-74	354	12.9 \pm 0.6*	0	10.5	79	11.5 \pm 1.3*	1.3	12.7
75-79	214	13.1 \pm 0.8*	0	12.3	50	10.9 \pm 1.4*,**	2.0	26.0**
≥ 80	123	13.0 \pm 1.1*	0	17.9	30	11.9 \pm 2.3*	0	20.6
<i>p</i> trend		0.660	0.022			0.249	<0.0001	
Total	1169	12.8 \pm 0.6*	0	12.3	269	12.1 \pm 0.5*	1.1	13.7

[†]All values are shown as mean \pm SE or percentage of participants analyzed by SUDAAN.

[‡]Plasma or serum folate concentrations <3 ng/mL (6.8 nmol/L) indicate folate deficiency; ≤ 6 ng/mL (13.5 nmol/L) indicate folate insufficiency.

*Significantly different from the male values of the same age group and the corresponding period of time. ($p < 0.0001$).

**Significantly different from the Elderly NAHSIT 1999-2000 value of the corresponding age ($p < 0.0001$).

these age groups demonstrated two-fold increases in the prevalence of folate insufficiency. Overall, the prevalence of folate insufficiency increased from 18.4% in Elderly NAHSIT 1999-2000 to 28.4% in NAHSIT 2005-2008 in older men and from 12.3% to 13.7% in older women. The poorest folate status was observed in men over the age of 80 yrs in NAHSIT 2005-2008.

Plasma tHcy levels were also measured in the last two surveys, as shown in Table 3. Plasma tHcy concentrations were significantly higher in men than in women in each age group, and significantly increased with age in both surveys (p for trend <0.0001). A notable observation in

our study was the significantly higher plasma tHcy concentration in NAHSIT 2005-2008 compared to Elderly NAHSIT 1999-2000 in all age groups. Furthermore, using the cut-off of 15 μ mol/L for hyperhomocysteinemia,¹⁶⁻¹⁸ we found that the prevalence of hyperhomocysteinemia increased from 23.4% in Elderly NAHSIT 1999-2000 to 50.9% in NAHSIT 2005-2008 in men and from 11.2% to 34.9% in women. Hyperhomocysteinemia significantly increased with age in both surveys (p for trend <0.0001).

To further investigate whether the higher prevalence of folate insufficiency in Taiwanese adults aged 19-30 yrs (Table 1) was associated with their dietary habits, the

intake frequency of folate-rich foods such as dark green vegetables, other vegetables, and fruit by various age groups was examined in NAHSIT 2005-2008 (Table 4). There was a significant age trend for intake of dark green vegetables, other vegetables, and fruit, indicating that younger Taiwanese consumed less fruit and vegetables. The significantly lower intake of dark green vegetables and fruit by adults aged 19-30 yrs could explain the decrease in blood folate levels and the higher prevalence of folate insufficiency observed in this age group.

DISCUSSION

Several studies have reported a high risk of folate deficiency in adults and older persons,^{19,20} and emphasize the importance of maintaining good folate status. In this report, we assessed trends in blood folate, and the prevalence of folate insufficiency and hyperhomocysteinemia in Taiwanese adults and older persons using data from three national surveys. We found a high prevalence of folate insufficiency in men and women aged 31-44 yrs in the latest NAHSIT 2005-2008 survey, which had increased 2- to 3-fold from NAHSIT 1993-1996. It is possible that the use of serum for folate determination in NAHSIT 2005-2008, as opposed to plasma in NAHSIT 1993-1996 and Elderly NAHSIT 1999-2000, has resulted

in underestimation of folate levels in the most recent survey. However, as our mean serum folate levels for each corresponding age group are higher compared to those of other studies,²¹⁻²⁵ it is unlikely that folate levels were underestimated in NAHSIT 2005-2008. In addition, adults aged ≥ 45 yrs had higher serum folate levels in NAHSIT 2005-2008 compared to plasma folate levels in NAHSIT 1993-1996. Mean plasma tHcy levels were also higher in NAHSIT 2005-2008, which further supports the existence of low folate levels as plasma tHcy levels are inversely related to folate status.²⁶ Therefore, it seems unlikely that the sharp increase in prevalence of folate deficiency and insufficiency in adults aged < 45 yrs in the recent survey was due to differences in the blood samples used for estimation (serum vs plasma).

