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Association of *DSM-5* Betel-Quid Use Disorder With Oral Potentially Malignant Disorder in 6 Betel-Quid Endemic Asian Populations

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IMPORTANCE Betel-quid (BQ) is the fourth most popular psychoactive agent worldwide. An emerging trend across Asia is the addictive consumption of BQ, which is associated with oral cancer and other health consequences.

OBJECTIVE To investigate the validity and pattern of *DSM-5*–defined BQ use disorder (BUD) and its association with oral potentially malignant disorder (OPMD) among Asian populations.

DESIGN, SETTING, AND PARTICIPANTS In-person interviews were conducted from January 1, 2009, to February 28, 2010, among a random sample of 8922 noninstitutionalized adults from the Asian Betel-quid Consortium study, an Asian representative survey of 6 BQ-endemic populations. Statistical analysis was performed from January 1, 2015, to December 31, 2016.

MAIN OUTCOMES AND MEASURES Participants were evaluated for BUD using *DSM-5* criteria for substance use disorder and for OPMD using a clinical oral examination. Current users of BQ with 0 to 1 symptoms were classified as having no BUD, those with 2 to 3 symptoms as having mild BUD, those with 4 to 5 symptoms as having moderate BUD, and those with 6 or more symptoms as having severe BUD.

RESULTS Among the 8922 participants (4564 women and 4358 men; mean [SD] age, 44.2 [0.2] years), *DSM-5* symptoms showed sufficient unidimensionality to act as a valid measure for BUD. The 12-month prevalence of *DSM-5*–defined BUD in the 6 study populations was 18.0% (mild BUD, 3.2%; moderate BUD, 4.3%; and severe BUD, 10.5%). The 12-month proportion of *DSM-5*–defined BUD among current users of BQ was 86.0% (mild BUD, 15.5%; moderate BUD, 20.6%; and severe BUD, 50.0%). Sex, age, low educational level, smoking, and drinking were significantly associated with BUD. Among individuals who used BQ, family use, high frequency of use, and amount of BQ used were significantly linked to moderate to severe BUD. Compared with individuals who did not use BQ, those who used BQ and had no BUD showed a 22.0-fold (95% CI, 4.3-112.4) risk of OPMD ($P < .001$), whereas those with mild BUD showed a 9.6-fold (95% CI, 1.8-56.8) risk ($P = .01$), those with moderate BUD showed a 35.5-fold (95% CI, 4.3-292.3) risk ($P = .001$), and those with severe BUD showed a 27.5-fold (95% CI, 1.6-461.4) risk of OPMD ($P = .02$). Individuals with moderate to severe BUD who used BQ and had the symptom of tolerance had a 153.4-fold (95% CI, 33.4-703.6) higher risk of OPMD than those who did not use BQ, and those with moderate to severe BUD who used BQ and had a larger amount or longer history of BQ use had an 88.9-fold (95% CI, 16.6-476.5) higher risk of OPMD than those who did not use BQ.

CONCLUSIONS AND RELEVANCE This international study gathered data about BQ users across 6 Asian populations, and it demonstrates that *DSM-5* symptoms could fulfill a BUD construct. Most current Asian users of BQ already have BUD, which is correlated with risk of OPMD. Among individuals with moderate to severe BUD who used BQ, tolerance and a larger amount or longer history of BQ use are the key symptoms that correlated with enhanced risk of OPMD. These findings play an important role in providing a new indication of an additional psychiatric management plan for users of BQ who have BUD.

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Editorial
Supplemental content

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Betel-quid (BQ) is the fourth most popular self-administered psychoactive agent worldwide, after caffeine, alcohol, and nicotine.[1] More than 600 million people use BQ within the Indo-Asia-Pacific biogeographic region, and its use is spreading into Asian migrant communities in Western countries.[2] The prevalence of BQ use among adults is particularly high in India, Pakistan, and Sri Lanka (8.4%-40.0%); Nepal, Malaysia, and Indonesia (10.3%-47.8%); mainland China and Taiwan (2.3%-29.0%); Palau and the Solomon Islands (72.0%-83.0%); and among Bangladeshi migrants in the United Kingdom (30.0%-90.0%).[3,4] In these places, BQ is easily available in ready-made packaging at low prices ($0.05-$0.30 per BQ),[5] and chewing BQ in public is often socially accepted.[4]

Betel-quid is a masticatory mixture consisting of a fresh, unripe, or dried *Areca catechu* nut usually wrapped (with or without tobacco) in a betel leaf from the *Piper betel* vine, smeared with aqueous lime, and packed with flavoring ingredients.[3,4,6,7] Arecoline is the principal active agent in the areca nut,[3] with a chemical structure analogous to that of nicotine.[8] Its biological profile is that of a nonselective agonist of the muscarinic acetylcholine receptors, acting on the α_4 and β_2, as well as the α_6 and β_3, subunits of nicotinic acetylcholine receptors, which are the 2 groups of receptors most closely associated with the addictive properties of nicotine.[9,10] A high quantity of BQ use can induce cocaine-like physiological states, such as anxiety, dilated pupils, tachycardia, and elevated blood pressure.[11] Tolerance and withdrawal have been observed in long-term BQ users.[5,7,12,13]

Use of BQ is not formally identified as an addictive behavior according to global substance evaluations.[14] Nonetheless, studies have begun to use the *DSM-IV* to measure the dependent use of BQ.[5,7,13,15,16] In the *DSM-5*, abuse and dependence as defined in the *DSM-IV* were merged into a single disorder with a severity metric based on the symptom count.[17] Changes to the criteria for substance use disorder (SUD) in the *DSM-5* include the removal of the legal problems criterion, the addition of craving, and a diagnostic minimum threshold of at least 2 symptoms.[18] However, no epidemiologic data on BQ use were updated using the *DSM-5*.

