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ORIGINAL PAPER

Areca nut chewing is associated with common mental disorders: a population-based study

Tzu-Yu Lin[1] · Huan-Cheng Chang[2,3] · Kuang-Hung Hsu[1,3,4]

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Abstract

Introduction Forms of habitual substance use including cigarette smoking and alcohol consumption have been documented as risk factors of common mental disorders (CMDs). The effects of areca nut chewing on biophysiological tests, metabolic syndromes, and liver function have been reported previously; however, the relationship between areca nut chewing and CMDs remains unclear. This study examined the association between areca nut chewing and CMDs and explored the relationships between areca nut chewing and biophysiological indicators.

Methods A total of 4477 community dwellers who had enrolled in a cohort study and participated in health examinations in 2 consecutive years were selected for analysis in the present study. The community cohort was established in northern Taiwan during 2006–2012. The Chinese health questionnaire (CHQ-12) was used as a self-reported screening instrument to assess the potential for developing psychotic mental disorders (CHQ-12 score ≥ 3) among the community residents. Biophysiological tests performed 1 year before CMD assessment were analyzed to examine the causal pathways between areca nut chewing and CMDs. Multiple logistic regression and stratified analyses were performed.

Results A total of 18.23% of the participants were diagnosed as having CMDs. Factors including areca nut chewing [odds ratio (OR) 1.828; 95% confidence interval (CI) 1.165–2.869], sex (women; OR 1.828; 95% CI 1.165–2.869), age (30–49; OR 1.302; 95% CI 1.073–1.579), and socioeconomic status (lower status; OR 1.373; 95% CI 1.084–1.738) were associated with CMDs in a multiple logistic regression model. Areca nut chewers exhibited significantly more triglycerides (220.04 vs. 124.16 mg/dL) and white blood cells (65.17 102/μL vs. 60.36 102/μL) and significantly higher diastolic blood pressure (78.83 vs. 75.84 mmHg) and glutamic oxaloacetic transaminase (30.30 vs. 25.45 U/L) than did the controls.

Conclusions This study demonstrated the association between areca nut chewing and CMDs and its effects on biophysiological tests in a community-based population in Taiwan. The findings suggest the existence of mechanistic effects of areca nut chewing on CMDs exerted through multiple pathways that may interact with pre-existing biophysiological abnormalities. Lifestyle variables should be considered for the prevention and management of mental disorders in the future.

Keywords Common mental disorders · Areca nut chewing · Biophysiological tests · Community cohort · Population-based study

Introduction

The global population of areca nut chewers is between 600 and 1200 million people, most of whom are from Asian countries and Austronesian and Austroasiatic populations

Tzu-Yu Lin and Huan-Cheng Chang contributed equally to this paper.

✉ Kuang-Hung Hsu
khsu@mail.cgu.edu.tw

[1] Healthy Aging Research Centre, Chang Gung University, Taoyuan, Taiwan

[2] Division of Family Medicine, Taiwan Landseed Hospital, Taoyuan, Taiwan

[3] Department of Health Care Management, College of Management, Chang Gung University, No. 259, Wen-Hwa 1st Road, Kwei-Shan, Taoyuan 333, Taiwan

[4] Department of Urology, Chang Gung Memorial Hospital, Taoyuan, Taiwan

[1–3]. Approximately, 2.5 million Taiwanese people are estimated to habitually engage in areca nut chewing. The majority of these people are men [3]. Areca nut chewing is considered as a culturally appropriate habit that is beneficial for ritual ceremonies, therapy, stamina, and digestion in Asia [4]. Previous literatures have documented the causality between areca nuts chewing and oral cancer. However, many studies have demonstrated adverse effects on non-cancer diseases, such as increased risks of systemic inflammation, obesity, metabolic syndromes (MSs), diabetes mellitus (DM) type 2, hypertension, liver disorders, cardiovascular diseases (CVDs), and all-cause mortality [2, 5–7]. Moreover, one study reported an association between areca nut chewing and the risk of chewers' offspring developing MSs [8].