Young adults aged < 45 yrs have poorer folate status than adults aged ≥ 45 yrs, and this difference was even more marked in NAHSIT 2005-2008. In addition, a trend for decreasing folate deficiency and insufficiency with increasing age was only observed in this most recent survey. We also found a significant age trend for increasing consumption frequency of dark green vegetables, other vegetables, and fruit in our study (Table 4). Taiwanese adults aged 19-30 yrs consumed dark green vegetables and fruit significantly less often than other age groups.

Table 3. Plasma homocysteine levels and prevalence of hyperhomocysteinemia in Taiwanese population aged ≥ 65 yrs from Elderly NAHSIT 1999-2000 to NAHSIT 2005-2008[†]

Age (yrs)	Elderly NAHSIT 1999-2000			NAHSIT 2005-2008		
	n	tHcy ($\mu\text{mol/L}$)	tHcy $> 15 \mu\text{mol/L}$ (%) [‡]	n	tHcy ($\mu\text{mol/L}$)	tHcy $> 15 \mu\text{mol/L}$ (%) [‡]
Male						
65-69	421	12.6 \pm 0.5	17.6	103	15.2 \pm 0.9**	44.7**
70-74	377	13.1 \pm 0.6	21.8	85	15.6 \pm 1.3**	47.1**
75-79	203	14.1 \pm 0.6	32.0	60	17.4 \pm 2.0**	48.3**
≥ 80	93	15.6 \pm 1.5	37.7	45	19.2 \pm 1.4**	64.4**
<i>p</i> trend		< 0.001	< 0.0001		0.002	0.002
Total	1094	13.3 \pm 0.6	23.4	293	16.7 \pm 1.0**	50.9**
Female						
65-69	467	9.7 \pm 0.6*	6.2	110	12.3 \pm 1.1*,**	27.3**
70-74	350	10.8 \pm 0.6*	10.0	79	14.0 \pm 1.0*,**	36.7**
75-79	198	11.3 \pm 0.6*	14.6	50	15.0 \pm 1.3*,**	40.0**
≥ 80	120	12.7 \pm 1.0*	28.3	30	17.9 \pm 2.3*,**	50.0**
<i>p</i> trend		< 0.001	< 0.0001		< 0.0001	< 0.0001
Total	1135	10.6 \pm 0.7*	11.2	269	14.4 \pm 1.1*,**	34.9**

[†]All values are shown as mean \pm SE or percentage of participants analyzed by SUDAAN.

[‡]Plasma total homocysteine (tHcy) levels $> 15 \mu\text{mol/L}$ indicate hyperhomocysteinemia.

*Significantly different from the male values of the same age group and the corresponding period of time ($p < 0.0001$).

**Significantly different from the Elderly NAHSIT 1999-2000 value of the corresponding age ($p < 0.0001$).

Table 4. Average weekly consumption frequency of major folate-rich foods by age from NAHSIT 2005-2008[†]

Age (yrs)	Frequency (times/week)		
	Dark green vegetables	Other vegetables [‡]	Fruits [§]
19-30	5.8 \pm 0.4 ^b	11.8 \pm 0.5 ^{ab}	5.8 \pm 0.4 ^b
31-44	7.3 \pm 0.3 ^a	13.2 \pm 0.4 ^a	7.2 \pm 0.3 ^a
45-64	7.2 \pm 0.2 ^a	11.7 \pm 0.3 ^b	8.1 \pm 0.3 ^a
≥ 65	7.4 \pm 0.4 ^a	11.0 \pm 0.4 ^b	7.4 \pm 0.3 ^a
<i>p</i> trend	< 0.001	0.015	< 0.001

[†]All values are shown as mean \pm SE analyzed by SUDAAN. The data with different superscript letters in each column indicate the significant difference among various age groups ($p < 0.05$ by ANOVA).

[‡]Other vegetables include light color vegetables, carrot, potato, beans, melon and sea-vegetables.

[§]Fruits include fresh fruit and fruit juice.

One possible explanation for this finding is that older people in Taiwan are less likely to have a Westernized diet, whereas Western-style diets with increased amounts of fast-food have become popular among the younger generations in Taiwan over the past two decades. Younger Taiwanese who grew up during a period of economic prosperity in the 1980s, became used to fast-food during their childhood and may have formed different dietary habits to those from older generations. As a result, older people who maintain a traditional Chinese diet, comprised of a wide range of vegetables, have better folate status.