Prolonged BQ use is linked with oral potentially malignant disorder (OPMD).[4,19] During BQ chewing, the areca nut–derived nitrosamines and reactive oxygen species produced in the oral cavity can induce genetic damage to exposed oral keratinocytes.[3] Persistent BQ exposures predispose oral cells to preneoplastic lesions, leading to full malignant neoplasms.[20-23] Frequency of use is a central determinant of this outcome; however, a subsequent controlling addiction, manifesting as impaired control, social impairment, risky use, and pharmacologic symptoms, underlying its increased use should also be considered. Our understanding of the psychiatric dimensions associated with addictive consumption of BQ needs to be improved.

In response to the scope of BQ use and the potential health problems in Asia-Pacific countries, the Asian Betel-quid Consortium conducted a joint study to evaluate the effects of BQ use disorder (BUD) on oral health and offered strategies to activate outreach measures for the prevention of oral diseases.[4-7]

Key Points

Question Can *DSM-5*–defined betel-quid use disorder determine the risk of oral potentially malignant disorder in Asian populations with wide use of betel-quid?

Findings In the Asian Betel-quid Consortium study of 8922 participants from 6 populations, betel-quid use disorder met *DSM-5* criteria for a substance use disorder, had a high prevalence among users of betel-quid, and was correlated with risk of oral potentially malignant disorder, especially if users of betel-quid demonstrated symptoms of tolerance and used larger amounts or had a longer history of betel-quid use.

Meaning To reduce the risk of oral potentially malignant disorder, any betel-quid use warrants intervention, and because the prevalence of betel-quid use disorder among users of betel-quid reaches as high as 86%, effective treatment modules addressing dependency on betel-quid should be developed and evaluated.

We define individuals with BUD as users of BQ who met all the *DSM-5* SUD diagnostic criteria. We sought to elucidate the following 3 research issues: the validity of *DSM-5* symptoms for measuring BUD use and the patterns of BUD use among current chewers; the country-dependent parameters that determine BUD; and the association between BUD and OPMD.

Methods

Participants

Six cross-sectional studies were concurrently conducted across East Asia (Taiwan and mainland China), Southeast Asia (Malaysia and Indonesia), and South Asia (Nepal and Sri Lanka) between January 1, 2009, and February 28, 2010, under the Asian Betel-quid Consortium study. Research details are described in a previous article.[4] eTable 1 in the Supplement shows the sociodemographic factors. The number of recruited participants from each study region ranged from 1002 to 2356, indicating a high rate of response (68%-100%). An identical study protocol was administered to all study populations and approved by the Ethics Review Committee of Kaohsiung Medical University (Taiwan), Central South University (mainland China), the University of Malaya (Malaysia), Airlangga University (Indonesia), Kathmandu University (Nepal), and the University of Peradeniya (Sri Lanka). Written informed consent was collected from all participants.

Diagnostic Instrument

A survey questionnaire was designed using proper materials from World Health Organization (WHO) surveys and national prevalence studies. The collected data consisted of sociodemographic factors; disease history; age of initial BQ consumption; quantity of daily use; frequency of use; years of consumption; types of BQ, alcohol, and cigarettes used; family history of substance use; and years since cessation for those who no longer used BQ.

Our interview questions were adapted from the Structured Clinical Interview for *DSM-IV*, Text Revision Axis I Disorders for SUDs and Schedules for Clinical Assessment in Neu-

ropsychiatry (SCAN).[24,25] All included symptoms were updated to fully match the *DSM-5* SUD diagnostic criteria. We merged the *DSM-IV*-derived BQ symptoms for abuse and dependence, removed the legal problem criterion, and used the SCAN-derived craving symptom for *DSM-5*-defined BUD.[18] Questions were initially written in English and translated into the primary language or dialect of each study population. All questions were back-translated into English so that their content and semantic equivalence could be verified by bilingual specialists. The standardized questionnaire was used in all study areas, and our interviews were conducted in local languages.

BQ Use Disorder

Following WHO guidelines,[3] a lifetime BQ user was defined as an individual who had used at least 1 quid of any type of BQ product per day for a minimum of 6 months. Among lifetime users, current users were defined as those who had used BQ within the preceding 12 months before the interview, and past users were those who had not used BQ for at least 12 months before the interview.

We used 11 *DSM-5* symptoms to assess BUD for current users according to the data obtained. These symptoms included the following: large amount or longer history of BQ use (BQ is used in larger amounts or over a longer period than intended); unsuccessful cutdown (unsuccessful efforts to reduce or control BQ use); time spent chewing (spending a large amount of time chewing BQ); craving (having a strong desire or sense of compulsion to use BQ); neglected major roles (recurrent use of BQ results in a failure to fulfill major role obligations at work or home); social or interpersonal problems (continual BQ use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of its use); given up activities (a reduction in important social, occupational, or recreational activities owing to BQ use); hazardous use (recurrent substance use in situations in which it is physically hazardous); continued use despite knowing problems (continual BQ chewing despite an awareness of the physical or psychological problems caused by chewing); tolerance; and withdrawal. The symptoms were grouped into 4 pathologic behavioral categories named *impaired control* (large amount or longer history of BQ use, unsuccessful cutdown, time spent chewing, and craving), *social impairment* (neglected major roles, social or interpersonal problems, and given up activities), *risky use* (hazardous use and continued use despite knowing problems), and *pharmacologic symptoms* (tolerance and withdrawal).

