

Betel-quid use is associated with heart disease in women¹⁻⁴

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ABSTRACT

Background: Betel quid (*Areca catechu*) is used by $\approx 10\%$ of the world population. Betel-quid use is associated with the metabolic syndrome—a risk factor for heart disease.

Objective: The objective was to test whether betel-quid use is associated with heart disease in adults.

Design: Nonpregnant adults aged 20–64 y ($n = 1932$, 52% women) from the nationally representative Nutrition and Health Survey in Taiwan (1993–1996) were studied for independent associations between betel-quid use and heart disease after adjustment for lifestyle factors, age, obesity, diabetes mellitus, hypertension, and concentrations of serum total cholesterol and HDL cholesterol.

Results: The prevalence of betel-quid use was higher in men than in women (31% compared with 2.4%; $P < 0.001$). The prevalence of heart disease was not significantly different between men and women (3.3% compared with 2.3%; $P = 0.12$). The prevalence of betel-quid use decreased, whereas the prevalence of heart disease increased, with age. Betel-quid users were younger, drank more, had a lower dietary fruit intake, had a higher Framingham risk score, and had higher serum triacylglycerol concentrations than did the nonusers. At a mean consumption rate of 10 times/d (the third quartile of betel-quid consumption in betel-quid users), betel-quid use was independently associated with the Framingham risk score in subjects without heart disease only if obesity was not included as an adjustment factor ($P = 0.007$). Moreover, the daily rate of betel-quid use was independently associated with prevalent heart disease; the odds ratio associated with a betel-quid consumption rate of 10 times/d was 1.37 (95% CI: 1.1, 1.6; $P = 0.003$) in women.

Conclusion: Betel-quid use is independently associated with heart disease in women. *Am J Clin Nutr* 2007;85:1229–35.

KEY WORDS Betel quid, *Areca catechu*, heart disease, Framingham risk score, diabetes, metabolic syndrome

INTRODUCTION

Heart disease is the leading cause of death worldwide (1). Moreover, about one-half of the world's future heart disease burden is predicted to occur in the Asia-Pacific region (2). The cardinal risk factors for heart disease include obesity, hyperlipidemia, hypertension, diabetes mellitus (DM), and smoking (2, 3). In contrast, moderate alcohol drinking may protect against heart disease (4, 5).

Many of the risk factors for heart disease have reached epidemic proportions worldwide. The world population in the year 2000 was 6 billion (6); the global burden of obesity or overweight was 1.3 billion people (7), of hypertension was 1 billion (8), and of DM was 150 million people (9). The number of patients with

DM is predicted to rise to 300 million in the year 2025, the majority of whom will be in Asia (10). Obesity, hypertension, and DM are frequently associated with hypertriglycerolemia and low HDL-cholesterol concentrations—2 conditions that are independently associated with coronary artery diseases (11).

Betel quid (*Areca catechu*), usually chewed in combination with *Piper betle* (inflorescence or leaf) and lime (12), is used by $\approx 10\%$ of the world population, including Taiwan (13). Betel-quid use is associated with the risk of oral cancer, liver cirrhosis, and hepatocellular carcinoma (14, 15). Moreover, we and others have shown that betel-quid use is associated with obesity, hypertension, DM, hyperlipidemia, and the metabolic syndrome (16–18)—the cardinal risk factors for heart disease (2, 3). Indeed, sporadic case reports suggest that betel-quid use may predispose to acute myocardial infarction (19, 20) and cardiac arrhythmias (21).

Therefore, data from the stratified multistage probability-sampled Nutrition and Health Survey in Taiwan (NAHSIT, 1993–1996) (22, 23) was used to study the association between betel-quid use and heart disease in adults.

SUBJECTS AND METHODS

Study population

NAHSIT was a stratified multistage probability-sampled study (22, 23). The detailed procedure of the study was described in our previous study (18). Briefly, Taiwan (with ≈ 21 million inhabitants in 1993–1996) was stratified into 7 strata, and 3 townships in each stratum were selected with the selection probability proportional to the population size of the township. A total of 9961 persons aged 4–96 y were recruited. Nonpregnant adults aged 20–64 y ($n = 3910$) were included in this study. This study

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² The views expressed herein are solely those of the authors.