Similar trends of better folate status in older people have been reported in other studies, and have generally been attributed to the preference for more "healthy" or "traditional" diets among older people.²⁷⁻²⁹ Longitudinal studies and dietary surveys indicate that young adults tend to gradually abandon traditional diets in favor of more "westernized" diets, and thus consume higher amounts of saturated fat, meat, and cheese, and lower amounts of fruit, vegetables, legumes, and fiber.^{30,31} Similarly, older women tend to consume vegetables daily and take daily folic acid supplementation,³² probably due to food preferences or greater health consciousness among women. In addition, dietary intervention among young male adults resulting in increased intake of vegetables, fruit and whole grain bread has been shown to lead to increased folate intake and reduced plasma tHcy,³³ further supporting the importance of dietary patterns for good folate status.³⁴

In contrast, data from NAHSIT 2005-2008 demonstrated that the prevalence of folate deficiency and insufficiency increased with age among older Taiwanese aged ≥ 65 yrs. This indicates that although older Taiwanese have better folate status than younger adults aged < 65 yrs, within the older population the older elderly have poorer folate status than the younger elderly. Comparison with data from Elderly NAHSIT 1999-2000 shows that the folate status of older persons ≥ 75 yrs, especially men, has worsened in the past decade. This could be the result of chewing problems due to poor dentition or poor appetite associated with aging. The poor folate status of Taiwanese men, apart from those aged 45-74 yrs, is an issue of concern.

In line with the observed decrease in folate levels, plasma tHcy levels among older Taiwanese increased about 1.2-fold in men and about 1.4-fold in women between Elderly NAHSIT 1999-2000 and NAHSIT 2005-2008. These high tHcy levels in older Taiwanese should continue to be monitored and improved upon. In agreement with other studies,^{35,36} plasma tHcy levels were higher in men than in women and significantly increased with age in older persons in our study. Age-related increases in tHcy could be due to a variety of reasons, including decline in renal function,³⁷ and increased cobalamin deficiency resulting from malabsorption of cobalamin by the aging gut.³⁸ Sex differences in tHcy levels could be due to the larger muscle mass and greater creatine phosphate synthesis in men,³⁹ the lowering effect of estrogens in women,⁴⁰ and differences in vitamin status³⁶ and tHcy formation between the sexes.³⁹

Using a cut-off of 15 $\mu\text{mol/L}$ to define hyperhomocysteinemia,¹⁶⁻¹⁸ we found that the prevalence of hyperhomocysteinemia in NAHSIT 2005-2008 was significantly higher in all age groups compared to Elderly NAHSIT 1999-2000. Further analysis showed that the prevalence of hyperhomocysteinemia among older Taiwanese increased about 2.1-fold in men, and about 3.1-fold in women from Elderly NAHSIT 1999-2000 through NAHSIT 2005-2008. This increasing prevalence of hyperhomocysteinemia in older Taiwanese in recent years is an important public health issue. As serum folate is a sensitive indicator of dietary folate intake,⁴¹ our results demonstrating a decrease in blood folate levels in older Taiwanese from Elderly NAHSIT 1999-2000 to NAHSIT 2005-2008, suggesting that increased dietary folate intake should be promoted. However, it may be difficult for older people to change deeply rooted long-term dietary patterns. One study has found that the use of fortified foods can be an easier way of improving folate status in older people,⁴² and this could be a possible alternative solution to encouraging changes to dietary habits in this age group in Taiwan.

Adults aged 19-30 yrs are in a critical period during which dietary habits contribute to the development of chronic disease.^{43,44} We are not certain whether the higher prevalence of folate insufficiency in adults aged 19-30 yrs was due to their lower consumption of green vegetables and fruit because of the cross-sectional nature of our study. The potential causes behind the increased prevalence of folate deficiency and insufficiency in adults aged 19-44 yrs warrant future study. Nonetheless, cross-sectional analyses from the Framingham Heart Study suggest that frequent consumption of certain foods, particularly fruit and vegetables, is correlated with low plasma levels of tHcy, perhaps as a result of the high folate content of these foods.⁴⁵ Our data also suggest that fruit and vegetables are important dietary components for the maintenance of adequate folate status.

