Original Article

Relationships of dietary choline and folate intake with serum hepatic inflammatory injury markers in a Taiwanese adult population

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Background and Objectives: The relationships of dietary choline and folate intake with hepatic function have yet to be established in the Taiwanese population. We investigated the associations of choline and folate intake with hepatic inflammatory injury in Taiwanese adults. **Methods and Study Design:** Blood samples and data on dietary choline components and folate intake from 548 Taiwanese adults without pathological liver disease were collected. Dietary intake was derived using a semiquantitative food-frequency questionnaire. Serum liver injury markers of alanine transaminase, aspartate transaminase, and hepatitis viral infection were measured. **Results:** Elevated serum hepatic injury markers (>40 U/L) were associated with low folate and free choline intake (p<0.05). Folate intake was the most significant dietary determinant of serum aspartate transaminase concentration (beta=−0.05, p=0.04), followed by free choline intake (beta=−0.249, p=0.055). Folate intake exceeding the median level (268 μg/d) was correlated with a reduced rate of hepatitis viral infection (p=0.032) and with normalized serum aspartate transaminase (odds ratio [OR]=0.998, 95% confidence interval [CI]=0.996-1, p=0.042) and alanine transaminase (OR=0.998, 95% CI=0.007-1, p=0.019). Total choline intake exceeding the median level (233 mg/d) was associated with normalized serum aspartate transaminase (OR=0.518, 95% CI=0.360-0.745, p=0.018). **Conclusions:** The newly established relationships of dietary intake of total choline and folate with normalized hepatic inflammatory markers can guide the development of dietary choline and folate intake recommendations for Taiwanese adults.

Key Words: choline intake, folate intake, hepatitis injury marker, Taiwanese population, hepatitis

INTRODUCTION

One-carbon nutrients such as choline and folate act as one-carbon donors and acceptors to mediate one-carbon metabolism and are mostly active in the liver.[1] Choline and its metabolic mediator, folate, interact to engender hepatic de novo DNA and RNA synthesis, macromolecule methylation, and lipid and protein synthesis.[2-4] The deprivation of hepatic choline and folate is associated with hepatic DNA damage,[5] aberrant DNA methylation patterns,[6,7] fatty liver, hepatofibrosis, and steatosis,[1,4,8] all of which are pathological progress markers of the predisposition of hosts to hepatocellular carcinoma (HCC).[9-11]

The primary criterion for estimating the adequate intake (AI) of choline used by the U.S. government is the prevention of liver damage, as determined by examining hepatic injury markers, serum alanine transaminase (ALT) and aspartate transaminase (AST) concentrations.[12] Because folate and choline share hepatic one-carbon metabolic pathways, insufficient folate intake may increase required choline levels. Rat studies have reported that a choline-deficient diet reduced hepatic folate content, whereas a folate-deficient diet lowered hepatic choline levels.[2-4] However, the clinical relationships between the two dietary intakes and serum liver injury markers remain relatively unexplored in humans.

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Manuscript received 02 February 2016. Initial review completed 24 March 2016. Revision accepted 09 May 2016.
doi: 10.6133/apjcn.082016.03

Chronic infection caused by the hepatitis viruses is strongly associated with liver inflammatory injury diagnosed according to elevated serum ALT and AST concentrations (>40 U/L), which are early biomarkers for hepatic progressive pathological injuries such as hepatofibrosis, cirrhosis, and hepatocellular carcinoma.[11,13] Approximately 350 million people worldwide have chronic hepatitis infections,[14] of whom 60% develop liver cancer.[15] The Taiwanese population is constantly exposed to hepatitis viral infection, yet the health associations of choline and folate intake with liver function markers have yet to be explored. Therefore, the objectives of the present study were to (1) evaluate the potential dietary choline and folate determinants of liver inflammatory injury markers and (2) establish the associations of choline and folate intake with liver function markers in Taiwanese participants.