A positive diagnosis of BUD required the presence of at least 2 of the 11 symptoms within 12 months before interview. We followed the *DSM-5* criteria for SUD; current users of BQ with 0 to 1 symptoms were classified as having no BUD, those with 2 to 3 symptoms as having mild BUD, those with 4 to 5 symptoms as having moderate BUD, and those with 6 or more symptoms as having severe BUD.[17]

Oral Potentially Malignant Disorder

All dental and medical professionals completed a standardized OPMD training course for diagnosing oral submucous fibrosis, oral leukoplakia, and oral lichen planus. The characteristics and site of each oral disorder were carefully examined using portable plane dental mirrors for soft-tissue retraction and dental lights for illumination, according to WHO clinical criteria.[26]

Statistical Analysis

Statistical analysis was performed from January 1, 2015, to December 31, 2016. Survey data modules of Stata, version 15 (StataCorp), were used to adjust for multistage sampling design and complex sampling weights. A 4-step procedure was used to analyze data. First, we performed a confirmatory factor analysis to test for a unidimensional BUD construct. Two goodness of fit criteria were used to determine unidimensionality (the root-mean-square error of approximation <0.05 and the comparative fit index >0.95).[27,28] After unidimensionality was established, the item parameters were generated from an Item Response Theory 2-parameter logistic model in Mplus, version 7.11 (Muthén & Muthén). Convergent validity between the antecedent, concurrent, and subsequent correlates and the unidimensional BUD factor scores were conducted through correlation analyses. Cohen conventions for interpreting the effect size of the correlations were used to determine the strength of the associations between each correlate and BUD factor scores.[29] Second, we estimated the prevalence and proportion of BUD in each study region based on weighted data. Third, we constructed multinomial logistic regression models to evaluate the associations of sociodemographic factors with no BUD, mild BUD, moderate BUD, and severe BUD compared with nonusers of BQ.[30] Adjusted odds ratios (AORs) were used to assess the association of chewing characteristics with pathologic behaviors and BUD diagnoses for current users of BQ. Fourth, 4-stage modeling and global tests of joint significance via stepwise addition of each variable block were used to study the association of OPMD with demographic factors, characteristics of BQ use, *DSM-5* symptoms, and BUD diagnosis. Because low OPMD prevalences were observed in Malaysia and Nepal, we performed sensitivity analyses to evaluate the associations between BUD and OPMD, before and after excluding the Malaysian and Nepalese data.

Results

Measurement Validity of *DSM-5* Symptoms for BUD

An excellent fit was calculated for a unidimensional construct to measure the BUD factor scores (root-mean-square error of approximation, 0.026; comparative fit index, 0.995; **Table 1**). The factor loadings for *DSM-5* symptoms ranged from 0.701 to 0.985. Item parameters showed that hazardous use provided the most information (item discrimination, 5.671), whereas social or interpersonal problems offered the least information (item discrimination, 0.983) among the 11 symptoms. The corresponding item difficulty parameters ranged from 1.039 to 2.898, which captured the latent trait level of BUD at which a user has a 50% probability of exhibiting the symptom. Regarding convergent validity, the antecedent correlates of educational level, family use of BQ, and friend use of

Table 1. Factor Loadings and Item Parameters for a Unidimensional Model of *DSM-5* Betel-Quid Use Disorder, Combined Results From 6 Asian Populations[a]

Factor Indicators	Confirmatory Factor Analysis, Factor Loadings	Item Response Theory, Item Parameters	
		Item Discrimination	Item Difficulty
Larger amount or longer history of betel-quid use	0.794	1.306	1.924
Unsuccessful cutdown	0.950	3.037	1.278
Time spent using betel-quid	0.714	1.020	2.171
Craving	0.970	3.957	1.130
Neglected major roles	0.841	1.554	1.845
Social or interpersonal problems	0.701	0.983	2.898
Given up activities	0.959	3.368	1.295
Hazardous use	0.985	5.671	1.039
Continued use despite knowing problems	0.929	2.515	1.337
Tolerance	0.886	1.915	1.628
Withdrawal	0.980	4.988	1.105
Model fit information			
χ^2 Value for model fit test	310.850	NA	NA
df	44	NA	NA
P value	<.001	NA	NA
Root-mean-square error of approximation	0.026	NA	NA
Comparative fit index	0.995	NA	NA

Abbreviation: NA, not applicable.

[a] For a total of 8733 participants.

BQ were significantly associated with BUD factor scores (eTable 2 in the Supplement). Betel quid-associated concurrent correlates and substance-associated subsequent correlates had a strong correlation with BUD factor scores (correlation coefficients, 0.64-0.92).

Prevalence and Severity of BUD

The prevalence of current chewers across the 6 populations was 6.7% to 39.5%, with the highest prevalence observed in Nepal (**Table 2**). In East Asia (Taiwan and mainland China), the 12-month prevalence of current users of BQ with BUD was 4.7% to 8.1%, in Southeast Asia (Malaysia and Indonesia), the 12-month prevalence of current users of BQ with BUD was 14.8% to 29.4%, and in South Asia (Nepal and Sri Lanka), the 12-month prevalence of current BQ users with BUD was 8.4% to 39.2% (18.0% overall). In East Asia (Taiwan and mainland China), the proportion of BUD in current users of BQ was 61.1% to 70.8%, in Southeast Asia (Malaysia and Indonesia), the proportion of BUD in current users of BQ was 75.8% to 98.5%, and in South Asia (Nepal and Sri Lanka), the proportion of BUD in current users of BQ was 55.8% to 99.3% (86.0% overall).

