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Development and preliminary validation of a mandarin Chinese language questionnaire measuring betel quid dependency among adults in Taiwan

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ABSTRACT

The purposes of this study were to develop the Chinese-version betel quid dependence instrument (BQDI) and to test its reliability and validity. An item pool relevant to betel quid dependence was generated. A panel of three experts assessed content validity including content relevance, clarity, and domain coverage. A cross-sectional study was conducted, consisting of 113 participants from a construction site, betel quid stalls, and a teaching hospital in Taichung, Taiwan. Construct validity was assessed by hypothesizing a significant correlation between the BQDI score and number of pieces-years for betel quid chewing and betel quid biomarkers. The overall Cronbach's alpha coefficient was 0.94. Factor analysis indicated the BQDI consisted of a three-factor structure, including physical and psychological cravings, lack of resistance to betel quid, and maladaptive use. We observed significant associations of BQDI total and factor scores with arecaidine (adjusted odds ratio [OR] for medium total BQDI score: 12.87, 95% CI: 1.45–114.5; high total BQDI score: 28.9, 3.53–236.6) and N-methylnipecotate (medium total BQDI score: 6.18, 1.21–31.62; high total BQDI score: 13.10, 2.72–63.03, respectively). Our results provide preliminary good internal consistency and construct validation of the Chinese-version BQDI as a measure of betel quid dependence in community adults.

1. Introduction

Cancer is the leading cause of death in Taiwan, and oral cancer is the fifth most common cancer in Taiwan with a mortality rate ranked fourth in Taiwanese males (M.O.H.W., 2016). From 1979 to 2013, the age-standardized incidence of oral cancer in adult males increased eight times. As oral cancer incidence is increasing at an alarming rate among men in Taiwan, the median age of oral cancer death is decreasing rapidly as well. Taiwanese men have died from oral cancer at a significantly younger age than other cancers, with a median age of 54 years. Betel quid use accounts for the majority of oral cancer incident cases in Taiwan (Ko et al., 1995; Tsai et al., 2013). In Taiwan, approximately 1.5 out of 10 adult of males report that they are betel quid chewers (Tsai et al., 2013). These data indicate the need for oral cancer prevention action in Taiwan.

Betel quid ranks as the fourth most commonly used psychoactive substance in the world (Zdrojewicz et al., 2015). Approximately 600 million men and women use varieties of betel quid globally. Areca nut is the seed of the fruit of the oriental palm *Areca catechu*. It is the basic ingredient of a variety of widely used chewed products. Alkaloids are

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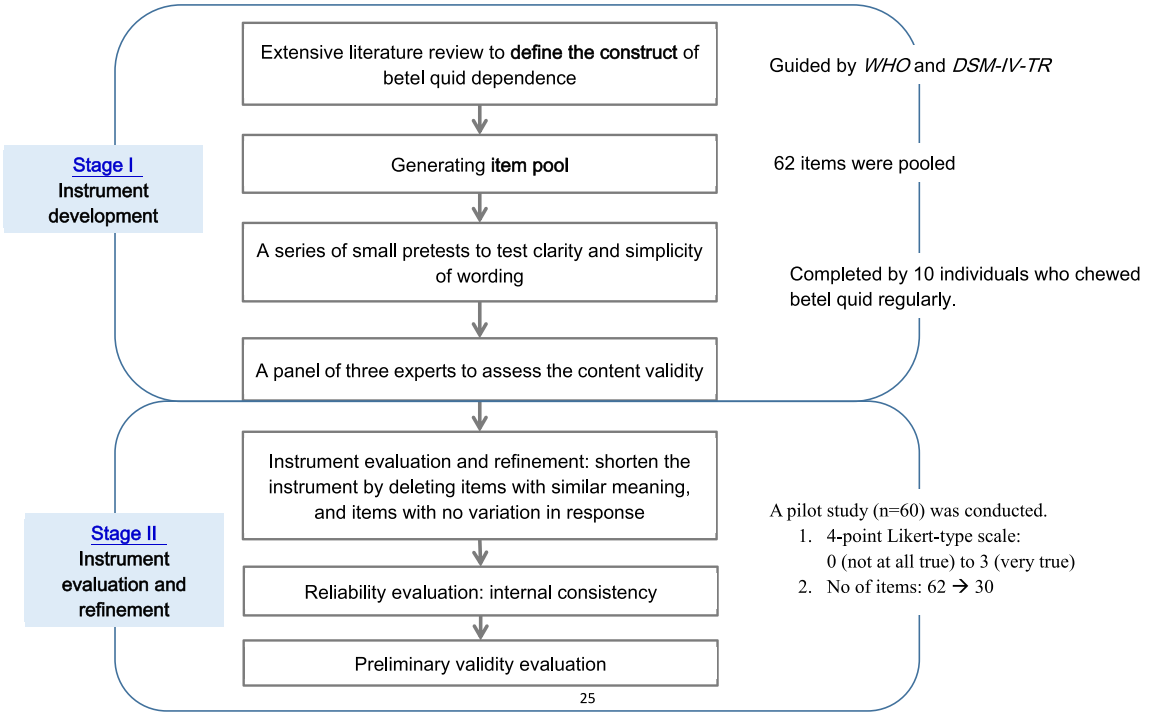