According to previous studies, arecoline (along with other three alkaloids: guvacine, arecaidine, and guvacoline) is hazardous to human health. Guvacine and arecaidine, are hydrolyzed derivatives of guvacoline and arecoline, respectively, and can stimulate the autonomic nervous system and central nervous system (CNS) but inhibit gamma-aminobutyric acid (GABA) uptake, thereby affecting the parasympathetic nervous system [3]. In addition, both arecoline and arecaidine per se could affect the release of catecholamine through the GABA pathway, in which dopamine is a neurotransmitter that exerts euphoric effects on the brain [2, 9–12]. Further CNS reactive evidence has been found in some psychiatry studies, which have reported that areca nut may act as an antidepressant agent and may reduce symptoms in patients with schizophrenia [4, 13–15]. In addition, a synergistic effect on mental disorders was observed among psychiatric patients who simultaneously consumed tobacco and alcohol [4, 13, 15]. Therefore, common mental disorders (CMDs) are a crucial consideration in examining the adverse mental outcomes caused by areca nut chewing.

The worldwide prevalence of CMDs is increasing. According to statistics, the prevalence was 18.6 and 12.3% among US and Taiwanese adults in 2012, respectively [16, 17]. CMDs may affect general health, mortality, and the financial burden on health care systems. People with CMDs are more likely to suffer from chronic diseases such as CVDs, diabetes, MSs, and hyperlipidemia [4, 18–20]. People with CMDs may experience various mechanisms of neurovegetative syndromes, oxidative stress, and inflammation processes that share biopathways with MS prognoses. In addition to inflammation, lipid metabolism, presented as lipidemia profile, was associated with mental disorders such as depression [21], problematic conduct such as violent behaviors [22, 23], and suicide attempts [24] through the mechanism of CNS influence.

CMDs were more likely to occur among specific high-risk groups including women, elderly people, single people, and people with low educational levels. In addition, adverse habitual behaviors including cigarette smoking, alcohol consumption, caffeine consumption, and areca nut chewing have been associated with physical and mental illness [25–29]. A general prescription for patients with severe mental illness is to modify the habitual behaviors that characterize their lifestyles [30].

Most related studies have indicated that addiction to areca nut chewing may be associated with poor physical health or oral cancer. Studies on the effect of areca nut chewing on CMDs among the general population are still limited and further investigations are warranted. The present study examined the association between areca nut chewing and CMDs and explored the biophysiological indicators related to areca nut chewing.

Methods

Study design and sample size

This study adopted a community cohort design and was conducted in Pingzhen District, Taoyuan City, Taiwan. Pingzhen has a population of approximately 210,710; the most common ethnicity is Hakka, followed by Fukien, mainland Chinese, and aboriginals. The study cohort consisted of a probability proportionate to size sample of 5881 participants aged ≥ 30 years randomly selected from 18 of 46 villages in Pingzhen during 2006–2012. The distributions of age, race, and socioeconomic status among all the participants were similar to those of the corresponding resident populations of the 18 study villages.

A total of 4497 participants who participated in 2 consecutive years of examination were eligible for this study. After eliminating 20 participants with incomplete data from biophysiological tests or CMD assessments, 4477 participants were analyzed in this study. All the study participants provided written informed consent and agreed to participate in this study.

Outcome measurement

CMDs

Considering cultural differences, Cheng and Williams (1986) originally developed a 12-item version of the CHQ-12 to adapt the questionnaire for relevance to Chinese culture, thereby assisting the Taiwanese population in completing the questionnaire [31]. The CHQ-12 evolved from the GHQ and contained four dimensions: anxiety, depression, sleep disturbance, and additional somatic symptoms. The CHQ-12 was used as a self-reported screening instrument to assess potential nonpsychotic mental disorders among community residents. Participants rated the frequency of experiencing each minor mental symptom during the preceding

2 weeks. Each item was scored using a 4-point Likert scale (0 = not at all, 1 = same as usual, 2 = a little more frequently than usual, and 3 = much more frequently than usual). The instrument score was calculated based on the literature and ranged from 0 to 12. A higher score indicated more severe psychiatric morbidity. Participants with a CHQ-12 score of ≥ 3 were defined as having CMDs. This instrument has excellent internal consistency for community populations, with a Cronbach's α coefficient of 0.84 and sensitivity and specificity rates of 79.7 and 83.6%, respectively [32, 33].