Demographic Factors Associated With BUD

In mainland China, men and younger people were more likely to have any type of BUD (eTable 3 in the Supplement). By contrast, in Malaysia, women and older people had a higher prevalence of BUD. A higher educational level correlated with a lower risk of mild to severe BUD in Taiwan, Malaysia, and Sri Lanka. Cigarette smokers in mainland China were more likely to have all types of BUD (AOR, 3.5-5.7), whereas Malaysian and Indonesian smokers were less likely to have mild to severe BUD (AOR, 0.02-0.30). Alcohol drinkers in Taiwan and Malaysia had a 2.9- to 32.1-fold risk of mild to severe BUD, whereas alcohol drinkers in Indonesia had a 0.3- to 0.4-fold risk of moderate to severe BUD.

Use Characteristics Associated With BUD

Table 3 shows that, in the combined data of users of BQ, family use was associated with a 2.3-fold higher likelihood of impaired control and a 0.6-fold lower likelihood of social impairment than did no family use of BQ. Having friends who used BQ was associated with a 2.8-fold higher likelihood of social impairment than did not having friends who used BQ. Overall, family use was associated with a 2.0- to 3.0-fold risk of developing moderate to severe BUD compared with no BUD, and having friends who used BQ was associated with a 3.6-fold risk of developing mild BUD compared with no BUD. In addition, high frequency of use was associated with impaired control (AOR, 1.2 [95% CI, 1.1-1.3]), social impairment (AOR, 1.1 [95% CI, 1.0-1.2]), risky use (AOR, 1.4 [95% CI, 1.2-1.6]), pharmacologic symptoms (AOR, 1.2 [95% CI, 1.0-1.4]), and moderate (AOR, 1.3 [95% CI, 1.1-1.5]) to severe (AOR, 1.6 [95% CI, 1.4-2.0]) BUD. The amount of BQ used was also associated with impaired control (AOR, 1.1 [95% CI, 1.1-1.2]), risky use (AOR, 1.1 [95% CI, 1.0-1.1]), pharmacologic symptoms (AOR, 1.1 [95% CI, 1.0-1.1]), and mild (AOR, 1.1 [95% CI, 1.0-1.1]), moderate (AOR, 1.1 [95% CI, 1.0-1.2]), and severe (AOR, 1.2 [95% CI, 1.1-1.2]) BUD.

OPMD and BUD

The overall prevalence of OPMD was higher in users of BQ with moderate to severe BUD (26.8%-27.2%) than in those with no BUD or mild BUD (4.3%-5.8%) and nonusers of BQ (4.2%) (eTable 4 in the Supplement). The symptoms of tolerance, larger amount or longer history of BQ use, and continued use

despite knowing problems showed the highest prevalence of OPMD (40.8%, 31.6%, and 29.3%, respectively) (eTable 5 in the Supplement). These 3 symptoms also exhibited 4.3-, 2.9-, and 2.0-fold higher likelihoods of OPMD compared with users of BQ without these symptoms, after adjustment for demographic and risk factors, use characteristics, and other symptoms (**Table 4**; model 3). Higher risk of OPMD was associated with a higher number of pharmacologic symptom behaviors (AOR, 3.4 [95% CI, 1.7-6.6] for 1 increase in symptom numbers; $P < .001$ for linear trend). We found that having no BUD

Table 2. Prevalence and Pattern of 12-Month *DSM-5* BUD Symptoms

Factor	Taiwan (n = 1548)[a]	Mainland China (n = 2356)[b]	Malaysia (n = 1003)[c]	Indonesia (n = 1941)[d]	Nepal (n = 1002)[e]	Sri Lanka (n = 1072)[f]	*P* Value[g]	Overall (N = 8922)
Prevalence of BQ use, mean (SE) %								
Past use	2.7 (0.5)	2.9 (0.3)	1.6 (0.4)	0.7 (0.2)	0.0 (0.0)	1.8 (0.4)	<.001	1.9 (0.2)
Current use	6.7 (0.9)	13.3 (0.7)	19.6 (1.5)	29.8 (2.0)	39.5 (3.0)	15.1 (1.2)	<.001	20.9 (1.0)
Prevalence of current BQ use with BUD, mean (SE), %								
None (0-1 symptoms)	2.0 (0.4)	5.2 (0.5)	4.7 (0.7)	0.4 (0.2)	0.3 (0.2)	6.7 (0.8)	<.001	2.9 (0.3)
Positive for BUD[h]	4.7 (0.8)	8.1 (0.6)	14.8 (1.3)	29.4 (2.0)	39.2 (3.0)	8.4 (0.9)	<.001	18.0 (0.9)
Mild (2-3 symptoms)	1.8 (0.5)	4.1 (0.4)	6.9 (0.9)	2.3 (0.5)	0.0 (0.0)	4.5 (0.7)	NA	3.2 (0.3)
Moderate (4-5 symptoms)	1.5 (0.5)	1.8 (0.3)	6.2 (0.8)	6.4 (0.8)	39.2 (3.0)	2.9 (0.6)	NA	4.3 (0.4)
Severe (≥6 symptoms)	1.4 (0.4)	2.2 (0.3)	1.7 (0.4)	20.7 (1.8)	0.0 (0.0)	1.0 (0.3)	NA	10.5 (0.9)
Proportion of BUD in current BQ users, mean (SE), %								
None (0-1 symptoms)	29.2 (5.7)	38.9 (2.8)	24.2 (3.2)	1.5 (0.6)	0.7 (0.4)	44.2 (4.1)	NA	14.0 (1.3)
Positive for BUD[h]	70.8 (5.7)	61.1 (2.8)	75.8 (3.2)	98.5 (0.6)	99.3 (0.4)	55.8 (4.1)	<.001	86.0 (1.3)
Mild (2-3 symptoms)	26.8 (6.0)	31.1 (2.7)	35.4 (3.7)	7.9 (1.7)	0.0 (0.0)	29.7 (3.8)	NA	15.5 (1.5)
Moderate (4-5 symptoms)	22.9 (5.8)	13.8 (2.0)	31.9 (3.4)	21.3 (2.5)	99.3 (0.4)	19.5 (3.4)	NA	20.6 (1.8)
Severe (≥6 symptoms)	21.1 (5.5)	16.2 (2.1)	8.5 (2.0)	69.4 (3.0)	0.0 (0.0)	6.6 (2.0)	NA	50.0 (2.6)