Fig. 1. The steps in two stages including instrument development and instrument evaluation and refinement for BQDI development.

the major constituents of the betel quid nut (Jayalakshmi and Mathew, 1982) and the most important biologically chemical constituents. The nut contains at least six related alkaloids, including arecoline, arecaidine, guvacine and guvacoline, etc (Lord et al., 2002). Arecoline is generally the main alkaloid. In Taiwan, there are two common types of betel quid used: betel quid, and Laohwa quid. Betel quid is made from an unripe areca nut and white slaked lime paste with a piece of betel leaf. Laohwa quid is made from placing a piece of inflorescence of *Piper Betel Linn* and red slaked lime paste into an unripe areca nut. A less common type of betel quid used was stem quid, which is made with *Piper Betle Linn* stem in an unripe areca fruit (Lam and Gritz, 2012; Yap et al., 2008).

Betel quid with or without tobacco is widely used in the Indian subcontinent as well as throughout Asia and the Pacific region, including countries such as Cambodia, China, Taiwan, Thailand, Indonesia, Malaysia, and the Philippines (Gupta and Ray, 2004; Lee et al., 2014; Sullivan and Hagen, 2002; Zhang and Reichart, 2007). Betel quid is the second most valuable crop in Taiwan, behind rice (Agriculture and Food Agency, 2016). The International Agency for Research on Cancer (IARC) reported that the addictive and carcinogenic properties of betel quid are attributed to arecoline. In 1994, IARC identified arecoline as the likely cause of oral submucous fibrosis, which is a precursor of oral cancer (IARC, 2004). Betel quid use is associated with oral leukoplakia, oral mucosa fibrosis, and oral cancers with odds ratios of 22.3, 40.7, and 6.9, respectively (Lee et al., 2003).

To design prevention and education programs for betel quid cessation, we need an instrument for measuring betel quid dependence that is confirmed to be reliable and valid. One prior instrument for betel quid dependence had been developed based on DSM-IV-TR, which was validated among male prisoners in Taiwan (Ko et al., 1995; Lee et al., 2012). To have an instrument for betel quid dependence that is theoretically anchored in the framework of substance dependence, guided by World Health Organization (WHO) and DSM-IV-TR for improving content validity by broadening the adequacy of items, we developed and tested the reliability and validity of the Chinese-version betel quid dependence instrument (BQDI) among Taiwanese community volunteers. The items guided by WHO are perception-related measures whereas those guided by DSM-IV are behavior-related measures. For example, an item 'A strong desire or sense of compulsion to take the substance' for withdrawal is based on WHO while the item 'The substance is often taken in larger amounts or over a longer period than was intended' is based on DSM-IV. To test the construct validity of the Chinese-version BQDI, we hypothesized that the Chinese-version BQDI score was associated with biomarkers of betel quid, and a lower score on the Chinese-version BQDI would reveal lower urine concentration of arecaidine, a bio-active alkaloid in betel quid, and N-methylnipecotate, a betel quid metabolite.

2. Materials and methods

2.1. Study design and subjects

This study was a cross-sectional study, consisting of 113 participants recruited from Taichung city, Taiwan who were native Mandarin speakers. In order to recruit a sufficient number of study subjects in the shortest time period, we went to a construction site, betel quid stalls, and a teaching hospital to find betel quid users. To increase participation rate, we found key persons in occupational groups and these key persons helped us to recruit our participants. We contacted the manager of a construction site and the owners of betel quid stalls before recruitment. With their help, only one or two individuals refused to participate. At the end of study enrollment, less than one-fourth of individuals refused to participate in the hospital setting. We explained the purposes of this study and what tests/questionnaire would be collected from those who agreed to participate. After our explanation, they signed informed consent forms, provided urine samples, and completed the questionnaires by themselves. The inclusion criteria for participants for the present study were adults aged 18 years and older, in good health, and betel quid chewers for more than six months (current or former). An individual was asked what health status he/she had in general and if he/she replied his/her health was good, very good, or excellent, he/she was defined as in good health. In addition, subjects must not have a current or past history of cancer or stroke. Fewer than ten of the screened study subjects were excluded.