³ Supported by grant no. DOH93-TD-D-113-021(2) from the Department of Health, Taiwan. NAHSIT was sponsored by the Department of Health in Taiwan (DOH FN8202, DOH-83-FS-41, DOH-84-FS-11, DOH-85-FS-11, and DOH-86-FS-11) and carried out by Wen-Harn Pan (Institute of Biomedical Sciences, Academia Sinica) and Po-Chao Huang (Department of Biochemistry, National Taiwan University).

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Received August 10, 2006.

Accepted for publication December 6, 2006.

was approved by the institutional ethics committee. All NAHSIT enrollees provided written informed consent.

Enrollees who had not received a physical examination or phlebotomy ($n = 970$), who had fasted for <8 h ($n = 148$), who had hemolyzed blood ($n = 109$), or who had missing data on betel-quid use ($n = 42$), smoking or drinking ($n = 93$), DM or hypertension ($n = 31$), blood glucose ($n = 140$), serum biochemistry (total cholesterol, triacylglycerol, and HDL cholesterol) ($n = 649$), or dietary intakes (sodium and protein) ($n = 50$). Thus, the data from a total of 1932 persons were available for analysis in this study. Note that some participants met more than one exclusion criteria.

Interview

The details of the interview and physical examination were described in our previous study (18). Briefly, the household interview and physical examination were completed by trained technicians (23). Dietary intakes for those aged 20–64 y were estimated from a 24-h dietary recall and a food-frequency questionnaire. The food-frequency questionnaire (24) estimated the frequency of intake of 36 food items within 1 mo. The 24-h dietary recall (25) included a recall of foods consumed within the 24 h before the administration of the 24-h dietary-recall questionnaires. Nutrient intakes were calculated from each food item based on the Nutrient Composition Data Bank for Foods of Taiwan Area (26). Intakes of carbohydrate, fat, and protein were expressed as a percentage of daily energy intake.

Smoking was coded as pack-years [packs (20 cigarettes per pack)/d \times years]. Alcoholic drinks in Taiwan were classified into 9 categories according to the concentration of alcohol (27), and alcohol drinking was coded as drink-years (drinks/d \times years). Note that a “drink” was defined as the amount of an alcoholic drink that contains 0.5 oz (13.7 g) of alcohol (5). Alcohol drinking status was classified into nil, moderate (≤ 1 drink/d for women and ≤ 2 drinks/d for men), and heavy (> 1 drink/d for women and > 2 drinks/d for men) (5). Betel-quid use was coded in 2 ways: 1) yes or no and 2) times/d.

Body weight was measured with the use of a weighing scale, while the subjects were wearing light clothing, to the nearest 0.1 kg (18). Body height without shoes was measured to the nearest 0.1 cm in a standing position (18). Waist circumference was measured horizontally with the use of a soft measuring tape at the level of the natural waist, which was identified as the level at the hollow molding of the trunk when the trunk was bent laterally (28).

Blood pressure was measured with a mercury sphygmomanometer after the subjects had rested for 5 min in the supine position (29). Systolic and diastolic blood pressures were recorded as the first and fifth phases of Korotkoff sounds, respectively. Two blood pressure measurements were made 30 s apart. If the 2 measurements differed by > 10 mm Hg, a third measurement was made and the 2 closest readings were averaged. The weighing scale, measuring tapes, and mercury sphygmomanometer were standardized by Bureau of Standards, Metrology and Inspection—authorized agencies initially and at 6-mo intervals (18).

Hypertension was defined as a blood pressure ≥ 140 (systolic)/90 (diastolic) mm Hg, physician-diagnosed hypertension, or current use of antihypertensive agents. DM was defined as a fasting (whole) blood glucose concentration ≥ 110 mg/dL, physician-diagnosed DM, or current use of hypoglycemic agents. Abdominal obesity was defined as a waist circumference > 90 cm in men and a waist circumference > 80 cm in women for

Asians (30, 31). The definition of the metabolic syndrome was modified from that of the National Cholesterol Education Program Adult Treatment Panel III (3, 32), as described in our previous study (18).