Abbreviations: BQ, betel-quid; BUD, BQ use disorder; NA, not applicable.

[a] Kaohsiung and Pingtung.

[b] Changsha, Liuyang, Changde, Yongzhou, LouDi, and Xiangxi Prefecture.

[c] Pulau Carey, Simpang Morib, Klang, Kampung Sembirai, Kota Belud, Kampung, Tebedu/Mongkos, and Serian.

[d] Deli Serdang, Pacitan, Banyuwangi, Jembrana, Mataram, Tana Toraja, and Wamena.

[e] Kathmandu, Chitwan, Nawalparasi, and Pokhara.

[f] Gangawata Korale, Udunuwara, and Yatinuwara.

[g] For the difference in characteristics of BQ use across study regions that was obtained adjusted for sex and age.

[h] Classified as none, mild, moderate, and severe according to *DSM-5* criteria.

Table 3. Association of Use Characteristics With Pathologic Behaviors and BQ Use Disorder Among Current Users of BQ, Combined Results From 6 Asian Populations[a]

Use Characteristic	Distribution (n = 2097)	Adjusted Odds Ratio (95% CI)[b]						
		Pathologic Behavior				BQ Use Disorder[c]		
		Impaired Control	Social Impairment	Risky Use	Pharmacologic Symptom	Mild vs None	Moderate vs None	Severe vs None
Categorical characteristic, %								
Family BQ use, yes vs no	52.7/47.3	2.3 (1.4-3.8)	0.6 (0.4-0.9)	1.1 (0.7-1.7)	1.3 (0.8-2.2)	1.6 (0.9-2.8)	3.0 (1.6-5.7)	2.0 (1.1-3.6)
Friend BQ use, yes vs no	81.3/18.7	1.8 (0.9-3.4)	2.8 (1.4-5.3)	0.7 (0.4-1.2)	2.0 (0.9-4.1)	3.6 (1.4-9.1)	1.1 (0.5-2.7)	2.4 (0.9-5.8)
Swallowing BQ juice, yes vs no	34.3/65.7	1.2 (0.7-2.2)	1.0 (0.6-1.6)	1.0 (0.5-1.9)	1.0 (0.5-1.7)	1.8 (0.9-3.4)	1.8 (0.8-3.9)	0.9 (0.4-1.9)
BQ use with tobacco, yes vs no	51.2/48.8	0.4 (0.2-1.0)	0.4 (0.2-1.0)	0.8 (0.3-2.4)	1.0 (0.3-4.2)	0.4 (0.1-1.4)	0.4 (0.1-1.1)	0.3 (0.1-0.7)
Continuous characteristic, median (IQR)								
Starting age, y	23 (18-33)	1.0 (0.9-1.0)	1.0 (0.9-1.1)	1.1 (1.0-1.1)	1.0 (0.9-1.0)	1.0 (0.9-1.0)	1.0 (0.9-1.0)	1.0 (0.9-1.0)
Frequency, d/wk	7 (5-7)	1.2 (1.1-1.3)	1.1 (1.0-1.2)	1.4 (1.2-1.6)	1.2 (1.0-1.4)	1.0 (0.9-1.2)	1.3 (1.1-1.5)	1.6 (1.4-2.0)
Amount, quid/d	5 (3-10)	1.1 (1.1-1.2)	1.0 (0.9-1.0)	1.1 (1.0-1.1)	1.1 (1.0-1.1)	1.1 (1.0-1.1)	1.1 (1.0-1.2)	1.2 (1.1-1.2)
Use duration, y	12 (5-27)	1.0 (0.9-1.0)	1.0 (0.9-1.0)	1.0 (0.9-1.0)	1.0 (0.9-1.0)	1.1 (1.0-1.1)	1.0 (0.9-1.1)	1.0 (0.9-1.0)

Abbreviations: BQ, betel-quid; IQR, interquartile range.

[a] The adjusted odds ratios of *DSM-5* pathologic behaviors (yes vs no) were used to measure the association of use characteristics with pathologic behavior, and the adjusted odds ratios of BQ use disorder (mild, moderate, and severe compared with none) were used to measure the association of use characteristics with severity of BQ use disorder.

[b] Adjusted for sex, age, educational level, cigarette smoking, alcohol drinking, amount of BQ used, and duration of BQ use, and study area.

[c] Users with 0 to 1 *DSM-5* symptoms were defined as having no BQ use disorder, those with 2 to 3 symptoms as having mild BQ use disorder, those with 4 to 5 symptoms as having moderate BQ use disorder, and those with 6 or more symptoms as having severe BQ use disorder.