Studies have reported upward trends in folate status in the US and the UK following mandatory folic acid fortification.^{46,47} Considering the abundance of a diverse variety of fruit and vegetables, and a lower prevalence of folate deficiency in Taiwan when compared to the US and Europe before fortification,⁴⁸⁻⁵¹ as well as controversies about the benefits and harms of high intake of folic acid from fortified food or dietary supplements,⁵² no folate fortification policy has been implemented in Taiwan. However, the trend of decreasing blood folate levels in young adults and older persons aged over 75 yrs is an issue of concern, and strategies to increase daily intake of folate have become important. Vegetables are the main source of folate in the diet and fruit is the second main folate food source in Taiwan.¹³ However, fruit contributes only one-sixth of the folate intake from vegetables to folate intake (11.8% vs. 66%), indicating that there is great room for improvement for increasing folate intake through fruit. A large variety of fruit is produced in Taiwan that may not be commonly consumed in other countries and contains considerably high folate.⁵³ Although folate supplementation could be one of the strategies used to enhance folate status in older persons, promotion of increased fruit intake through fresh juice, and fruit in-

cluded in lunch boxes or fast-food could be feasible alternatives for young adult who nowadays prefer convenience and often neglect dietary balance.

In summary, this study provides information about trends in blood folate levels, and the prevalence of folate insufficiency and hyperhomocysteinemia in Taiwanese adults and older persons. Overall, folate status in Taiwanese men has worsened from NAHSIT 1993-1996 to NAHSIT 2005-2008, while Taiwanese women have maintained a similar folate status over this period. Folate status has also worsened over this time in adults aged 19-45 yrs in both men in women, however, no significant change in folate status was observed in adults aged 45-74 yrs. The trends in folate status are mirrored by trends in tHcy status. Although the direction of causal effects can not be clarified in this cross-sectional study, changes in dietary patterns in younger generations could be contributing to the observed trends in folate status. Encouraging increased fruit and vegetable consumption could be an important strategy for improving folate status in Taiwanese adults.

ACKNOWLEDGEMENTS

Data analyzed in this paper (article) were collected by the research project "2004-2008 Nutrition and Health Survey in Taiwan (NAHSIT 2005-2008)" sponsored by the Department of Health in Taiwan (DOH94-FS-6-4 and DOH94-TD-F-113-002). This research project was carried out by the Institute of Biomedical Sciences of Academia Sinica and the Research Center for Humanities and Social Sciences, Center for Survey Research, Academia Sinica, directed by Dr. Wen-Harn Pan and Dr. Su-Hao Tu. The Center for Survey Research of Academia Sinica is responsible for data distribution. The assistance provided by the institutes and aforementioned individuals is greatly appreciated. The views expressed herein are solely those of the authors.

AUTHOR DISCLOSURES

All authors declared no conflict of interest.