METHODS

Study participants

During 2002-2009, Taiwanese adults were enrolled to participate in the Viral-Hepatitis-Screening Program, Health and Physical Examination Program, and B Vitamin and HCC Cancer Prevention Program, directed by the medical research centers at ChiMei Hospital (CMH) and National Taiwan University Hospital (NTUH). After blood and imaging examinations, including B-type ultrasonography and computed tomography, adult patients aged >20 years who were seropositive for hepatitis viral infection and had no pathological liver disease (fatty liver disease, steatosis, liver fibrosis, cirrhosis, or HCC) were selected from the three programs. Exclusion criteria were cardiac or renal disease, overt diabetes, active intravenous drug abuse, and chronic alcohol use. Using the same inclusion and exclusion criteria, healthy adults seronegative for hepatitis viral infection were selected. In total, 548 adults were recruited. The study protocol was approved by the Joint Medical Ethical Committee of CMH and NTUH, and by the Ethical Review Board of Fu-Jen University. Written informed consent was obtained from all the participants.

Blood sample collection and laboratory determination

Within 1 week following a physician's diagnosis, peripheral blood samples were collected after a 12-h fasting period, and they were chilled and transported to the central biomedical laboratory of the NTU and CMH medical centers. The serum samples were immediately separated upon arrival and were stored at -80°C until further analysis.

Serum AST and ALT concentrations were measured according to standard protocols (ITC Diagnostics, Taiwan). Hepatitis viral infection was determined on the basis of seropositivity for hepatitis B (HBV) surface antigen or the presence of hepatitis C virus antibody (anti-HCV). Serum HBV surface antigen was tested using an RIA kit (Abbott Laboratories, North Chicago, IL, USA). Anti-HCV was detected using an enzyme immunoassay kit (Abbott Laboratories).

Collection of data on dietary intakes

After the blood sample collection, the participants were interviewed individually and in-person by experienced, registered dietitians (RDs) to complete a structured general questionnaire and validated semiquantitative food-frequency questionnaire (qFFQ).[16-18] The participants were assisted by the RDs to answer how frequently they had consumed one standard serving of a specific food item from the five categories in the past year (frequency of consumption per d, wk, mo, and y or never consumed). The standard serving sizes provided with the questionnaire were based on a typical or natural portion size consumed in Taiwan.

Assessment of composition of dietary intakes

The qFFQ was included 170 food items with high folate and choline contents. These 170 food items comprised 21 staple foods, 85 vegetables and fruits, 44 meat and dairy products, 11 soybean products, and nine types of nuts and fats. The list was assembled on the basis of the top 50 most frequently consumed food items reported by the Nutrition and Health Survey in Taiwan (NAHSIT).

The food nutrient database created by the Taiwan Food and Drug Administration does not contain choline values; the choline content data for individual food items were added to the qFFQ nutrient database (Fu Jen data-coordinating lab center) by using the values from the U.S. Department of Agriculture (USDA) choline database and other scientific analytical reports.[14] Identical food items in the NAHSIT database were matched to those in our choline database to assign folate and choline values. Values for non-identical food items were determined on the basis of comparable food items or other available data. Using the constructed choline food database, we converted the participants' responses on the frequencies of their intake of a particular serving size for each food item into their mean daily intake. We linked these reports to our food composition database to provide information on the amount of nutrient consumption per serving. Thus, the daily nutrient intakes for each participant were derived.

Statistical analysis

Chi-squared and student *t* tests were used for categorical and continuous variables, respectively. A Pearson or Spearman correlation for associations between dietary intake and serum AST and ALT levels were calculated. Univariate and multivariate linear regression models were constructed to evaluate the determinants of liver injury by using serum ALT and AST levels as the dependent variables. A separate linear regression model was constructed to evaluate the effect of median folate and choline intake on liver injury markers. Logistic regression models were used to evaluate the predictive power of ALT and AST on the risk of liver injury by including conventional variables such as age and sex. Dependent variables that were not normally distributed were log-transformed. All statistical procedures were conducted using SPSS for Windows (version 11.01; SPSS Inc., Chicago, IL).