2.2. Measurements

2.2.1. Development for Chinese-version BQDI

The development of the tool was conducted in two stages, namely, item pool and instrument development; and instrument evaluation and refinement. The first stage included two steps – defining construct concepts of betel quid chewing dependence, and generating items and establishing content validity. The second stage included a survey and a test of construct validity and internal consistency reliability. The details of the two stages were as follows (Fig. 1).

2.2.1.1. Stage one: item pool and instrument development.

Step 1: Defining construct concepts of betel quid chewing dependence

The Chinese-version BQDI is theoretically anchored on the framework of substance dependence and guided by the WHO and by the DSM-IV-TR of the American Psychiatric Association (APA, 2000). Substance dependence is defined as a cluster of cognitive, behavioral, and psychological symptoms, indicating that the individual continues the use of the substance despite significant substance-related problems (APA, 2000).

Based on a review of the literature on dependence for smoking and betel quid chewing and criteria for dependence proposed by WHO and the diagnostic criteria of Substance Dependence in DSM-IV, three of the authors (TC Li, CS Liu, MS Tsai) constructed three core aspects of betel quid dependence. These aspects are physical and psychological urgent need (existence of a withdrawal syndrome is generally regarded as a hallmark of drug dependence), lack of resistance to betel quid, and maladaptive use (continued use despite knowledge of problems caused by or aggravated by use).

Step 2: Generating items and establishing content validity

According to the constructs of three domains, three of the authors (TC Li, CS Liu. MS Tsai) generated a pool of items relevant to the three core aspects of betel quid dependence, namely, physical and psychological urgent need, increasing dose, and maladaptive use. Initially, an item pool of 62 items measuring betel quid dependency was generated based on three previous studies and on extensive literature review (Winstock et al., 2000). Instruments borrowed from a review of literature on dependence included Wisconsin Inventory of Smoking Dependence Motives (WISDM) (Smith et al., 2010), Wisconsin Smoking Withdrawal Scale (WSWS) (Welsch et al., 1999), Questionnaire of Smoking Urges (QSU) (Cox et al., 2001), Diagnostic and Statistical Manual of Mental Disorders (DSM), DSM-IV Substance Dependence Criteria (APA, 2000) and The Tenth Revision of the International Classification of Diseases and Health Problems (ICD-10) defines the dependence syndrome (WHO, 2017). For those items borrowed from English instruments, we followed a cross-cultural adaptation process that is normally expected in cross cultural adaption of questionnaires, except for back-translation. The cross-cultural adaption process recommended by Gjersing et al. (Gjersing et al., 2010), includes the following steps: investigation of conceptual and item equivalence, direct translation of original instrument, a synthesized translated version, expert committee consolidation and pre-testing. These items and response scales were then iteratively refined. The questionnaire was then completed by 10 individuals who regularly chewed betel quid chewing. Certain wordings were modified because several individuals found items difficult to understand. A series of small pretests was conducted by rewording these items to improve clarity until all individuals reported that the questionnaire was clear and easily understood.

A panel of three experts assessed content validity of the 62-item scale. The three experts included one epidemiologic researcher in the field of measurement and validation of instruments, one family physician who is an expert in behavioral science, and one otolaryngologist who is an expert in constructs for betel quid dependence. The experts on the panel were given a rating form with the theoretical definition as well as a delineation of the three dimensions, objectives, and items. They were asked to review content relevance, clarity, and domain coverage.

2.2.2.2. Stage two: instrument evaluation and refinement. In the second stage, a pilot study (n = 60) was conducted to test whether each item could produce an adequate range of responses and to identify redundant items. A questionnaire consisting of the 62-item BQDI and a set of demographic questions was prepared for the pilot study. A 4-point Likert-type scale was used, ranging from 0 (not at all true) to 3 (very true). After the review by the expert group and the pilot study, the number of items was reduced by 32, from 62 to 30. The deleted questions included items with similar meaning to decrease redundancy and items with no variation in response (all responses for “not at all true”). The shortened version of the BQDI used for further data collection included 12 items aimed at measuring physical and psychological urgent need, 12 items dealing with resistance to betel quid dependence, and 6 items covering maladaptive use (Supplemental Table 1 for English and Supplemental Table 2 for Chinese). The reading level of BQDI is at grade 6. The total score for the respondent on the subscale is the sum of their rating for all of the items within the subscales. Because all items on the BQDI are positively worded, we do not need to reverse scoring when the total score is calculated.