Study variables

The dependent variable of this study was dichotomized into CMD (CHQ-12 score ≥ 3) and no CMD (CHQ-12 score < 3). The independent variable, areca nut chewing, was defined according to each individual's current and previous habits of areca nut chewing and classified into current, ever, and never behaviors. The confounding factors included sociodemographic characteristics, lifestyle habit factors, health status, and biophysiological test results. The sociodemographic characteristics were sex, age, educational level, marital status, and personal income. Socioeconomic status was categorized into four levels of education and personal income: low education/low income, low education/high income, high education/low income, and high education/high income. "Age of enrollment" was defined as the participant's age at the time of enrollment in this study. The lifestyle variables were dietary habits, cigarette smoking, alcohol consumption, physical activity, and caffeinated beverage consumption (coffee or tea). Dietary habits were defined based on whether the participant was a vegetarian or not. The lifestyle variables were dichotomized into current consumers and noncurrent consumers, including never experienced and quit behaviors. Health status was defined using biophysiological test results and self-reported disease histories collected 1 year before CMD assessment.

Statistical analysis

The categorical variables are presented as frequencies and percentages in this study. An independent sample *t* test was conducted to examine the bivariate association between CMDs and numerical variables or categorical variables. Multiple logistic regression analysis was performed to determine the association between CMDs and the study variables, including demographic information, lifestyle habits, and health status. The model selection strategy of multiple logistic regression analysis was based on univariate tests and backward selection. The multivariate-adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were analyzed. Stratified analyses were conducted to identify biophysiological tests associated with the pathway between areca nut chewing and CMDs. A two-sided p value of < 0.05 was considered statistically significant. These analyses were performed using SAS for Windows, version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 4477 participants were included in the analysis, of whom 816 (18.23%) were classified as having CMDs. A total of 111 (2.48%) participants reported as current areca nut chewers. The average length of areca nut use was 20.39 years and the average age of first use was 24.68 years. The areca nut chewers were frequently seen as women ($n = 106$, 95.50%), adults age under 50 years old ($n = 76$, 68.47%), and lower than senior high school graduated ($n = 92$, 82.88%) (Table 1). The chewers were also associated with other lifestyle factors, including non-vegetable favorers ($n = 59$, 53.15%), alcohol consumption ($n = 63$, 56.76%), less physical activity ($n = 61$, 54.95%), and frequent tea consumption ($n = 82$, 73.87%). In addition, areca nut chewing behavior was positively associated with the prevalence of CMDs ($p = 0.05$) and MSs ($p < 0.0001$). The areca nut chewers had a higher level of biophysiological tests such as cholesterol, TG, SBP, DBP, GOT, and WBC, compared to the nonchewing group (Table 2).

Multiple logistic regression analysis demonstrated that sex, age, socioeconomic status, and areca nut chewing were significantly associated with CMDs (Model I). Women were more likely than men to have CMDs (OR 1.428; 95% CI 1.179–1.730). Regarding educational level and income, participants of low education and low income had the highest risk of developing CMDs (OR 1.341; 95% CI 1.057–1.702). Regarding adverse habitual behaviors, areca nut chewers were at a higher risk of developing CMDs (OR 1.779; 95% CI 1.120–2.825). A reduced model (Model II) including only the significant variables in Model I demonstrated similar results. A stronger association was observed between areca nut chewing and CMDs (OR 1.828; 95% CI 1.165–2.869) in Model II than in Model I. Most areca nut chewers were men. Model III analyzed the data on men participants; age, socioeconomic status, and areca nut chewing were significant factors associated with CMDs (Table 3).

Figure 1 presents the significant effects of areca nut chewing on various aspects of biophysiological tests including triglycerides (TGs), diastolic blood pressure (DBP), glutamic oxaloacetic transaminase (GOT), and white blood cells (WBCs). Areca nut chewers had significantly more TGs (220.04 mg/dL vs. 124.16 mg/dL) and WBCs (65.17 $10^2/\mu L$ vs. 60.36 $10^2/\mu L$) and significantly higher DBP (78.83 mmHg vs. 75.84 mmHg) and GOT (30.30 U/L vs. 25.45 U/L) than did the controls (Fig. 1).