Heart disease was defined as an answer of “yes” to the question, “Do you have a physician-diagnosed heart disease?”. Note that “heart disease” in this study refers to prevalent (current) heart disease instead of incident (new onset) heart disease. The Framingham risk score, which was based on sex, age, cholesterol, HDL cholesterol, blood pressure, DM, and smoking, was calculated to provide an estimate of 10-y coronary risk (33) in NAHSIT participants without heart disease.

Measurements

Fasting whole-blood glucose was measured by using the glucose oxidase method (portable model 23A; YSI Co., Taipei, Taiwan) immediately after blood was drawn. Fasting morning blood samples were drawn and centrifuged ($1000 \times g$, 15 min, 4 °C) on site (18). Serum was stored at -70 °C until total cholesterol, HDL-cholesterol, and triacylglycerol concentrations were measured (Hitachi 747 autoanalyzer; Hitachi, Tokyo, Japan) (18).

Statistics

The statistical package STATA (version 8.2; Stata Corp, College Station, TX) was used. The data were expressed as means \pm SEMs. Statistical significance was defined as a P value < 0.05 ; otherwise, it was defined as nonsignificant.

The weighted “svy” or “robust” commands were used to account for the probability sampling weight, complex survey design, and stratification (34) in NAHSIT. The differences between 2 continuous variables were compared by unpaired t tests. The differences between 2 categorical variables were compared by chi-square tests. The differences between 2 nonnormally distributed variables (Framingham risk score and dietary intakes of cholesterol, sodium, and fruit) were compared by using nonparametric median tests. Linear regression analysis was used to test for the association of demographic and lifestyle variables, other than those used to estimate Framingham risk scores, with the Framingham risk score. Logistic regression analysis was used to test for the association of demographic and lifestyle variables with heart disease. Data were analyzed separately for men and women when there was a significant interaction between sex and the independent variables. Trend tests (18) for alcohol drinking status were also performed.

Note that a confounder is defined as a factor associated with both exposure (betel-quid use in this case) and outcome (Framingham risk score or heart disease in this case) (35). Abdominal obesity, alcohol drinking, and dietary fruit intake are all associated with both betel-quid use (18) and the Framingham risk score (5) and, therefore, are confounders to be adjusted in linear regression analyses. In contrast, variables of the Framingham risk score (sex, age, hypertension, DM, smoking, and concentrations of serum total cholesterol and HDL cholesterol) (33), abdominal obesity, alcohol drinking, and dietary fruit intake are all associated with both betel-quid use (18) and heart disease (5) and, therefore, are confounders to be adjusted in logistic regression analyses.



TABLE 1

Demographic characteristics of NAHSIT (Nutrition and Health Survey in Taiwan) participants who did or did not use betel quid, by sex¹