2.2.2. Demographic and betel quid and tobacco exposure variables

Data were collected regarding age, gender, past/current use of any tobacco, betel quid, knowledge of betel quid, type of betel quid, number of chew episodes/day, years chewed betel quid, number of betel quid used in all chews/day, duration of each chew episode, and time of day for each chew.

2.2.3. Urine sample collection and preparation

After sampling, urine samples were sent to the lab for testing within 24 h and were stored in anti-freeze tubes at −80 °C until analysis. For sample preparation, urine sample was mixed with internal standard (IS) mixture (arecoline-d5 (Santa Cruz, CA, USA), arecaidine-d5 (Santa Cruz, CA, USA), ethyl 1-methyl-3-piperidinecarboxylate (Sigma, MO, USA), and cotinine-d3 (Toronto, Canada) in 2% methanol containing 0.1% formic acid (FA) and separated using a solid-phase extraction (SPE) column (Oasis® MCX, Waters, Milford, MA, USA). The prepared samples were injected for liquid chromatography/tandem mass spectrometry (LC/MS/MS) analysis.

2.2.4. LC/MS/MS analysis

LC analysis was performed on a 3-μm T3 column (Atlantis@T3, 2.1 mm i.d × 150 mm, Waters, Milford, MA, USA). The mobile phase contained Solution A (100% deionized water and 0.1% FA) and Solution B (100% acetonitrile and 0.1% FA) and was kept at 200 μl/min flow rate. The LC gradient conditions consisted of: isocratic elution (95% Solution A) for 1 min, followed by a 1.5 min gradient to 50% Solution B, then a gradient to 60% Solution B in 1.5 min, then the final gradient to 5% Solution B in 1 min, and then kept at 5% Solution B for 5 min. The eluted compounds were detected by a Thermo Finnigan LCQ DECA XP mass spectrometer (Thermo Finnigan, CA, USA) employed with a low flow metal needle. We used the following selective reaction monitoring (SRM) transitions for the quantification: Arecaidine, m/z 142→44; N-methylnipecotate, m/z 144→126; Arecoline, m/z 156→44; Cotinine, m/z 177→146. We have evaluated the linearity, r^2 of calibration curves, instrument limit of detection/quantitation (LOD/LOQ), accuracy, precision by three replicates per level. Good linearity ($r^2 > 0.99$) of the calibration curves was obtained over the range from 40 to 0.25 ppm. LOD and LOQ values generally were defined as S/N (signal to noise) ratio > 3 and 6 respectively. Both inter-day precision

(reproducibility) and intra-day precision (repeatability) were found to be < 10% RSD. The intra- and inter-day accuracy were also < 10%.

2.3. Statistical analysis

2.3.1. Reliability

The internal consistency was assessed by Cronbach's alpha coefficient, which measures overall correlation among items within a scale. Cronbach's alpha should exceed 0.7 to be considered acceptable for group comparison and exceed 0.8 to be considered items on a scale with good internal consistency (Nunnally, 1978).

2.3.2. Validity

We assessed evidence of construct validity for BDQI by following the logic proposed by Carmines and Zeller (Carmines and Zeller, 1979). Construct validity is the extent to which a particular measure relates to other measures consistent with theoretically derived hypotheses concerning the concepts that are being measured. Based on multitrait-multimethod matrix (Nunnally and Bernstein, 1994), we hypothesized high correlation between BQDI scores and number of pieces-years for betel quid chewing or biomarkers of betel quid, i.e., trait correlation for convergent validity. We hypothesized that the correlation between BQDI scores and number of piece-years for betel quid chewing or biomarkers of betel quid would be higher than that between BQDI scores and number of pack-years for smoking for discriminant validity. If these correlations varying in a predictable manner were observed, it would provide evidence that BQDI is a valid instrument. Furthermore, factor analysis (Child, 1991), a technique of psychometric validation that assesses the agreement between hypothetical factors, was used to test the dimensions of BQDI. Factor analysis extracted principal components from the correlations among their items, and each principal component was a linear combination of items from the instrument for betel quid dependency. The extracted components were rotated using Promax method. If BQDI is a valid measure, the items of the same scale defined by the authors should load on a given factor in this sample, i.e., within such an assessment, a factor should be considered relevant only if its eigenvalue (a statistical measure of its power to explain variation between subjects) exceeds 1 (Manly, 1994).

Descriptive statistics of means and standard deviations were presented for continuous variables and frequency number and proportions for categorical analysis. Our data analysis approach was to restrict the analysis to subjects with complete data, i.e., complete set. Two-sample t tests were used to compare means of two groups and analysis of variance (ANOVA) for more than two groups. Pearson's chi-square test was used to examine associations between two categorical variables. Multivariate logistic regression analysis was used to explore the association among BQDI scores and arecaidine, N-methylnipecotate, and cotinine.