REFERENCES

- Choi SW, Mason JB. Folate and carcinogenesis: an integrated scheme. *J Nutr.* 2000;130:129-32.
- Moat SJ, Lang D, McDowell IF, Clarke ZL, Madhavan AK, Lewis MJ, Goodfellow J. Folate, homocysteine, endothelial function and cardiovascular disease. *J Nutr Biochem.* 2004;15:64-79.
- Duthie SJ, Whalley LJ, Collins AR, Leaper S, Berger K, Deary IJ. Homocysteine, B vitamin status, and cognitive function in the elderly. *Am J Clin Nutr.* 2002;75:908-13.
- Mattson MP, Kruman II, Duan W. Folic acid and homocysteine in age-related disease. *Ageing Res Rev.* 2002;1:95-111.
- Rampersaud GC, Kauwell GP, Bailey LB. Folate: a key to optimizing health and reducing disease risk in the elderly. *J Am Coll Nutr.* 2003;22:1-8.
- Clarke R, Collins R. Can dietary supplements with folic acid or vitamin B6 reduce cardiovascular risk? Design of clinical trials to test the homocysteine hypothesis of vascular disease. *J Cardiovasc Risk.* 1998;5:249-55.
- Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *Br Med J.* 2002;325:1202-9.
- Vasan RS, Beiser A, D'Agostino RB, Levy D, Selhub J, Jacques PF, Rosenberg IH, Wilson PW. Plasma homocysteine and risk for congestive heart failure in adults without prior myocardial infarction. *JAMA.* 2003;289:1251-7.
- Tanne D, Haim M, Goldbourt U, Boyko V, Doolman R, Adler Y, Brunner D, Behar S, Sela BA. Prospective study of serum homocysteine and risk of ischemic stroke among patients with preexisting coronary heart disease. *Stroke.* 2003;34:632-6.
- Pfeiffer CM, Johnson CL, Jain RB, Yetley EA, Picciano MF, Rader JI, Fisher KD, Mulinare J, Osterloh JD. Trends in blood folate and vitamin B-12 concentrations in the United States, 1988-2004. *Am J Clin Nutr.* 2007;86:718-27.
- Jacques PF, Selhub J, Bostom AG, Wilson PWF, Rosenberg IH. The effect of folic acid fortification on plasma folate and total homocysteine concentrations. *New Engl J Med.* 1999;340:1449-54.
- Lin BF, Lin RF, Yeh WT, Pan WH. The folate status in Taiwan population from the NAHSIT 1993-1996. *Nutr Sci J.* 1999;24:99-117.
- Chen KJ, Pan WH, Shaw NS, Huang RF S, Lin BF. Association between dietary folate intake and folate status of elderly Taiwanese. *Asia Pac J Clin Nutr.* 2005;14:244-9.
- Tu SH, Chen C, Hsieh YT, Chang HY, Yeh CJ, Lin YC, Pan WH. Design and sample characteristics of the 2005-2008 Nutrition and Health Survey in Taiwan. *Asia Pac J Clin Nutr.* 2011;20:225-37.
- Waters AH, Mollin DL, Pope J, Towler T. Studies on the folic acid activity of human serum. *J Clin Pathol.* 1961;14:335-51.
- Chen KJ, Pan WH, Yang FL, Wei IL, Shaw NS, Lin BF. Association of B vitamins status and homocysteine levels in elderly Taiwanese. *Asia Pac J Clin Nutr.* 2005;14:250-5.
- Kang SS, Wong PW, Malinow MR. Hyperhomocyst(e)inemia as a risk factor for occlusive vascular disease. *Ann Rev Nutr.* 1992;12:279-98.
- Jacobsen DW. Homocysteine and vitamins in cardiovascular disease. *Clin Chem.* 1998;44:1833-43.
- Rosenberg IH, Bowman BB, Cooper BA, Halsted CH, Lindenbaum J. Folate nutrition in the elderly. *Am J Clin Nutr.* 1982;36:1060-6.
- Selhub J, Jacques PF, Wilson PW, Rush D, Rosenberg IH. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. *JAMA.* 1993;270:2693-8.
- Li D, Sinclair A, Mann NJ, Turner A, Ball MJ. Selected micronutrient intake and status in men with differing meat intakes, vegetarians and vegans. *Asia Pac J Clin Nutr.* 2000;9:18-23.
- Tovar AR, Torres N, Barrales-Benitez O, López AM, Diaz M, Rosado JL. Plasma total homocysteine in Mexican rural and urban women fed typical model diets. *Nutr.* 2003;19:826-31.
- Moore SE, Mansoor MA, Bates CJ, Prentice AM. Plasma homocysteine, folate and vitamin B(12) compared between rural Gambian and UK adults. *Br J Nutr.* 2006;96:508-15.
- Abdollahi Z, Elmadfa I, Djazayeri A, Sadeghian S, Freisling H, Mazandarani FS, Mohamed K. Folate, vitamin B12 and homocysteine status in women of childbearing age: baseline data of folic acid wheat flour fortification in Iran. *Ann Nutr Metab.* 2008;53:143-50.
- Thuesen BH, Husemoen LL, Ovesen L, Jørgensen T, Fenger M, Linneberg A. Lifestyle and genetic determinants of folate and vitamin B12 levels in a general adult population. *Br J Nutr.* 2009;8:1-10.
- Lakshmi AV, Maniprabha C, Krishna TP. Plasma homocysteine level in relation to folate and vitamin B6 status in apparently normal men. *Asia Pac J Clin Nutr.* 2001;10:194-6.