Betel-quid use	Men		Women		P ²
	Betel-quid use (n = 277)	No betel-quid use (n = 619)	Betel-quid use (n = 79)	No betel-quid use (n = 957)	
Age (y)	36 ± 0.8 ³	39 ± 0.6	34 ± 5	38 ± 0.4	NS/0.007
Smoking (pack-years) ⁴	12 ± 1	5.4 ± 0.4 ⁵	1.6 ± 0.8	0.1 ± 0.04	< 0.001/—
Alcohol drinking (drink-years)	40 ± 10	10 ± 3	18 ± 10	0.1 ± 0.02	< 0.001/0.01
Alcohol drinking status (%) ⁶					< 0.001/< 0.001
Nil	23	54	30	88	
Moderate	32	36	38	11	
Heavy	45	10	32	1	
Framingham risk score (%) ^{7,8}	4 (4)	2 (5)	2 (1)	1 (1)	< 0.001/0.01
Heart disease (%)	1.5	3.5	3.2	2.3	NS/NS
Abdominal obesity (%)	9.2	10.9	16	16.4	0.03/NS
Diabetes mellitus (%)	3.8	3.7	2	4	NS/NS
Hypertension (%) ⁴	22	26	39	16 ⁹	NS/—
Metabolic syndrome (%)	11	9	6.7	9.8	NS/NS
Cholesterol (mg/dL)	192 ± 4	193 ± 3	186 ± 8	186 ± 3	0.01/NS
Triacylglycerol (mg/dL)	145 ± 9	120 ± 9	107 ± 10	94 ± 5	< 0.001/0.001
HDL cholesterol (mg/dL)	55 ± 1	54 ± 2	66 ± 4	61 ± 1	< 0.001/NS
Carbohydrate intake (% of energy)	52 ± 2	54 ± 1	45 ± 5	52 ± 2	NS/NS
Fat intake (% of energy)	29 ± 1	28 ± 1	36 ± 1	32 ± 1	0.004/NS
Cholesterol intake (g/d) ⁸	0.27 (0.34)	0.28 (0.3)	0.27 (0.5)	0.2 (0.25)	0.001/NS
Protein intake (% of energy)	15 ± 0.8	16 ± 0.2	17 ± 1	16 ± 0.4	NS/NS
Sodium intake (g/d) ⁸	2.8 (2.6)	2.9 (2.9)	2 (0.3)	2 (2.3)	NS/NS
Vegetable intake (times/wk)	25 ± 2	27 ± 1	28 ± 3	28 ± 2	0.01/NS
Fruit intake (times/wk) ⁸	3 (6)	6 (6)	4 (7)	7 (5)	0.01/0.01

¹ Fasting morning blood samples were drawn and centrifuged on site. Serum was stored at -70 °C until analyzed within a month for total cholesterol, triacylglycerol, and HDL-cholesterol concentrations with the use of a Hitachi 747 autoanalyzer (Hitachi, Tokyo, Japan). The differences between continuous variables (except Framingham risk score and dietary intakes of cholesterol, sodium, and fruit) were tested by using unpaired *t* tests. The differences between categorical variables were tested by using chi-square tests.

² Men compared with women/betel-quid use yes compared with no.

³ $\bar{x} \pm \text{SEM}$ (all such values).

⁴ *P* < 0.05 for the interaction between sex and betel-quid use.

⁵ *P* < 0.001.

⁶ Classified as nil, moderate (≤ 1 drink/d for women) and ≤ 2 drinks/d for men), or heavy (> 1 drink/d for women and > 2 drinks/d for men).

⁷ Calculated only for NAHSIT participants without heart disease.

⁸ All values are medians (interquartile range, ie, the difference between the third and first quartiles in parentheses) and were compared by using nonparametric median tests because of nonnormal distribution.

^{5,9} Significantly different from betel-quid use when the sex \times betel-quid use interaction was significant: ⁵*P* < 0.001, ⁹*P* < 0.01.

It requires ≥ 10 cases (of heart disease in this instance) for each independent variable in a logistic regression model (36). Moreover, subgroup analyses should only be performed when statistical tests of interaction are significant (37). Thus, to assess the independent effect of betel-quid use on heart disease, we analyzed all participants (*n* = 1932) with an interaction term (sex by betel-quid use) in which the number of outcomes (heart disease) was 127 and the number of independent variables was 11.

RESULTS

Demographic characteristics of NAHSIT enrollees, by participation

The recruitment rate was 49.4% (1932/3910) of those approached. There was a lower percentage of men in the participants' subgroup than in the nonparticipants' subgroup (48% compared with 54%; *P* = 0.005). Moreover, the participants were older than the nonparticipants (39 ± 0.4 compared with 37 ± 0.4 y; *P* = 0.002).

In contrast, there were no differences in betel-quid use, smoking, alcohol drinking, and heart disease between the participants and the nonparticipants. Note that the Framingham risk score, obesity, hypertension, DM, dietary intakes, and concentrations of serum cholesterol, triacylglycerol and HDL cholesterol could not be compared between the participants and nonparticipants because most of the nonparticipants did not provide these data.