3. Results

Table 1 shows the characteristics of the study subjects. Because all participants responded to all items, we do not have a problem with missing values in the analysis. Table 2 shows the factor structure of BQDI. The Kaiser–Meyer–Olkin measure of sampling adequacy was 0.861, and the Bartlett test of sphericity was acceptable (Chi-square = 2382.82, $p < 0.001$), indicating that BQDI correlation matrix was suitable for factor analysis. All factor loadings of each factor had coefficients greater than 0.4. The communality coefficients (h^2) ranged from 0.376 to 0.749. The three-factor model accounted for 55.6% of the total variance. The first factor accounted for 40.5% and consisted of items related to “physical and psychological urgent need.” The second factor accounted for 9.4% and consisted of items related to “lack of resistance to betel quid.” The third factor accounted for 5.7% and consisted of items related to “maladaptive use.” The correlations among the three factors ranged from 0.40 to 0.74. Cronbach's alpha coefficients of the three factors ranged from 0.78 to 0.93, indicating that the items on the three factors had good internal consistency.

Table 1
The distributions of sociodemographic factors, smoking and betel quid related measurements and biochemical parameters in the study sample for the preliminary validation of Chinese-version betel quid dependence instrument. ($N = 113$).

Variables	Subjects were included[†] N	Mean ± SD
Age (years)	113	40.0 ± 12.6
Age (years)		
< 40	63	(55.8%)
≥ 40	50	(44.2%)
Sex		
Male	104	(92.0%)
Female	9	(8.0%)
Aboriginal		
No	103	(91.1%)
Yes	9	(8.0%)
Unknown	1	(0.9%)
Betel nut		
Current	104	(92.0%)
Former	9	(8.0%)
Type of betel nut		
Betel quid	87	(77.0%)
Laohwa quid	24	(21.2%)
Stem quid	2	(1.8%)
Smoke		
Current	91	(80.5%)
Never or former	22	(19.5%)
Smoking related measurements		
Cigarette smoke exposure (pack-years)[‡,a]	95	16.2 ± 2.7
The time since your last smoke (hours)[‡,a]	96	0.7 ± 6.6
Questionnaire on Smoking Urges (QSU)[a]	94	34.7 ± 17.2
Betel quid related measurements		
Betel quid exposure (piece-years)[‡]	113	160.8 ± 5.5
The time since your last betel quid chewing (hours)[‡,b]	85	8.8 ± 22.2
Knowledge of betel quid[b]	104	5.9 ± 1.2
Betel quid dependence instrument	113	94.4 ± 39.2
Factor 1: Physical and psychological urgent need	113	37.5 ± 19.9
Factor 2: Lack of resistance to betel quid	113	30.3 ± 16.2
Factor 3: Maladaptive use	113	26.6 ± 9.5
Biochemical parameters		
Arecaidine (ng/mg creatinine)[‡]	113	1451 ± 15.5
N-methylnipecotate (ng/mg creatinine)[‡]	113	1772.2 ± 12.1
Cotinine (ng/mg creatinine)[‡]	113	333.6 ± 4.8

Values in parentheses are percentages

[†] Subjects with complete betel quid dependence instrument were included

[‡] Geometric mean and standard deviation are shown due the skew distribution of data

[a] Never smokers were excluded. Numbers do not equal to 97 due to missing information.

[b] Former betel nut chewers were excluded. Numbers do not equal to 104 due to missing information

Next, we validated this instrument with biomarkers of arecaidine, N-methylnipecotate, and cotinine. We hypothesized that betel quid related measurements should be correlated with arecaidine and N-methylnipecotate, but not with cotinine. We observed that the Pearson correlation coefficients between all betel quid related measurements and arecaidine and N-methylnipecotate were all statistically significant, ranging from 0.22 to 0.61. Our data supported the hypothesized correlation, thus providing evidence for scale-level convergent and discriminatory validity of the instrument (Table 3).

We further estimated the strength of association between the total score on the BQDI and the biomarkers by categorizing these variables according to their tertiles. We observed that the total score on the BQDI was associated with high levels of arecaidine (odds ratio [OR]: 9.93, 95% confidence interval [CI]: 1.17–84.04 for medium level of BQDI total score; 34.20, 4.24–274.80 for high level of BQDI total score) and N-methylnipecotate (5.62, 1.12–28.16 for medium level of BQDI total

Table 2
Coefficients of items for betel quid dependency instrument (BQDI) using principal components method with varimax rotation for evaluating the BQDI's constructs. (N = 113).