27. Planells E, Sánchez C, Montellano MA, Mataix J, Llopis J. Vitamins B6 and B12 and folate status in an adult Mediterranean population. *Eur J Clin Nutr.* 2003;57:777-85.
28. Alfthan G, Laurinen MS, Valsta LM, Pastinen T, Aro A. Folate intake, plasma folate and homocysteine status in a random Finnish population. *Eur J Clin Nutr.* 2003;57:81-8.
29. Scali J, Richard A, Gerber M. Diet profiles in a population sample from Mediterranean southern France. *Public Health Nutr.* 2001;4:173-82.
30. Voukiklaris GE, Kafatos A, Dontas AS. Changing prevalence of coronary heart disease risk factors and cardiovascular diseases in men of a rural area of Crete from 1960 to 1991. *Angiology.* 1996;47:43-9.
31. Hatzis CM, Bertias GK, Linardakis M, Scott JM, Kafatos AG. Dietary and other lifestyle correlates of serum folate concentrations in a healthy adult population in Crete, Greece: a cross-sectional study. *Nutr J.* 2006;5:5-15.
32. Evans L, Weisman CS. Folic acid supplementation in younger and older nonpregnant women of reproductive age: findings from the Central Pennsylvania Women's Health Study (CePAWHS). *Womens Health Issues.* 2010;20:50-7.
33. Stea TH, Uglem S, Wandel M, Mansoor MA, Frølich W. Association between folate intake from different food sources in Norway and homocysteine status in a dietary intervention among young male adults. *Br J Nutr.* 2009;102:899-906.
34. Martínez JJ, Ruiz FA, Candil SD. Baseline serum folate level may be a predictive factor of weight loss in a morbid-obesity-management programme. *Br J Nutr.* 2006;96:956-64.
35. Selhub J, Jacques PF, Bostom AG, D'Agostino RB, Wilson PW, Belanger AJ et al. Relationship between plasma homocysteine, vitamin status and extracranial carotid-artery stenosis in the Framingham Study population. *J Nutr.* 1996;126(S4):1258S-65.
36. Nygard O, Vollset SE, Refsum H, Stensvold I, Tverdal A, Nordrehaug JE, Ueland M, Kvale G. Total plasma homocysteine and cardiovascular risk profile: The Hordaland Homocysteine Study. *JAMA.* 1995;274:1526-33.
37. Norlund L, Grubb A, Fex G, Leksell H, Nilsson JE, Schenck H, Hultberg B. The increase of plasma homocysteine concentrations with age is partly due to the deterioration of renal function as determined by plasma cystatin C. *Clin Chem Lab Med.* 1998;36:175-8.
38. van Asselt DZ, de Groot LC, van Staveren WA, Blom HJ, Wevers RA, Biemond I, Hoefnagels WH. Role of cobalamin intake and atrophic gastritis in mild cobalamin deficiency in older Dutch subjects. *Am J Clin Nutr.* 1998;68:328-34.
39. Malinow MR. Homocyst(e)ine and arterial occlusive diseases. *J Intern Med.* 1994;236:603-17.
40. Alfthan G, Aro A, Gey KF. Plasma homocysteine and cardiovascular disease mortality. *Lancet.* 1997;349:97.
41. Food and nutrition Board and Institute of Medicine: "Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline." Washington, DC: National Academy Press; 2000.
42. Bermejo LM, Aparicio A, Rodríguez-Rodríguez E, López-Sobaler M, Andrés P, Ortega RM. Dietary strategies for improving folate status in institutionalized elderly persons. *Br J Nutr.* 2009;101:1611-5.
43. Wattanapenpaibon N. Cardiovascular risk in the Asia-Pacific region from a nutrition and metabolic point of view: vitamin deficiencies. *Asia Pac J Clin Nutr.* 2001;10:103-7.
44. Astorg P, Couthouis A, de Courcy GP, Bertrais S, Arnault N, Meneton P, Galan P, Hercberg S. Association of folate intake with the occurrence of depressive episodes in middle-aged French men and women. *Br J Nutr.* 2008;100:183-7.
45. Tucker KL, Selhub J, Wilson PWF, Rosenberg IH. Dietary intake pattern relates to plasma folate and homocysteine concentrations in the Framingham Heart Study. *J Nutr.* 1996;126:3025-31.
46. Pfeiffer CM, Johnson CL, Jain RB, Yetley EA, Picciano MF, Rader JI, Fisher KD, Mulinare J, Osterloh JD. Trends in blood folate and vitamin B-12 concentrations in the United States, 1988-2004. *Am J Clin Nutr.* 2007;86:718-27.
47. Clarke R, Sherliker P, Hin H, Molloy AM, Nexo E, Ueland PM, Emmens K, Scott JM, Evans JG. Folate and vitamin B12 status in relation to cognitive impairment and anaemia in the setting of voluntary fortification in the UK. *Br J Nutr.* 2008;100:1054-9.
48. Senti FR, Pilch SM. Analysis of folate data from the second National Health and Nutrition Examination Survey (NHANES II). *J Nutr.* 1985;115:1398-402.
49. Subar AF, Block G, James LD. Folate intake and food sources in the US population. *Am J Clin Nutr.* 1989;50:508-16.
50. Fabian E, Elmadfa I. Nutritional situation of the elderly in the European Union: data of the European Nutrition and Health Report (2004). *Ann Nutr Metab.* 2008;52:57-61.
51. Hamer DH, Sempértegui F, Estrella B, Tucker KL, Rodríguez A, Egas J, Dallal GE, Selhub J, Griffiths JK, Meydani SN. Micronutrient deficiencies are associated with impaired immune response and higher burden of respiratory infections in elderly Ecuadorians. *J Nutr.* 2009;139:113-9.
52. Smith AD, Kim YI, Refsum H. Is folic acid good for everyone? *Am J Clin Nutr.* 2008;87:517-33.
53. Lu HY, Hong YH, Lin BF. The feasibility study on the increase of dietary folate intake by the promotion of fruits consumption. *Nutr Sci J.* 2009;34:58-63.