Prevalence of betel-quid use and heart disease in NAHSIT participants, by sex and age

The overall (weighted) prevalence of betel-quid use was 16.9%, which was higher in men than in women (31% versus 2.4%, *P* < 0.001). In contrast, the crude prevalence of betel-quid use was 30.9% (277/896) and 7.6% (79/1036) in men and women (Table 1), respectively. The overall (weighted) prevalence of heart disease was 2.8%, which was not significantly different between men and women (3.3% compared with 2.3%; *P* = 0.12). In contrast, the crude prevalence of heart disease was 5.2%



TABLE 2Demographic characteristics of NAHSIT (Nutrition and Health Survey in Taiwan) participants with and without prevalent heart disease¹

Heart disease	Heart disease		P ²
	Yes (n = 47 M, 80 F)	No (n = 849 M, 956 F)	
Age (y)	53 ± 1 ³	38 ± 0.4	< 0.001
Smoking (pack-years)	6 ± 2.5	3.8 ± 0.3	NS
Alcohol drinking (drink-years)	9.6 ± 7	7 ± 2	NS
Alcohol drinking status ⁴			NS
Nil	67	65	
Moderate	27	27	
Heavy	6	8	
Betel-quid use (%)	10.8	17.3	NS
Abdominal obesity (%)	40	13	< 0.001
Diabetes mellitus (%)	17.7	3.6	0.002
Hypertension (%) ⁵			
Men	53	24	0.02
Women	71	15	< 0.001
Metabolic syndrome (%)	27	9.3	< 0.001
Total cholesterol (mg/dL)	202 ± 5	189 ± 2	0.03
Triacylglycerol (mg/dL)	128 ± 12	110 ± 4	0.03
HDL cholesterol (mg/dL)	54 ± 3	58 ± 1	NS
Carbohydrate intake (% of energy)	55 ± 2	53 ± 1	NS
Fat intake (% of energy)	27 ± 2	30 ± 1	NS
Cholesterol intake (g/d) ⁶	0.17 (0.27)	0.25 (0.31)	NS
Protein intake (% of energy)	18 ± 1	16 ± 4	NS
Sodium intake (g/d) ⁶	2.4 (2.4)	2.8 (2.6)	NS
Vegetable intake (times/wk)	25 ± 1	27 ± 2	NS
Fruit intake (times/wk) ⁶	5.5 (8)	3.5 (9)	NS

¹ Fasting morning blood samples were drawn and centrifuged on site. Serum was stored at -70 °C until analyzed within a month for total cholesterol, triacylglycerol, and HDL-cholesterol concentrations with the use of a Hitachi 747 autoanalyzer (Hitachi, Tokyo, Japan).

² The differences between continuous variables (except Framingham risk score and dietary intakes of cholesterol, sodium, and fruit) were tested by using unpaired *t* tests. The differences between categorical variables were tested by using chi-square tests.

³ $\bar{x} \pm \text{SEM}$ (all such values).

⁴ Classified as nil, moderate (≤ 1 drink/d for women and ≤ 2 drinks/d for men), and heavy (> 1 drink/d for women and > 2 drinks/d for men).

⁵ The data were reported separately for men and women when there was a significant interaction between sex and heart disease.

⁶ All values are medians (interquartile range, ie, the difference between the third and first quartiles, in parentheses) and were compared by using nonparametric median tests because of nonnormal distribution.

(47/896) and 7.7% (80/1036) in the men and women, respectively (**Table 2**). The (weighted) prevalence of heart disease was 1.8% in betel-quid users. In contrast, the crude prevalence of heart disease in betel-quid users was 7.3% (26/356). Additionally, among betel-quid users, there were 10 men and 16 women. Moreover, the prevalence of betel-quid use decreased ($P = 0.01$), whereas the prevalence of heart disease increased ($P = 0.001$) with increasing age in both sexes (data not shown).

Demographic characteristics of NAHSIT participants, by sex and betel-quid use

As shown in Table 1, smoking, alcohol drinking, Framingham risk score, serum total cholesterol and triacylglycerol concentrations, and dietary cholesterol intake were higher in men than in women. Conversely, the prevalence of abdominal obesity, serum HDL-cholesterol concentrations, and dietary intakes of fat, vegetable, and fruit were lower in men than in women. In contrast, there were no differences in age, DM, and the metabolic syndrome between men and women.