Table 1 Sociodemographic characteristics of study participants stratified by areca nut chewing group

Variables	Total ($n=4477$)		Areca nut chewers[a]				p value
			Others ($n=4366$)		Yes ($n=111$)		
	Number	%	Number	%	Number	%	
Sociodemographic characteristics							
Gender							**< 0.01**
Female	2479	55.37	2474	56.67	5	4.50	
Male	1998	44.63	1892	43.33	106	95.50	
Age							**< 0.01**
30–49	1890	42.22	1814	41.55	76	68.47	
50–59	1426	31.85	1400	32.07	26	23.42	
≧ 60	1161	25.93	1152	26.39	9	8.11	
Marital status							0.47
Married	4002	89.39	3,900	89.33	9	8.11	
Others	475	10.61	466	10.67	102	91.89	
Education level							**0.05**
College or above	1036	23.14	1017	23.29	19	17.12	
Senior high school	1412	31.54	1364	31.24	48	43.24	
Junior high school or lower	2003	44.74	1959	44.87	44	39.64	
Unknown	26	0.58	26	0.60	0	0.00	
Personal yearly income (USD)[b]							**< 0.01**
Unknown	391	8.73	385	8.82	6	5.41	
< 10,000	2525	56.4	2487	56.96	38	34.23	
10,000–25,000	1143	25.53	1095	25.08	48	43.24	
25,001–33,333	298	6.66	283	6.48	15	13.51	
> 33,333	120	2.68	116	2.66	4	3.60	

Significant p value are shown in bold

[a]Areca nut amount of use = 15.36 ± 20.77 pieces; length of use = 20.39 ± 9.86 years; age at the first use = 24.68 ± 8.28 years

[b]1USD = 30NTD

Discussion

In this community cohort study, the prevalence of CMDs was 18.23%, which resembled that reported in a previous study conducted in Taiwan (18.8–23.8%) [17]. In the present study, factors including being a woman, young age, low socioeconomic status, and areca nut chewing were associated with CMDs. This study confirmed the positive association between areca nut chewing and the occurrence of CMDs in a community-based cohort and elucidated the mechanistic effects by analyzing TG, DBP, GOT, and WBC results. The findings of the present study partially resemble and confirm some mechanisms published in previous studies that have demonstrated the relationship between areca nut chewing and therapeutic or euphoric effects among psychiatric patients [4, 13, 27]. The present study is one of the first to confirm the associations between the occurrence of CMDs, areca nut chewing, and the effects of areca nut chewing on biophysiological tests among the general population, not including psychiatric patients.

Characteristics of areca nut chewers

The present study demonstrated that areca nut chewers were more likely to be men, younger, and to exhibit more unhealthy lifestyles, including aspects such as alcohol consumption and physical inactivity. Our findings were in agreement with those of previous studies on Asian countries that have also demonstrated that men are more likely to chew areca nut for refreshment, alertness, and for maintaining stamina in countries including Taiwan, China, Sri Lanka, and Nepal [34]. However, areca nut chewing among women is more likely to be habitual or for cultural reasons in Palau, India, and Cambodia [10, 34]. Therefore, areca nut chewing behaviors were observed far less frequently in women ($N=5$, 4.50%) than in men ($N=106$, 95.50%) in the present study. The analysis also revealed that the association between areca nut chewing and CMDs was sustained in models including women and those not including women. The present study and previous studies have demonstrated that women are more likely to develop CMDs but less likely to engage in areca nut chewing behaviors than men. In the present study,

Table 2 Lifestyle and biophysiological factors of study participants stratified by areca nut chewing group

Variables	Total		Areca nut chewers				*p* value
			Others		Yes		
	Number	%	Number	%	Number	%	
Lifestyle factors							
Vegetable favorers							**< 0.01**
Yes	1485	33.17	1433	32.82	52	46.85	
No	2992	66.83	2933	67.18	59	53.15	
Smokers							**< 0.01**
Yes	758	16.93	3687	84.45	32	28.83	
Others	3719	83.07	679	15.55	79	71.17	
Alcohol users							**< 0.01**
Yes	556	12.42	493	11.29	63	56.76	
Others	3921	87.58	3873	88.71	48	43.24	
High physical activity participants							**< 0.01**
Yes	2954	65.98	2904	66.51	50	45.05	
Others	1523	34.02	1462	33.49	61	54.95	
Frequent coffee consumers							0.08
Yes	1418	31.67	1374	31.47	44	39.64	
Others	3059	68.33	2992	68.53	67	60.36	
Frequent tea consumers							**< 0.01**
Yes	2323	51.89	2241	51.33	82	73.87	
Others	2154	48.11	2125	48.67	29	26.13	
Health status							
Common mental disorders							0.05
No	3661	81.77	3578	81.95	83	74.77	
Yes	816	18.23	788	18.05	28	25.23	
Metabolic syndrome							**< 0.01**
No	2766	61.78	2733	62.60	33	29.73	
Yes	1711	38.22	1633	37.40	78	70.27	
Biophysiological factors (1 year before) (means ± SD)							
Cholesterol	203.51	± 38.57	203.48	± 38.42	204.60	± 44.11	0.79
HDL	59.39	± 15.30	59.55	± 15.31	53.34	± 13.36	**< 0.01**
LDL-C	124.82	± 33.97	125.03	± 33.82	116.77	± 38.69	**0.03**
TG	131.39	± 141.99	128.32	± 130.92	251.71	± 353.18	**< 0.01**
Glucose	93.11	± 29.23	93.13	± 29.34	92.46	± 24.71	0.78
SBP	125.33	± 19.73	125.21	± 19.74	129.84	± 19.05	**0.01**
DBP	75.86	± 11.97	75.71	± 11.88	82.01	± 13.94	**< 0.01**
GOT	25.27	± 17.40	25.11	± 17.26	31.63	± 21.38	**< 0.01**
WBC	6.05	± 1.63	6.02	± 1.61	7.05	± 1.80	**< 0.01**