Table 4. Odds of Oral Potentially Malignant Disorder Associated With Demographic and Risk Factors, Use Characteristics, and *DSM-5* BQ Use Disorder[a]

Factor	Adjusted Odds Ratio (95% CI)[b]			
	Model 1	Model 2	Model 3	Model 4
Demographic and risk factors				
Sex, male vs female	1.9 (1.2-3.1)	1.2 (0.7-2.1)	0.8 (0.4-1.4)	0.7 (0.4-1.2)
Age, y	1.0 (0.9-1.0)	1.0 (0.9-1.0)	1.0 (0.9-1.0)	1.0 (0.9-1.0)
Educational level, y	0.8 (0.5-1.3)	1.0 (0.8-1.3)	1.1 (0.9-1.3)	1.0 (0.8-1.3)
Study region[c]				
Mainland China vs Taiwan	0.8 (0.3-2.3)	0.4 (0.1-1.3)	0.4 (0.1-1.4)	0.4 (0.1-1.3)
Indonesia vs Taiwan	12.0 (3.5-41.3)	18.4 (5.7-59.0)	13.6 (4.5-41.3)	11.8 (3.6-38.1)
Nepal vs Taiwan	0.3 (0.1-1.6)	0.6 (0.1-3.8)	0.1 (0.0-0.7)	0.02 (0.0-0.2)
Sri Lanka vs Taiwan	0.1 (0.0-0.5)	0.1 (0.0-0.3)	0.1 (0.0-0.5)	0.1 (0.0-0.4)
Cigarette smoking, yes vs no	1.5 (0.8-2.8)	2.4 (1.1-5.4)	2.4 (1.1-5.1)	2.5 (1.1-5.5)
Alcohol drinking, yes vs no	2.7 (1.4-5.1)	2.6 (1.2-5.7)	2.6 (1.3-5.5)	2.8 (1.3-5.8)
P value for variable block added[d]	<.001	NA	NA	NA
Use characteristics				
Family use of BQ, yes vs no	NA	3.9 (2.4-6.3)	2.1 (1.3-3.5)	1.8 (1.1-2.8)
Friend use of BQ, yes vs no	NA	1.4 (0.6-3.3)	1.2 (0.6-2.4)	0.7 (0.4-1.5)
Swallowing BQ juice, yes vs no	NA	1.6 (0.8-2.9)	1.6 (0.9-2.8)	1.0 (0.5-1.9)
BQ use with tobacco, yes vs no	NA	0.6 (0.3-1.3)	0.7 (0.4-1.4)	NA
Frequency, d/wk	NA	1.5 (1.3-1.8)	1.3 (1.1-1.5)	1.0 (0.9-1.2)
Amount, quid/d	NA	0.9 (0.8-0.9)	0.9 (0.8-0.9)	0.9 (0.8-0.9)
Use duration, y	NA	1.0 (0.9-1.0)	1.0 (0.9-1.0)	1.0 (0.9-1.0)
P value for variable block added[d]	NA	<.001	NA	NA
DSM-5 symptoms (yes vs no)				
Impaired control				
Larger amount or longer history of BQ use	NA	NA	2.9 (1.5-5.6)	2.4 (1.2-4.7)
Unsuccessful cutdown	NA	NA	1.0 (0.5-2.2)	0.8 (0.4-1.8)
Time spent using BQ	NA	NA	0.7 (0.3-1.6)	0.8 (0.4-1.6)
Craving	NA	NA	0.9 (0.3-2.9)	0.6 (0.2-1.8)
Continuous symptom, No. of impaired control symptoms	NA	NA	1.3 (0.9-1.9)	1.1 (0.8-1.7)
Social impairment				
Neglected major roles	NA	NA	0.3 (0.2-0.7)	0.3 (0.1-0.7)
Social or interpersonal problems	NA	NA	1.1 (0.4-3.1)	1.0 (0.4-2.5)
Given up activities	NA	NA	2.0 (0.9-4.3)	1.6 (0.7-3.7)
Continuous symptom, No. of social impairment symptoms	NA	NA	0.8 (0.5-1.2)	0.7 (0.4-1.1)
Risky use				
Hazardous use	NA	NA	0.8 (0.3-1.9)	0.6 (0.3-1.3)
Continued use despite knowing problems	NA	NA	2.0 (1.0-3.9)	1.8 (0.9-3.7)
Continuous symptom, No. of risky use symptoms	NA	NA	1.4 (0.8-2.4)	1.3 (0.8-2.3)
Pharmacologic symptom				
Tolerance	NA	NA	4.3 (2.1-8.9)	4.1 (1.9-8.7)
Withdrawal	NA	NA	2.4 (0.8-7.7)	1.6 (0.6-4.4)
Continuous symptom, No. of pharmacologic symptoms	NA	NA	3.4 (1.7-6.6)	2.9 (1.4-6.1)
P value for variable block added[d]	NA	NA	<.001	NA
DSM-5-defined BQ use disorder[e]				
None vs nonuser of BQ	NA	NA	NA	22.0 (4.3-112.4)
Mild vs nonuser of BQ	NA	NA	NA	9.6 (1.8-56.8)
Moderate vs nonuser of BQ	NA	NA	NA	35.5 (4.3-292.3)
Severe vs nonuser of BQ	NA	NA	NA	27.5 (1.6-461.4)
P value for variable block added[d]	NA	NA	NA	<.001

Abbreviations: BQ, betel-quid; NA, nonappreciable owing to limited samples and collinearity.

[a] For a total of 7533 participants.

[b] Obtained after being adjusted for all variables in the model.

[c] Malaysia was omitted (no cases of oral potentially malignant disorder).