Betel-quid users were younger than the nonusers. Additionally, both male and female betel-quid users drank more, had a higher Framingham risk score and serum triacylglycerol concentration, and had a lower intake of dietary fruit intake than did the nonusers. Interestingly, male but not female betel-quid users smoked more than did the nonusers. In contrast, female but not male betel-quid users had a higher prevalence of hypertension than did the nonusers. Conversely, there were no differences in serum concentrations of total cholesterol and HDL cholesterol, dietary intakes other than fruit, and the prevalence of heart disease, abdominal obesity, DM, and the metabolic syndrome between the betel-quid users and the nonusers in either sex.

Demographic characteristics of NAHSIT participants with and without heart disease

As shown in Table 2, the participants with heart disease were older, had higher serum total cholesterol and triacylglycerol concentrations, and had a higher prevalence rate of abdominal obesity, DM, hypertension, and the metabolic syndrome than did those without heart disease. In contrast, there were no differences in betel-quid use or in any of the dietary intakes between participants with and without heart disease.

Association of the demographic and lifestyle factors with the Framingham risk score in NAHSIT participants in a linear regression analysis

As shown in **Table 3**, betel-quid use (yes or no) was positively associated with the Framingham risk score, whereas the daily rate of betel-quid use was positively associated with the Framingham risk score only in participants without heart disease. Note that there were no interactions between sex, heart disease, and betel-quid use.

In the multivariate analysis, the effect of betel-quid use was adjusted for abdominal obesity, dietary fruit intake, and alcohol drinking. We found that betel-quid use [yes or no: 1.76 ± 0.5 (coefficient \pm SEM); $r = 0.33$, $P = 0.004$], but not the daily rate of betel-quid use (0.25 ± 0.13 ; $r = 0.31$, $P = 0.08$) was independently and positively associated with the Framingham risk score. However, the daily rate of betel-quid use was independently and positively associated with the Framingham risk score if we excluded abdominal obesity from the adjustment factors (0.46 ± 0.14 ; $r = 0.1$, $P = 0.007$). Note that there were no interactions between sex, heart disease, and betel-quid use in the above multivariate analyses.

As shown in Table 3, abdominal obesity was positively associated with the Framingham risk score, but dietary intakes of carbohydrate and fat were associated positively and negatively with the Framingham risk score, respectively, only in women. In contrast, alcohol drinking was positively associated with the Framingham risk score in participants with heart disease, whereas alcohol drinking was associated positively and negatively with the Framingham risk score in men and women, respectively, in participants without heart disease. However, alcohol drinking status (nil, moderate, or heavy) was not associated with the Framingham risk score.

Association of betel-quid use with prevalent heart disease in a multiple logistic regression analysis

The effect of betel-quid use was adjusted for sex, age, abdominal obesity, concentrations of serum total cholesterol and HDL

TABLE 3

Association of the demographic and lifestyle factors with Framingham risk scores in NAHSIT (Nutrition and Health Survey in Taiwan) participants¹

	Framingham risk score	
	Coefficient (95% CI)	P
Betel-quid use (yes or no)	1.5 (0.7, 2.3)	0.001
Daily rate of betel-quid use (10 times/d), heart disease present ²	-1.8 (-4.3, 0.7)	NS
Daily rate of betel-quid use (10 times/d), heart disease absent ²	0.54 (0.28, 0.8)	0.001
Abdominal obesity (yes or no)	5.2 (3.6, 6.8)	< 0.001
Alcohol drinking (drink-years), heart disease present ³	0.01 (0.008, 0.013)	0.001
Alcohol drinking (drink-years), heart disease absent ³		
Men	0.009 (0.002, 0.02)	0.02
Women	-0.008 (-0.02, -0.0001)	0.047
Alcohol drinking status ^{3,4}	-0.01 (-0.14, 0.12)	NS ⁵
Carbohydrate intake (% of energy) ⁶		
Men	-1.86 (-6, 2.5)	NS
Women	3.3 (2, 4.6)	< 0.001
Fat intake (% of energy) ⁶		
Men	2.5 (-2, 6)	NS
Women	-2.9 (-3.7, -2)	< 0.001
Cholesterol intake (g/d)	-0.19 (-0.95, 0.6)	NS
Protein intake (% of energy)	-0.48 (-5.7, 4.7)	NS
Sodium intake (g/d)	0.006 (-0.06, 0.07)	NS
Vegetable intake (times/d)	-0.005 (-0.03, 0.02)	NS
Fruit intake (times/d)	-0.02 (-0.06, 0.02)	NS