RESULTS

Anthropometric and serum biochemical factors associated with dietary intake of folate and choline components

As shown in Table 1, age, sex, and obesity (assessed ac-

cording to body mass index [BMI]) were not correlated with dietary folate intake. Mean habitual folate intake was significantly lower in the participants with hepatitis viral infection (294±202 μg/d) than in those without hepatitis viral infection (340±209 μg/d, p=0.011). Lower folate intake was significantly correlated with elevated serum AST and ALT. A higher prevalence of low folate intake (<estimated average requirement values) was associated with hepatitis viral infection and elevated hepatic inflammatory markers. Age, sex, and BMI were not correlated with dietary folate intake.

Old age (>65 y) and female sex were significantly associated with lower total choline intake. Low total choline intake (<50% AI) was correlated with elevated serum AST levels. Regarding the total choline intake components, lower free choline intake was associated with elevated serum AST (p<0.001) and ALT (p=0.012) and with positive viral infection rates (p<0.005). Low phosphocholine intake was correlated with elevated serum AST and positive hepatitis viral infection.

Determinants of serum AST and ALT concentrations of the study participants and subgroups

Sex and age were not associated with liver injury markers (Table 2). Regarding dietary intake, folate and free choline were identified as the most crucial dietary determinants of serum AST among all study participants. Single-unit increments in folate and choline intake were associated with 0.05 (p=0.04) and 0.25 IU/L decreases in serum AST concentration (p=0.05), respectively. Similar relationships were observed between folate and free choline and serum ALT, though with less statistical power. Hepatitis viral infection was the most significant determinant of serum AST and ALT (p<0.0001). Adjusting for viral infection negated the dietary determination power for serum AST and ALT (data not shown). For all study participants, elevated serum AST was inversely correlated with intake of folate (r=−0.087, p=0.04) and free choline (r=−0.083, p=0.05). Within the subgroup of participants without a hepatitis infection, intakes of free choline (r=−0.110, p=0.046) and phosphocholine (r=−0.134, p=0.015) were significantly and inversely correlated with serum AST. Such correlations were not significant for the subgroup with hepatitis viral infection.

Interactive associations of median choline and folate intake with serum AST, ALT, and hepatitis viral infection

Using the median cut-offs values for low and high intakes of choline and folate, we assessed the associations and interactions of low folate and total choline intakes with serum liver injury markers (Table 3). The data revealed that low folate consumption (<median intake=268 μg/d), but not low total choline intake was marginally associated with elevated serum AST (p=0.074) and strongly correlated with viral infection (p=0.0328). No interactive effects were observed between low choline or folate intake and liver injury.

Choline and folate intake values associated with serum hepatic injury markers

The logistic regression analysis revealed that participants with folate intakes exceeding the median level (>268 μg/d) exhibited 30%-50% lower risks of hepatitis inflammation (serum AST and ALT >40 U/L) than did those with low folate intakes (p<0.001 and 0.049, respectively; Table 4). This remained significant after adjustment for multiple factors including age, sex, choline intake, and serum concentrations of folate and homocysteine (adjusted odds ratio [OR]=0.998, 95% confidence interval [CI]=0.996-1; p=0.0428 and 0.019, respectively). The study participants with a total choline intake exceeding the median level (233 mg/d) exhibited a 49% reduced risk of hepatic inflammatory injury (serum AST >40 U/L) compared with those with a low choline intake (<233 mg/d serum AST >40 U/L; 95% CI=0.360-0.745, p=0.018). Multiple factorial adjustments negated these significant associations.