Original Article

Trends in folate status in the Taiwanese population aged ≥ 19 yrs from the Nutrition and Health Survey in Taiwan 1993-1996 to 2005-2008

Kuan-Ju Chen PhD¹, Wen-Harn Pan PhD^{2,3,4}, Yi-Chin Lin PhD⁵, Bi-Fong Lin PhD²

¹Department of Hospitality Management, Chung-Hwa University of Medical Technology, Tainan, Taiwan, ROC

²Department of Biochemical Science and Technology, National Taiwan University, Taipei, Taiwan, ROC

³Institute of Biomedical Science, Academia Sinica, Taipei, Taiwan, ROC

⁴Nutrition Medicine Research Program, Division of Preventive Medicine and Health Services Research, Institute of Population Health Sciences, National Health Research Institutes, Miaoli, Taiwan, ROC

⁵Department of Nutrition, Chung Shan Medical University, Taichung, Taiwan, ROC

臺灣 19 歲以上成人葉酸營養狀況的變遷趨勢：從 NAHSIT 1993-1996 到 NAHSIT 2005-2008

本研究探討臺灣 19 歲以上成人葉酸營養狀況的變遷。三次臺灣營養健康家戶調查(NAHSIT)的女性血中葉酸濃度顯著高於男性。NAHSIT 2005-2008 調查結果，男性成人的葉酸缺乏率 (5.2%，血清葉酸 < 3 ng/mL)與葉酸不足率 (34.1%，血清葉酸 < 6 ng/mL)，較 NAHSIT 1993-1996 與臺灣老人營養健康狀況調查(1999-2000)的葉酸營養狀況差，尤其 19-30 歲男性的葉酸不足率高達 48.6%；而 31-44 歲男女性成人的葉酸不足率增加了 2-3 倍，不容忽視。老人葉酸不足率 (男性 28.4%，女性 13.7%) 比臺灣老人營養健康狀況調查(1999-2000)的結果更高，尤其是男性老人在 80 歲以上的葉酸不足率高達 40%。兩次調查結果顯示，老年男性之年齡別血漿同半胱胺酸濃度平均值皆顯著高於女性，且血中同半胱胺酸濃度有隨年齡增加而上升之趨勢。NAHSIT 2005-2008 調查的老人，血漿同半胱胺酸濃度與同半胱胺酸濃度 > 15 $\mu\text{mol/L}$ 的盛行率皆顯著較臺灣老人營養健康狀況調查(1999-2000)的老人高。進一步分析 NAHSIT 2005-2008 之富含葉酸食物的攝取狀況，結果顯示 19-30 歲成人的深綠色蔬菜及水果類攝取頻率，顯著低於其他年齡層。過去十五年間，臺灣成人的葉酸營養狀況仍未改善，尤其是年輕族群的葉酸營養狀況變差，值得注意。而近年來臺灣成人血中同半胱胺酸濃度與高同半胱胺酸血症盛行率有增高的趨勢，建議衛生行政單位仍需關注國人葉酸營養狀況並研擬對策加以改善。

關鍵字：葉酸營養狀況、NAHSIT、營養調查、同半胱胺酸、高同半胱胺酸血症