¹ *n* = 1932 (*n* = 47 men and 80 women with heart disease; *n* = 849 men and 956 women without heart disease). Linear regression analysis was used to assess the association between independent (demographic and lifestyle factors) and dependent (Framingham risk score) factors.

² The data were reported separately for participants with and without prevalent heart disease for the independent variable when there was a significant interaction between heart disease and that independent variable.

³ The data were reported separately for men and women with and without prevalent heart disease for the independent variable when there was a significant interaction between sex, heart disease, and that independent variable.

⁴ Classified as nil, moderate (≤ 1 drink/d for women and ≤ 2 drinks/d for men), and heavy (> 1 drink/d for women and > 2 drinks/d for men).

⁵ *P* for linear trend.

⁶ The data were reported separately for men and women for the independent variable when there was a significant interaction between sex and that independent variable.

cholesterol, hypertension, DM, smoking, alcohol drinking, and dietary fruit intake. As shown in **Table 4**, betel-quid use was not associated with prevalent heart disease when analyzed as a categorical variable (yes or no) in either sex. However, betel-quid

use was independently and positively associated with prevalent heart disease when analyzed as a continuous variable only in women (OR associated with a betel-quid consumption rate of 10 times/d: 1.37; 95% CI: 1.1, 1.6; *P* = 0.003). Note that a betel-quid consumption rate of 10 times/d was chosen because it was the third quartile of betel-quid consumption in betel-quid users. There were no interactions between age and betel-quid use in the above analyses.

TABLE 4

Association of betel-quid use with prevalent heart disease in multiple logistic regression analysis in NAHSIT (Nutrition and Health Survey in Taiwan) participants¹

Betel-quid use	Odds ratio (95% CI)	P
Yes or no ²		
Men	0.2 (0.02, 2.4)	NS
Women	2.6 (0.7, 10)	NS
Daily rate, 10 times/d ³		
Men	0.5 (0.14, 1.9)	NS
Women	1.37 (1.1, 1.6)	0.003

¹ *n* = 1932 (*n* = 896 men and *n* = 1036 women). Multiple logistic regression analysis was used to assess the effect of betel-quid use on prevalent heart disease after adjustment for sex, age, abdominal obesity, concentrations of serum total cholesterol and HDL cholesterol, hypertension, diabetes mellitus, smoking, alcohol drinking, and dietary fruit intake.

² *P* = 0.03 for interaction between sex and betel-quid use (yes or no).

³ *P* = 0.01 for interaction between sex and the daily rate of betel-quid use. A daily consumption rate of (10 times/d) was chosen because it was the third quartile of betel-quid consumption in betel-quid users.

DISCUSSION

We found that betel-quid use is associated with heart disease and the Framingham risk score in women. This finding extends our previous finding that betel-quid use is associated with the metabolic syndrome in adults (18). In view of the large world population that uses betel quid (13) and the effect of heart disease on global health (1), these findings have important implications.

In this study, the prevalence of heart disease was not significantly different between sexes. However, there were many imbalances of heart disease risk factors between the sexes. Thus, data were analyzed separately for men and women whenever necessary.

In NAHSIT participants without heart disease, the daily rate of betel-quid use was independently associated with the Framingham risk score only after abdominal obesity was excluded from

the adjustment factors. Thus, abdominal obesity may be an intermediate variable along the causal pathway between betel-quid use and the Framingham risk score, not needing to be adjusted for (35).