DISCUSSION

In this study, we used the qFFQ and observed that Taiwanese adults aged 51±12 years exhibited a habitual mean dietary total choline intake of 267 mg/day. The intake data of the study participants were consistent with NAHSIT statistics showing that the mean choline intake of free-living healthy Taiwanese people aged 45-64 years (n=1,939) was 270 mg/d, as assessed through 24-h recall.[19-22] No health outcome has been identified on the basis of such actual choline intakes among Taiwanese adults. The results of the present study indicate that choline intakes exceeding the median intake level (233 mg/d) were associated with normalized serum AST concentrations (OR=0.518, 95% CI=0.360-0.735, p<0.001). Our findings are comparable to the previously reported choline intake values corresponding to different spectra of liver injuries in various races and both sexes.[23] A choline-deficient diet (<50 mg/d) can lead to increased serum ALT and AST in healthy adults with fatty livers and steatohepatitis.[4,24] A choline intervention study reported that a choline intake of 300 mg/d was sufficient to prevent elevated serum ALT and AST in Mexican–American males.[25] In the Shanghai Women's and Men's Health Studies, a total choline intake of 284 mg/d predicted a reduced risk of nonalcoholic fatty liver disease (NAFLD) in women.[26] Postmenopausal women with NAFLD who were on a choline diet of 212 mg/day exhibited highly hepatic fibrosis.[27] Although sex and age were not significant determinants of serum AST and ALT in the present study, higher rates of low choline intake (<50% intake of AI) were correlated with the elderly population and female sex. Adjustment for age and sex negated the relationships between low choline intake and hepatic inflammatory markers. Estrogen levels and genetic variation may influence the dietary choline requirements in females, aiding them in maintain normal liver function markers.[28] To further assess the total choline intake that optimally maintains normal liver function markers in the Taiwanese population, various widely used dependent variables should be considered.

Components of total choline intake include dietary derivatives of free choline, phosphocholine, and phosphotidylcholine (PC). The current study is the first to identify free choline as a determinant of elevated serum AST in Taiwanese adults (estimate beta=−0.25, p=0.05). The unique metabolic role of low free choline intake in main-

Table 1. Associations of folate and choline dietary intake with the anthropometric and clinical variables of the study participants[†]

Variables	Subjects numbers	Total folate intake[‡]		Total choline intake[§]		Free choline (mg/day)	Phosphocholine (mg/day)	Phosphotidylcholine (mg/day)
		Mean intake (μg/day)	Low intake n (%)	Mean intake (mg/day)	Low intake n (%)			
Age, year								
≥65 y	87	292±189	61 (70)	218±115	54 (62)	58.6±38.8	11. 2±8.3	111±59.8
<65 y	461	328±210	281 (61)	270±140	191 (41)	62.6±40.3	11.6±8.0	154±89.4
p value		0.143	0.106	<0.001***	<0.001***	0.390	0.620	<0.001***
Sex, n								
Male	321	324±199	201 (62)	284±145	132 (41)	62.8±38.9	11.8±7.8	165±94.7
Female	227	319±218	141 (62)	230±120	113 (50)	60.8±41.7	11.2±8.3	123±67.3
p value		0.748	0.905	<0.001***	0.045*	0.574	0.369	<0.001***
Body mass index[¶]								
≥27	74	328±221	44 (59)	264±153	38 (51)	62.8±40.5	11.7±7.4	149±98.7
<27	394	324±209	243 (61)	257±132	177 (44)	62.7±41.4	11.9±8.4	142±82.0
p value		0.906	0.720	0.693	0.309	0.974	0.869	0.583
HBV/HCV/HAV infection, n								
Positive	210	293±202	148 (70)	254±147	105 (50)	55.9±40.2	10.7±8.4	148±92.9
Negative	338	340±209	194 (57)	267±131	140 (41)	65.7±39.6	12.1±7.7	147±82.9
p value		0.011*	0.002**	0.297	0.050	0.005**	0.039*	0.832
HBV	155	315±211	101 (65.1)	273±151	67 (43.2)	61.8±43.0	12.3±8.9	154±94.8
HCV	52	228±161	45 (86.5)	195±118	37 (71.1)	37.7±22.6	5.7±3.4	129±84.9
p value		0.002**	0.003**	<0.001***	0.001**	<0.001***	<0.001***	0.086
Serum aspartate transaminase[¶]								
Hepatitis ≥40 U/L	183	277±190	134 (73)	236±139	104 (56)	53.5±39.3	10.4±8.5	137±86.5
Normal <40 U/L	350	346±213	198 (56)	276±137	136 (38)	67.0±40.3	12.3±7.8	153±87.6
p value		<0.001***	<0.001***	0.002**	<0.001***	<0.001***	0.007**	0.046*
Serum alanine transaminase[¶]								
Hepatitis ≥40 U/L	22	299±188	149 (66)	259±146	111 (49)	57.2±37.3	11.1±8.3	150±94.3
Normal <40 U/L	309	339±220	183 (59)	264±133	129 (41)	66.1±42.2	12.3±7.8	145±82.3
p value		0.013*	0.086	0.681	0.074	0.012*	0.217	0.482