Item	**Factor 1** Physical and psychological urgent need	**Factor 2** Lack of resistance to betel quid	**Factor 3** Maladaptive use
I often chew betel quid involuntarily.	0.65*		
I always start chewing betel quid within 30 min of when I get up in the morning.	0.66*		
My life is full of reminders of chewing betel quid.	0.65*		
The betel quid is with me, like a close friend.	0.76*		
When I see betel quid, it lures me to chew it intensively.	0.68*		
Others who chew betel quid think that I am heavily addicted to it.	0.65*		
My betel quid addiction is already out of control.	0.68*		
I think I was a betel quid addict.	0.78*		
I feel myself having trouble stopping chewing betel quid.	0.66*		
You continue to chew betel quid even if your teeth wiggle or you have sensitive teeth.	0.63*		
You continue chewing betel quid even if your experience canker sores or mouth ulcers.	0.57*		
The amount of betel quid gradually increases every time you chew it, from the first time you used it.	0.69*		
The flavor of betel quid is pleasing.		0.61*	
Chewing betel quid can help me maintain concentration.		0.44*	
I rely on chewing betel quid to control my hunger and my diet.		0.75*	
Chewing betel quid makes me feel better instantly.		0.51*	
Without betel quid, I will feel lonely.		0.57*	
I experience strong craving for betel quid if I completely stop chewing it for a few hours.		0.60*	
I want a betel quid now.		0.69*	
I feel very anxious or upset when I cannot chew betel quid.		0.67*	
When you want to chew betel quid, but it is not available, you will spend a lot of time to find it.		0.58*	
When you want to chew betel quid, but it is not available, you will travel a great distance to buy it.		0.68*	
You reduced or gave up some of your social, work or leisure activities because of betel quid chewing.		0.63	
You experienced depression or drowsiness after you reduced or completely stopped chewing betel quid.		0.63*	
I would like to reduce the amount of betel quid that I chew.			0.72*
I hope I can stop chewing betel quid.			0.75*
Some people criticize me for chewing betel quid which makes me feel troubled.			0.67*
A family member or friend advised me to chew less betel quid.			0.69*
If I chew betel quid I will feel bad or guilty.			0.65*
You periodically feel the need to increase the amount of betel quid that you chew in order to achieve a pleasant or refreshing effect.			0.40
Accounting for total variance	40.5%	9.4%	5.7%

Reliability evaluation: Cronbach's α coefficient: 0.78 ~ 0.93
* Convergent validity: A correlation ≥ 0.4

Table 3
Pearson correlation coefficients between biochemical parameters of arecaidine, Nmethylnipecotate, and cotinine, and measurements for mental health, smoking, and betel quid chewing.

Variables	Total n	Arecaidine† (ng/mg creatinine)	N-methylnipecotate† (ng/mg creatinine)	Cotinine† (ng/mg creatinine)
Age(years)	113	0.36***	0.32***	−0.10
Smoking related measurement				
Accumulate exposure of cigarette (pack-years)†,a	95	0.31**	0.21*	0.19
The time since your last smoke (hours)†,a	96	0.06	0.10	−0.33**
Questionnaire on Smoking Urges (QSU)a	94	0.05	0.03	0.34***
Betel quid related measurement				
Accumulate exposure of betel quid (piece-years)†	113	0.57***	0.49***	0.09
The time since your last betel quid chewing (hours)†,b	85	−0.71***	−0.67***	−0.10
Knowledge of betel quidb	104	−0.08	0.01	0.07
Betel quid dependence instrument	113	0.52***	0.55***	0.01
Factor 1: Physical and psychological urgent need	113	0.56***	0.57***	0.04
Factor 2: Lack of resistance to betel quid	113	0.41***	0.44***	−0.02
Factor 3: Maladaptive use	113	0.28**	0.34***	−0.01

† Log-transformed data are used due the skew distribution of data
a Never smokers were excluded. Numbers do not equal to 97 due to missing information.
b Former betel nut chewers were excluded. Numbers do not equal to 104 due to missing information.
* $p < 0.05$;
** $p < 0.01$;
*** $p < 0.001$

Table 4
The external validation analysis of betel quid dependence instrument and questionnaire on smoking urges for nicotine dependence by using biochemical indicators as external variables.