[d] Obtained from global tests for the variable block added in the previous model.

[e] Users with 0 to 1 *DSM-5* symptoms were defined as having no BQ use disorder; those with 2 to 3 symptoms, mild BQ use disorder; those with 4 to 5 symptoms, moderate BQ use disorder; and those with 6 or more symptoms, severe BQ use disorder.

Table 5. Combined and Conditional Associations of *DSM-5* Symptoms Among Users of BQ and BQ Use Disorder With OPMD, Combined Results[a]

Group	*DSM-5* Symptom	Users, %		Combined Association, AOR (95% CI)[c]	Conditional Association,[b] AOR Ratio (95% CI)[c]
		OPMD (n = 371)	Non-OPMD (n = 7162)		
Nonusers	NA	43.8	81.8	1 [Reference]	NA
BQ use disorder group[d]	Larger amount or longer history of BQ use (impaired control)	NA	NA	NA	NA
None or mild	No	4.1	5.7	14.7 (5.1-42.6)	1 [Reference]
None or mild	Yes	0.1	0.8	3.7 (0.3-38.9)	0.2 (0.03-2.4)
Moderate or severe	No	26.5	7.8	38.8 (7.6-197.0)	1 [Reference]
Moderate or severe	Yes	25.6	3.8	88.9 (16.6-476.5)	2.3 (1.1-4.6)
BQ use disorder group[d]	Neglected major roles (social impairment)	NA	NA	NA	NA
None or mild	No	4.0	6.0	13.1 (4.5-38.2)	1.3 (0.2-7.6)
None or mild	Yes	0.2	0.5	10.4 (1.6-66.6)	1 [Reference]
Moderate or severe	No	42.9	6.4	39.7 (7.8-201.7)	3.3 (1.6-6.9)
Moderate or severe	Yes	9.1	5.3	12.1 (2.1-68.0)	1 [Reference]
BQ use disorder group[d]	Continued use despite knowing problems (risky use)	NA	NA	NA	NA
None or mild	No	3.8	5.7	14.9 (5.0-44.3)	1 [Reference]
None or mild	Yes	0.3	0.9	11.6 (1.9-71.3)	0.8 (0.1-4.5)
Moderate or severe	No	12.6	4.5	38.8 (7.7-194.3)	1 [Reference]
Moderate or severe	Yes	39.4	7.1	71.1 (12.4-408.4)	1.8 (0.9-3.8)
BQ use disorder group[d]	Tolerance (pharmacologic symptom)	NA	NA	NA	NA
None or mild	No	3.6	6.2	15.6 (5.4-44.6)	1 [Reference]
None or mild	Yes	0.5	0.4	23.2 (3.4-157.9)	1.5 (0.2-9.6)
Moderate or severe	No	15.1	7.5	37.0 (7.1-192.7)	1 [Reference]
Moderate or severe	Yes	37.0	4.1	153.4 (33.4-703.6)	4.1 (1.9-9.1)

Abbreviations: AOR, adjusted odds ratio; BQ, betel-quid; OPMD, oral potentially malignant disorder.

[a] Malaysia was omitted because there were no cases of OPMD.

[b] The AORs of *DSM-5* symptoms were obtained conditionally on BQ use disorder group.

[c] Obtained after adjustment for sex, age, educational level, cigarette smoking, alcohol drinking, family use of BQ, frequency of use, amount of BQ use, year of use, all *DSM-5* symptoms, and study region.

[d] Users with 0 to 1 *DSM-5* symptoms were defined as having no BQ use disorder, those with 2 to 3 symptoms as having mild BQ use disorder, those with 4 to 5 symptoms as having moderate BQ use disorder, and those with 6 or more symptoms as having severe BQ use disorder.

was associated with a 22.0-fold (95% CI, 4.3-112.4) higher risk of OPMD compared with nonusers of BQ, having mild BUD was associated with a 9.6-fold (95% CI, 1.8-56.8) higher risk, having moderate BUD was associated with a 35.5-fold (95% CI, 4.3-292.3) higher risk, and having severe BUD was associated with a 27.5-fold (95% CI, 1.6-461.4) higher risk (Table 4; model 4). No interaction effects on OPMD were observed between BUD and the consumption of alcohol and cigarettes. Sensitivity analyses, before and after excluding the Malaysian and Nepalese data, confirmed similar results.

Combined and Conditional Effects of BUD Symptoms and Diagnosis

Table 5 shows that, compared with nonusers of BQ, users of BQ with moderate to severe BUD and the symptom of larger amount or longer history of BQ use had an 88.9-fold (95% CI, 16.6-476.5) higher risk of OPMD, and users of BQ with moderate to severe BUD and the symptom of tolerance had a 153.4-fold (95% CI, 33.4-703.6) higher risk of OPMD. The risks of these 2 symptoms were significantly higher (larger amount or longer history of BQ use: AOR ratio, 2.3 [95% CI, 1.1-4.6]; tolerance: AOR ratio, 4.1 [95% CI, 1.9-9.1]) than in users of BQ with BUD of equal severity but without the corresponding symptoms. Users of BQ with moderate to severe BUD without the symptom of neglected major roles had a 39.7-fold (95% CI, 7.8-201.7) higher risk of OPMD. This risk was higher (AOR ratio, 3.3 [95% CI, 1.6-6.9]) than in users of BQ with BUD of equal severity but with this symptom.