[†]Data are presented as the mean±SD for the continuous variables and as proportions (%) for the categorical variables. Variables that were not normally distributed were first log-transformed. The continuous variables were compared using the student *t* test. The Chi-squared test was used for categorical variables. Differences were considered to be statistically significant at $^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$.

[‡]Low folate intake deficiency was defined as total intake below the folate EAR value for Taiwanese adults (320 μg/day).

[§]Low choline intake deficiency was defined as total choline intake less than 50% of the AI value for Taiwanese adult men (225 mg/day) and female (195 mg/day).

[¶]Several subjects have missing BMI and serum AST and ALT data because of technical problems in the measurements.

Table 2. Potential determinants of serum AST and ALT levels in the study participants[†]

Independent Variables	Dependent variables of liver injuries			
	Serum AST, IU/L		Serum ALT, IU/L	
	Estimate	*p* value	Estimate	*p* value
Ages, y	-0.25	0.551	-1.27	0.067
Sex, women/men	7.50	0.485	31.4	0.069
Viral infection	101	<0.001***	161	<0.001***
Dietary intakes				
Folate, ug	-0.050	0.044*	-0.077	0.057
Total choline, mg	-0.040	0.290	-0.023	0.700
Free choline, mg	-0.249	0.055	-0.394	0.061
Phophocholine, mg	-0.677	0.296	-0.947	0.366
Phosphotidylcholine, mg	-0.040	0.504	0.014	0.882

[†]Linear regression models were constructed to evaluate the determinants of liver injuries by using serum ALT and AST concentrations as the dependent variables. Differences were considered to be statistically significant at $^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$.

Table 3. Association of median choline and folate intake with AST, ALT, and viral infection rates[†]

Folate intake[§], μg	Total choline intake[‡], mg			*p* values		
	Low (<233)	High (≥233)	Total	Folate intake	Choline intake	Interaction
	Serum AST levels, median (Q1, Q3)			0.074	0.688	0.441
Low <268	34 (23, 85)	27 (22, 70)	31 (23, 82)			
High ≥268	27 (23, 49)	27 (21, 40)	27 (21, 44)			
Total	32 (23, 78)	27 (21, 46)				
	Serum ALT levels, median (Q1, Q3)			0.142	0.873	0.652
Low <268	36 (22, 118)	33 (21, 110)	35 (22, 115)			
High ≥268	32 (20, 77)	32 (18, 57)	32 (20, 58)			
Total	35 (22, 98)	32 (20, 64)				
	Virus infection, n (%)			0.032*	0.573	0.963
Low <268	94 (44)	30 (48)	124 (45)			
High ≥268	18 (29)	68 (32)	86 (31)			
Total	112(40)	98 (35)				

[†]Data were analyzed using a linear regression model. The data are presented as median (Q1, Q3) for the serum AST and ALT levels for each stratified dietary group of folate and choline intake. [*]Statistical significance was set at $p<0.05$.
[‡]The total choline intake of the study subjects was stratified by median level (233 mg) as being low (0< total choline <233 mg) or high (total choline ≥233 mg).
[§]The folate intake of the study subjects was stratified by median level (268 μg) as being the low (0< folate take <268 μg) or high (folate intake ≥268 μg).