an underestimation of the association between areca nut chewing and CMDs was anticipated by including women in the analysis. If more women with areca nut chewing habits can be observed in the future, we may be able to address the interactive effects of areca nut chewing and sex on CMDs.

Relationship between areca nut chewing and CMDs

The tradition of betel nut chewing is inherent among the Pingpu tribe peoples, an aboriginal group in Taiwan who used to chew or exchange areca nuts during celebrations such as marital events, seasonal festivals, and social activities. Effects of areca nut chewing such as flushing, excitability, and euphoria enhance the sensation of entertainment and celebration. Currently, areca nut chewers are more likely to be labor-intensive workers with low educational levels who are likely to imitate the areca nut chewing behaviors of their peers [13, 25]. Although we adjusted for major sociodemographic factors including sex, age, educational level, and income, areca nut chewing has been shown to be

Table 3 Multiple logistic regression model for factors associated with CMDs

N = 4477	Model I[a]			Model II[b]			Model III[c]		
Variables	Odd ratio	95%		Odd ratio	95%		Odd ratio	95%	
	OR	Upper	Lower	OR	Upper	Lower	OR	Upper	Lower
Gender									
Female	**1.43***	**1.18**	**1.73**	**1.43***	**1.20**	**1.70**			
Male	1.00			1.00					
Age									
30–49	**1.26***	**1.04**	**1.53**	**1.30***	**1.07**	**1.58**	**1.90***	**1.32**	**2.73**
50–59	1.00			1.00			1.28	0.90	1.82
≧60	1.03	0.83	1.28	1.02	0.82	1.27	1.00		
Socioeconomic status									
Others	1.04	0.79	1.43	1.06	0.77	1.46	1.47	0.88	2.44
Low education* low income	**1.34***	**1.09**	**1.70**	**1.37***	**1.08**	**1.74**	**1.82***	**1.24**	**2.65**
Low education* high income	1.13	0.79	1.63	1.16	0.81	1.66	**1.74***	**1.11**	**2.73**
High education* low income	1.14	0.91	1.43	1.14	0.91	1.43	**1.58***	**1.09**	**2.29**
High education* high income	1.00			1.00			1.00		
Vegetarian favorers									
Yes	1.15	0.98	1.35						
No	1.00								
Alcohol users									
Yes	1.03	0.80	1.35						
Others	1.00								
Areca nuts chewers									
Yes	**1.78***	**1.12**	**2.83**	**1.83***	**1.17**	**2.87**	**1.73***	**1.09**	**2.76**
Others	1.00			1.00			1.00		
High physical activity participants									
Yes	1.00								
Others	1.15	0.97	1.35						
Tea consumers									
Yes	1.00								
Others	1.10	0.94	1.28						
Metabolic syndrome									
No	1.00								
Yes	1.01	0.85	1.21						

[a]Adjusted for sex, age, socioeconomic status, vegetarian favorers, alcohol consumers, areca nut chewers, physical activity participants, tea consumers, and metabolic syndrome