	Total	High arecaidine (≥ 16,114.51 vs < 16,114.51 ng/mg creatinine)		High N-methylnipecotate (≥ 13,651.08 vs < 13,651.08 ng/mg creatinine)		High cotinine (≥ 1061.45 vs < 1061.45 ng/mg creatinine)	
Independent variables	*n*	Risk %	OR (95% CI)	Risk %	OR (95% CI)	Risk %	OR (95% CI)
Univariate logistic regression model							
Model I							
Betel quid dependence instrument							
Low (score < 72)	37	2.7%	1.00	5.4%	1.00	32.4%	1.00
Medium (72 ≤ score < 109)	37	21.6%	**9.93 (1.17, 84.04)***	24.3%	**5.62 (1.12, 28.16)***	21.6%	0.58 (0.20, 1.63)
High (score ≥ 109)	39	48.7%	**34.20 (4.24, 274.80)*****	46.2%	**15.83 (3.35, 74.90)*****	20.5%	0.54 (0.19, 1.52)
Model II							
Questionnaire on Smoking Urges (QSU)							
Low (score < 24)	29	34..5%	1.00	34.5%	1.00	17.2%	1.00
Medium (24 ≤ score < 43)	32	18.8%	0.44 (0.14, 1.52)	21.9%	0.53 (0.17, 1.66)	34.5%	2.51 (0.75, 8.42)
High (score ≥ 43)	33	27.3%	0.71 (0.24, 2.11)	27.3%	0.71 (0.24, 2.11)	33.3%	2.40 (0.72, 8.01)
Age- and gender-adjusted logistic regression model							
Model I							
Betel quid dependence instrument							
Low (score < 72)			1.00		1.00		1.00
Medium (72 ≤ score < 109)			**12.87 (1.45, 114.50)***		**6.18 (1.21, 31.62)***		0.54 (0.19, 1.55)
High (score ≥ 109)			**28.9 (3.53, 236.60)****		**13.10 (2.72, 63.03)****		0.63 (0.21, 1.85)
Model II							
Questionnaire on Smoking Urges (QSU)							
Low (score < 24)			1.00		1.00		1.00
Medium (24 ≤ score < 43)			0.91 (0.23, 3.62)		0.78 (0.21, 2.86)		2.16 (0.57, 8.16)
High (score ≥ 43)			0.86 (0.27,2.73)		0.78 (0.25, 2.38)		2.38 (0.69, 8.24)

High level of biomarker was defined as the biomarker concentration greater than the highest quartile for each biomarker.
Each measurement was divided into low, medium, and high groups by tertile.

score; 15.83, 3.35–74.90 for high level of BQDI total score). In addition, ORs increased as the level for betel quid dependence increased, indicating a dose–response relationship. In contrast, the Questionnaire on Smoking Urges score is not associated with high level of arecaidine or N-methylnipecotate, or cotinine. After adjusting for age and gender, the significant associations remain similar (Table 4).