Discussion

The 11 *DSM-5* symptoms of BUD could be modeled as a unidimensional BUD construct. We applied these measures and uncovered a high prevalence of *DSM-5*–defined BUD across the 6 BQ-endemic Asian populations investigated. The 12-month prevalence of BUD was 18.0%, and 86.0% of the users of BQ had some form of BUD. The prevalence of BUD in this study exceeds that reported for *DSM-5*–defined drug use disorder (3.9%)[31] and is comparable to the results of national surveys in the United States for the prevalence of *DSM-5*–defined alcohol (13.9%) and nicotine (20.0%) use disorders.[32,33]

We identified several country-specific factors associated with BUD. First, in mainland China, male sex was associated with BUD, and in Malaysia, female sex was associated with BUD. Age was negatively associated with BUD in mainland China and

positively associated with BUD in Malaysia and Indonesia. These findings accurately capture the ethnodemographic circumstances in those regions; BQ use is an emerging trend in mainland China and is popular among young working-class men,[34] whereas in Malaysia and Indonesia, BQ use is associated with the social customs of Austronesian language-speaking matrilocal societies, and thus has a longer history of use and is more closely associated with older female groups.[35] Second, as seen in other SUDs,[31,33] a lower educational level was associated with mild to severe BUD in Taiwan, Malaysia, and Sri Lanka. Therefore, preventive and interventional strategies should consider the socioeconomic characteristics of the groups using BQ. Third, nationwide reports have revealed that *DSM-5*-defined alcohol, nicotine, and drug use disorders are interrelated.[31-33] Similarly, our analysis found that cigarette-smoking users of BQ were associated with no BUD to mild BUD in Taiwan and all BUD types in mainland China, and alcohol-drinking users of BQ were associated with specific BUD types in all study regions except for Indonesia. A negative association was found between cigarette smoking and mild to severe BUD in Malaysian and Indonesian users of BQ. For these 2 countries, BQ users tended not to be cigarette smokers (BQ users vs nonusers: AOR, 0.05; 95% CI, 0.03-0.08). A possible explanation is a lower purchasing power for cigarettes because the price of cigarettes is higher than that of BQ and BQ is often used by people with relatively lower income in these 2 populations.

Our study showed that a high frequency of use of BQ and using high amounts of BQ correlated with all 4 pathologic behaviors (except between social impairment and amount) and were associated with moderate to severe BUD, thereby confirming the link between dose-enhanced use and substance addiction. The initiation of BQ use is often a result of use among peers or family members.[36] In this study, BQ users with friends who chewed exhibited a higher likelihood of social impairment and developing mild BUD. By contrast, BQ users with family members who used BQ had a lower likelihood of social impairment (AOR, 0.6) but a higher likelihood of impaired control (AOR, 2.3) and significant levels of moderate to severe BUD, possibly because BQ use is accepted in certain family and social situations, whereas alcohol consumption and cigarette smoking may be deemed objectionable.[37] Based on these findings, family-based interventions should be incorporated into BUD prevention and treatment strategies.

Use of BQ poses the greatest risk of developing OPMD among the principal risk factors.[19,38] Based on *DSM-IV* criteria, 1 previous study found a 2.5- to 51.5-fold risk of OPMD among dependent users of BQ.[5] Our study used *DSM-5* criteria to identify 9.6- to 22.0-fold risks of OPMD among users of BQ with no BUD to mild BUD and 27.5- to 35.5-fold risks of OPMD among users of BQ with moderate to severe BUD from 6 Asian populations. Frequency and amount of BQ use correlated with BUD; however, our findings revealed that the association between BUD and OPMD was more substantial after adjustment for use characteristics, symptoms, and other covariates. This finding indicates that addictive consumption of BQ is linked to riskier biological outcomes.

A closer investigation into symptom-specific BUD revealed that a 2.0- to 4.3-fold risk of OPMD was associated with continued use despite knowing problems, having a larger amount or longer history of BQ use, and tolerance (Table 3; model 3). These symptoms potentially underlie the development of OPMD among users of BQ. Users of BQ with moderate to severe BUD and the symptom of tolerance had a conditionally higher risk of OPMD (AOR ratio, 4.1 [95% CI, 1.9-9.1]), as did those with a larger amount or longer history of BQ use (AOR ratio, 2.3 [95% CI, 1.1-4.6]), thereby emphasizing the role of pharmacologic symptoms and impaired control behaviors in BUD-associated risk of OPMD. The symptom of neglected major role of social impairment was associated with a lower risk of OPMD because sharing BQ in family and workplace environments can improve interpersonal relationships.[36]

Strengths and Limitations

The strength of this consortium study was that our investigations were conducted under a single framework using an identical protocol, measuring tools, and diagnostic instruments. A major limitation of this study was its cross-sectional design, which precluded any causal interpretations. Our findings represent only a snapshot of the BUD situation in the study populations. Caution must be exercised when generalizing the findings of this study to other areas because use of BQ might differ even within a single country. We believe that our research framework and methods could be applied to areas or countries where BQ use is prevalent. Further issues regarding intercountry variations in BUD and OPMD are explained in more detail in the eAppendix in the Supplement. Our data are of significance to global research and policy agendas for the BQ and areca nut.[39]

Conclusions

Symptoms, as defined by the *DSM-5*, have a unidimensional construct that underlies BUD. Current BQ users in Asian populations exhibit a high prevalence of *DSM-5*-defined BUD. Tolerance and larger amount or longer history of BQ use were the pathologic symptoms that most correlated with the enhanced risk of OPMD among users of BQ with moderate to severe BUD. We hypothesized that BUD is an intermediary step during the progression from BQ use toward developing OPMD. Appropriate psychiatric treatment should be considered when assisting patients in controlling BQ use to minimize the risk of developing OPMD.

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