taining the liver function markers of the study participants remains elusive. Plasma free choline is proposed to be a specific and relatively sensitive marker of choline consumption; accordingly, it mainly contributes to the status of hepatic choline.[8] A hepatic free choline moiety provides a direct substrate to hepatic PC synthesis for supporting the organelle membrane reconstruction required for regenerating damaged livers.[29] Deprivation of free choline has been demonstrated to impede PC synthesis, promote lipid peroxidation, diminish liver repair capability, and induce programmed cell death in rodenthepatocytes.[30] In particular, exposure to a toxin or hepatitis viral infection deregulated the hepatic PC biosynthesis of HBV-infected mice, resulting in hepatic inflammatory injuries with necrosis and apoptotic cell death.[31] Sufficient free choline intake may be required for the regeneration and repair of liver inflammatory injuries in virus-infected humans. Because hepatitis viral infection was the most critical determinant of serum liver inflammatory markers in the study participants, further research is warranted to investigate whether low free choline intake may increase susceptibility to hepatitis viral-infected liver inflammatory injuries, and, if so, to determine through which mechanism this occurs.

One of the major findings of this study was that the folate intake was the most significant dietary determinant of serum hepatic injury markers, with a stronger effect than choline intake components. Folate intake exceeding the median intake level was associated with normalized serum AST and ALT concentrations, independent of age, sex, choline intake, and plasma homocysteine. The data suggest a prevailing dietary effect of folate intake in maintaining liver function. Several plausible hypotheses may explain this observation. Unlike choline as the conditional essential nutrient, sufficient hepatic folate content greatly depends on dietary provision. Dietary deprivation of folate has been well documented to deplete hepatic folate levels, resulting in elevated oxidative damage, the deregulation of DNA methylation, *p53* genetic aberration, and apoptotic cell death in the liver of rodents.[32,33] Low blood folate and one-carbon genetic polymorphisms were associated with an increased risk of liver injury in humans.[34] Furthermore, for 74% of the virus-infected study participants with seropositive HBV surface antigen, integrating HBV-DNA sequences into the host cell genome may result in chromosomal instability, inhibitory DNA excision repair, and deregulated apoptosis in the target liver.[35] Such chronic HBV infection is accompanied by

Table 4. Logistic regression analysis of liver injury risk stratified by median dietary folate and choline intakes[†‡]

Liver injuries markers	Total folate intake, μg		Total choline intake, mg	
	Low (<268)	High (≥268)	Low (<233)	High (≥233)
Serum AST levels, U/L				
>40 (ref), n	111	71	110	72
<40, n	155	196	155	196
Crude OR, 95% CI	1	0.506 (0.351, 0.729)*	1	0.518 (0.360, 0.745)*
p value		<0.001		<0.001
Multiple adjusted OR, 95% CI	1	0.998 (0.996, 1.00)*	1	1 (0.998, 1.00)
p value		0.042		0.947
Serum ALT levels, U/L				
>40 (ref), n	120	98	117	101
<40, n	146	169	148	167
Crude OR, 95% CI	1	0.706 (0.499, 0.998)*	1	0.765 (0.541, 1.08)
p value		0.049		0.129
Multiple adjusted OR, 95% CI	1	0.998 (0.007, 1.00)*	1	1 (0.999, 1.00)
p value		0.019		0.283

[†]The data were analyzed using the multiple regression method and are presented as crude ORs and multiple adjusted ORs. Adjustable factors include age, sex, folate or choline intake, and serum folate and homocysteine levels. *ORs were considered to be statistically significant in relation to a reference OR of 1 at $p<0.05$.
[‡]Median intake levels of folate and total choline were used as the cut-off point for the low and high intake groups.

inflammatory liver injury, which stimulates central carbon metabolism and nucleotide synthesis for the repair of hepatic lesions.[36] Low folate intake may aggravate dietary demand for the regeneration of lost hepatocytes. That folate intake lower than the median level was associated with a higher rate of hepatitis viral infection and elevated liver injury markers may support this hypothesis.