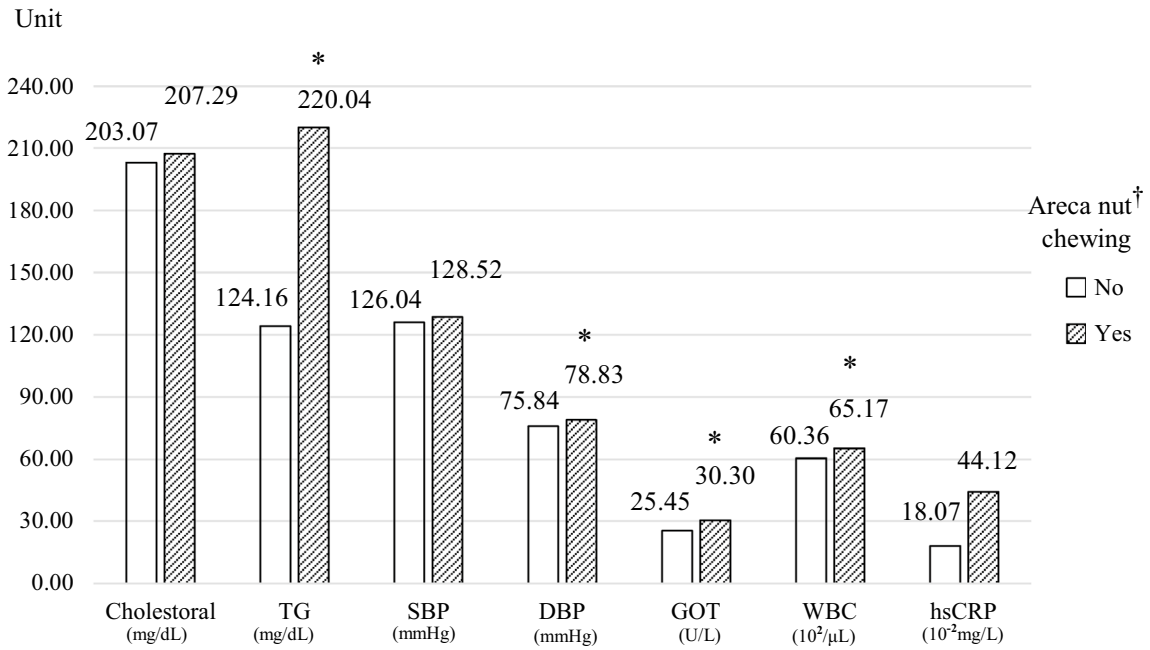
[b]Adjusted for sex, age, socioeconomic status, and areca nut chewers

[c]Males only and adjusted for age, socioeconomic status, and areca nut chewers

independently associated with CMDs in the present study. The findings of this study provide insights into long-term noncancerous effects that are still not clearly understood. Previous studies have proposed a possible mechanism that correlates arecaidine and guvacine exposure with psychiatric illnesses through the blocking of GABA uptake [10, 13, 25, 35]. Although the causality between areca nut chewing and CMDs requires further confirmation, the effects of areca nut chewing detected through cholinergic neurotransmitters administered to habitual chewers are applicable to the general population as opposed to psychiatric patients only.

Areca-nut-chewing-related biophysiological tests

In this study, more TGs and WBCs and higher DBP and GOT were observed among areca nut chewers. The adverse effects of areca nut chewing on metabolic function and the immune system have been extensively documented over the past two decades [2, 9, 11, 12, 36, 37]. Arecoline affects the autonomic nervous system and cholinergic neurotransmitter system, which triggers metabolic inflammation in humans because of an increased concentration of acetylcholine. The cholinergic neurotransmitter system



† Adjusted for the variables of sex, age, areca nut chewing, socioeconomic status, and waist circumference.

Fig. 1 Association between areca nut chewing and biochemical tests

also increases the heart rate, blood pressure, hyperlipidemia, and hyperglycemia because of an overreaction of the sympathetic nervous system [2, 36–38]. Furthermore, studies have demonstrated a dose–response relationship between areca nut exposure and blood pressure [12, 39, 40].

Areca nut consumption is associated with the impairment of hepatic function and lipid disorders. Our findings of higher levels of total cholesterol and more TGs are reinforced by review articles, which have demonstrated the adverse effects of arecoline on low- and high-density lipoproteins [2, 37]. Furthermore, some studies have proposed that the risks of MSs associated with areca nut chewing could be the result of islet beta-cell glucose receptor blocking, which causes inflammation and insulin resistance [9].