Alcohol drinking was associated positively with the Framingham risk score in participants with heart disease. In contrast, alcohol drinking was associated positively and negatively with the Framingham risk score in men and women, respectively, in participants without heart disease. However, alcohol drinking was associated negatively with the Framingham risk score in women regardless of heart disease ($P = 0.015$), but not in men ($P = 0.2$), only after adjustment for serum creatinine concentration—a heart disease risk factor (38) (data not shown). This observation is different from the notion that moderate, but not heavy, alcohol drinking, is negatively associated with the risk of coronary heart disease (39). However, this observation is consistent with that of a recent study, which showed that alcohol drinking is linearly and negatively associated with the risk of coronary heart disease in women (4).

In contrast, alcohol drinking was not associated with prevalent heart disease. This observation is consistent with the finding of an international case-control study (including Chinese participants), which showed that alcohol drinking is not associated with acute myocardial infarction after adjustment for multiple risk factors (40).

In the univariate analysis, the prevalence of heart disease was not different between betel-quid users and nonusers in men and women, despite the imbalances of some of the heart disease risk factors with sex. Moreover, the prevalence of betel-quid use decreased with age, whereas the prevalence of heart disease increased with age. Thus, the role of betel-quid use in heart disease was analyzed by multiple logistic regression analysis after adjustment for the multiple heart disease risk factors assessed, and we found that the daily rate of betel-quid use, but not betel-quid use (yes or no), was independently associated with prevalent heart disease in women.

The sex-specific effect of betel-quid use was also observed in a previous study, which showed that betel-quid use was associated with hyperglycemia only in women (17), although a recent large community-based study showed that betel-quid use was associated with hyperglycemia in both sexes (16). Similarly, transient hyperglycemia in DM increases the glomerular filtration rate only in women (41). Interestingly, DM and hypertension are greater risk factors for heart disease in women than in men (42). Moreover, women have a higher resting heart rate than do men (42), a heart disease risk factor (43), which is further increased by betel-quid use (44).

There are several possible mechanisms for the association between betel-quid use and heart disease. The first 2 mechanisms relate to the fact that betel quid contains substances with both sympathetic and parasympathetic activities (44). First, betel-quid activates the sympathetic nervous system (44), which is a heart disease risk factor (45) associated with obesity (46), hypertension (47), and the metabolic syndrome (48)—the cardinal heart disease risk factors (2, 3). Other adverse cardiovascular effects of sympathetic activation include reduced vascular conductance, impaired baroreflex buffering, and decreased heart responsiveness to β -adrenergic stimulation, etc (49).

Second, there is a harmonious vagosympathetic interaction in normal cardiac autonomic regulation, whereas a high activity of the heart from both autonomic systems may be arrhythmogenic

(50). Moreover, *Piper betle* inflorescence extract, chewed in combination with *Areca catechu* nut in betel quids, also activates both cardiac autonomic systems in rats (51).

Finally, betel-quid use is associated with obesity, hypertension, hypertriglycerolemia, DM, and the metabolic syndrome (16–18)—the heart disease risk factors (2, 3). Note that although betel-quid use was not associated with abdominal obesity or the metabolic syndrome in the univariate analysis, the daily rate of betel-quid use was associated with abdominal obesity and metabolic syndrome in multivariate analysis both in the present study (data not shown) and our previous study (18).

This study and all secondary analyses had several limitations (52). First, being a secondary analysis, sampling and measurement issues were inevitable (52). However, NAHSIT was a nationally representative study, whereas there was no selection bias associated with participation other than sex and age, which were adjusted for in the multivariate analyses. Moreover, all relevant measurements were made with standard methods. Second, disease (heart disease in this case) was defined by the participant's recall and not by using gold-standard diagnoses. Third, because this was a cross-sectional study, causality could not be established. Finally, it is not known whether the subjects changed their diets after having been diagnosed with heart disease. However, this event is unlikely because betel-quid use was not a known risk factor for heart disease in 1993–1996. We conclude that, although men used more betel-quid chews than women, betel-quid use is independently associated with heart disease only in women. 

The assistance provided by Academia Sinica with the data distribution was greatly appreciated.

The authors' responsibilities were as follows—J-YG: design and analysis of the study; H-CC: data collection and analysis; J-FT: statistical analyses; L-YC: fund raising and collaborative analysis of the study. All authors reviewed and approved the final manuscript. None of the authors had a conflict of interest.

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