Notably, dietary intakes of folate and choline appear to be associated with different specific viral hepatitis types. HCV-infected participants had significantly lower intakes of folate and total choline compared with the HBV-infected subjects. The reasons for this discrepancy are unclear. A preliminary study that we conducted found that the HCV group had lower intakes of protein and fat and a higher intake of carbohydrates than did the HBV group, whereas energy consumption did not differ between the two groups (unpublished data). The different dietary intake pattern of macronutrients may partially, if not completely, account for the discrepancy of folate and choline intake among the HBV and HCV groups. Another notable point is that previously reported mutual interactive effects of choline and folate intakes on liver injury[37] were not observed in the present study. The possible reasons for such discrepancies include the different sources of choline and folate-rich food items from various geographic areas, discrepancies in intestinal microbiome action and absorption, and deviation in one-carbon flow and biochemical utilization in response to these variations and betaine intake, one of the choline metabolites acting as the methyl donor in folate-metabolic cycle.[38] Recent studies have reported that the gut microbial metabolism of choline produces trimethylamine, which upon host absorption is converted in the liver to trimethylamine-N-oxide (TMAO), a risk factor for coronary artery disease.[39] Dietary sources of choline and different intestinal microbiota composition may modulate choline bioavailability and accumulation of the proatherogenic TMAO metabolite.[40] How the bioavailability of food choline and folate intake affect liver inflammatory injury among the designated population through microbiota actions and TMAO production warrants further research.

Our findings should be interpreted in the context of several limitations. The most critical limitation is the small sample size, which reduced the statistical power of the subgroup analysis. The insufficient statistical power of the multivariate analysis may render the current results only pilot results. The second limitation is the possibility of errors associated with the use of the qFFQ to conduct dietary assessments. The participants may have misreported their daily intakes or under-estimated portion sizes. In addition, the dietary assessment error induced by using only U.S.-based food composition databases may have generated a potential selection bias engendered through the exclusion of traditionally consumed local food items for which choline data values were unavailable. Excess alcohol consumption is a significant predictor of liver disease; however, participant alcohol intake was not assessed quantitatively. The liver function test as serum AST concentration can be elevated by liver-related illnesses or other diseases such as cardiac disorders. These may marginally influence but not change the main outcomes because our study design excluded people with chronic alcohol use as well as pathological liver and cardiac diseases. A universal HBV vaccination program for infants was launched in Taiwan in 1984,[41] however, this has not meaningfully benefitted the adult population in this study (which had a mean age of 52 years) and thus likely did not affect the potential significance of the current results. Finally, because of the inherent limitations associated with cross-sectional studies, we cannot conclude that low folate and choline intakes have a causal relationship with hepatitis-associated liver injuries.

Despite these limitations, our data provide notable clinical implications. The AI of choline required for the Taiwanese population[42] was first established in 2012. Because studies on choline nutrition in Taiwan are scant, the Choline Panel has determined the AI of choline for Taiwanese adults by multiplying the reference weights of Taiwanese males and females with the value of 7 mg/kg of body weight, as reported to prevent liver dysfunction

in the U.S. population.[12] According to the present results, we propose median choline and folate intakes according to serum hepatic injury markers in Taiwanese adult participants. The median intake values not only encompass the estimated choline AI and folate RDA values but also provide an evidence-based insight to the recommended adequate dietary intake reference values associated with choline for the study population. Future studies on food bioavailability, biochemical markers for choline, and the construction of a Taiwanese choline food data bank are necessary to validate dietary intake reference values. Such data can be used as a reference in the development of health guidelines for nutritional assessment, dietary planning, and food nutrition labels, and are fundamental to nutrition supporting strategies for preventing chronic hepatic diseases.

ACKNOWLEDGEMENTS

The authors thank the study participants for their cooperation and contributions.

AUTHOR DISCLOSURES

None of the authors have any financial or personal conflicts of interest. This study was supported by grants from the Department of Health (DOH-95-TD-F-113–007 and DOH-96-TD-F-113-96003) and the National Science Council of Taiwan, ROC (NSC-99-2320-B-030-005-MY3).

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