The present study demonstrated that areca nut chewing is associated with higher levels of high-sensitivity C-reactive protein (hsCRP) and a high WBC count. This result is consistent with previous studies that have demonstrated the adverse effects of areca nut chewing on the immune system [2, 9, 11]. Shafique and colleagues (2012) first evidenced a positive association between areca nut chewing and the immune system by measuring hsCRP in men. Another Taiwanese study further confirmed increased levels of plasma tumor necrosis factor (TNF)-alpha and leptin among areca nut chewers [37].

Several epidemiological and experimental studies have demonstrated that areca nut chewing is associated with hepatic impairment or liver cancer. The present study confirmed this association by demonstrating elevated levels of aspartate aminotransferase and alanine aminotransferase among areca nut chewers. The underlying mechanisms of the adverse effects of areca nut chewing on the liver may be the inhibition of Vitamin D intake, carcinogenicity of safrole (an ingredient of areca leaves), and enhancement of liver fibrosis through the increase in collagen synthesis [7, 10, 41]. Several population-based studies have demonstrated that areca nut chewing is an independent risk factor for hepatic diseases such as liver cirrhosis [7, 41].

Biophysiological tests and CMDs

Many studies have reported that people with CMDs (depression and anxiety disorders) or severe mental disorders (schizophrenia and bipolar disorder) are more likely to be at high risk of cardiometabolic diseases because of adverse drug reactions, inflammation pathways, unbalanced diets, and substance use disorder [18, 42]. Many psychiatry and bariatrics studies have addressed the positive association between obesity and CMDs accompanied with disease comorbidities such as MSs, DM, and CVDs [18, 20, 43, 44]. Consequently, the association between the lipid profile

and mental disorders is crucial for studying the mechanisms of and preventive strategies for psychiatric illnesses. However, controversial results have been reported in the literature regarding the relationship between the lipid profile and signs and symptoms of mental disorders, including depressive symptoms, suicide attempts, and violent behaviors [22–24]. Liao et al. [22] conjectured that total cholesterol and TG levels may play a crucial role in transporting neurotransmitters and modulating their effects, actions that can lead to psychiatric problems. A retrospective cohort study conducted in the United Kingdom reported a higher level of fasting blood glucose and higher body mass index but lower levels of total cholesterol and blood pressure among psychiatric patients compared with controls [45]. Our findings evidenced elevated levels of selected aspects of biophysiological tests among areca nut chewers; however, the effects of these aspects on CMDs remain uncertain. Other studies have proposed that pathways such as those of the adrenal hormone and brain homeostasis could be the underlying mechanisms of mental illnesses; however, the relationships of these pathways with the elevation of selected biophysiological tests is beyond the scope of the present study and warrants further investigation.

Our finding on the elevated numbers of WBCs among areca nut chewers is consistent with those of previous studies that have demonstrated a positive relationship between CMDs and inflammation biomarkers, including pro- and anti-inflammation cytokines (TNF-alpha and IL-6), oxidative stress (8-OHdG and F2 isoprostanes), and C-reactive protein, because of their common connections to the immune system and depression [46–49]. Some neural studies have reported that patients with depression or schizophrenia have unbalanced immune inflammation conditions resulting from the dysfunction of glutamate neurotransmission in the CNS [22, 46]. Furthermore, most biophysiological tests are related to the inflammation system.

Previous studies have demonstrated adverse effects of areca nuts chewing, including all-cause-mortality, oral cancer, proteinuria, and cardiovascular diseases [5, 6, 14]. However, its effects on mental health are barely mentioned except for psychiatric patient studies in India [13]. In addition to smoking cessation, the discovery of areca nuts chewing as a risk factor of developing CMDs is a crucial public health issues in the future. The present study suggests a more aggressive preventive strategy and provides mechanistic findings for the future professional society to manage mental health problems among high-risk residents.

Limitations

The major strength of this study was its confirmation of the relationship between areca nut chewing and CMDs among the general population and evidence of biophysiological mechanisms. However, some limitations of this study must be considered for future investigations. First, a cross-sectional design may limit the interpretation of the causal pathways between areca nut chewing and CMDs. Our findings indicated significantly higher levels in biophysiological tests conducted 1 year before CMD assessment among areca nut chewers; however, the causality remains to be clarified. Second, this study used a simple and well-established instrument to detect CMDs. Further confirmation of CMD diagnoses with clinical instruments such as the CIS-R and professional personnel is required. Third, we included several confounding factors in this study. The synergistic effects of areca nut chewing and confounders such as cigarette smoking and alcohol consumption on CMDs must be considered in future study designs.

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