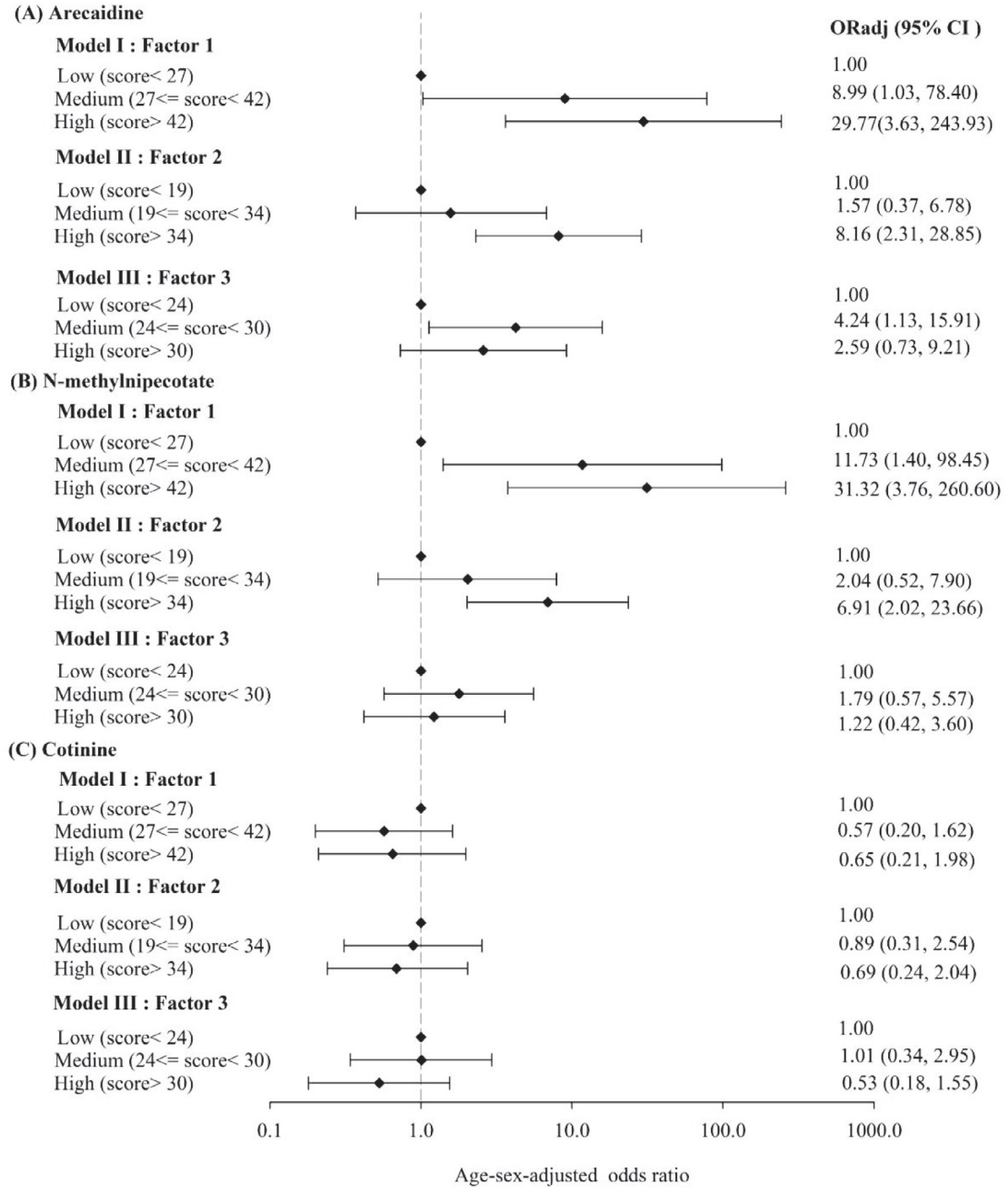
Fig. 2 shows the external validation for the BDQI factors by using biomarkers as external variables. Using the same criteria to categorize factor scores of the BQDI, both factors 1 and 2 are associated with high level of arecaidine and N-methylnipecotate, but not with high level of cotinine. This analysis demonstrates the scale-level convergent and discriminant validity for factors 1 and 2 of the instrument.

4. Discussion

In this study, we developed a Chinese-version BQDI and evaluated its psychometric characteristics and external validation by relating its scale scores with biomarkers of arecaidine and N-methylnipecotate. The BQDI was designed to determine the betel quid dependence status of adult chewers. Cronbach's alpha coefficients of the BQDI in this study were acceptable and all were above 0.7. The factor analysis results revealed that the items clustering together support the assumptions of the theoretical constructs. The psychometric properties of the BQDI reflected in our analyses appear satisfactory.

We used major urinary metabolites of betel quid, such as arecaidine and N-methylnipecotate, as external variables. The approach for construct validation we adopted was multitrait-multimethod matrix for two traits (betel quid dependence and tobacco dependence) measured by two methods (self-report instrument and biomarkers). Construct validation demands that correlations between BQDI score and arecaidine and N-methylnipecotate (trait correlation) be high to reflect convergent validity and that trait correlation be higher than the correlation between BQDI scores and cotinine level (heterotrait heteromethod correlation) to reflect discriminant validity. The significant associations of total BQDI score and scores of physical and psychological urgent need as well as lack of resistance to betel quid scales with high level of arecaidine and N-methylnipecotate, but not with a high level of cotinine in this study indicate that the BQDI is a good instrument with discriminative validity. We failed to detect significant associations between the maladaptive use scale and high levels of arecaidine and N-methylnipecotate. We only observed weak associations between the maladaptive use score and N-methylnipecotate concentration. This weak association might be due to the fact that this scale measures negative feeling about betel quid use, and one of the reasons that most current users did not quit is because they did not receive negative input about betel quid from interpersonal communication. The findings of associations between BQDI scores and betel quid biomarkers demonstrated that the BQDI had construct validity. The strength of the questionnaire lies in its comprehensive coverage of content relevant to betel quid dependence and its ease of administration. The results of psychometric tests conducted in this study provide initial support for the validity and reliability of the instruments. The significant associations of BQDI scores with arecaidine and N-methylnipecotate supported the discriminatory ability of BQDI to distinguish persons with high or low level of arecaidine and N-methylnipecotate. However, further testing for user's sensitivity to change needs to be undertaken before this instrument can be widely applied.

In the literature, one betel quid dependence instrument with good internal consistency has been developed (Lee et al., 2012), BQDS. In this study, factor analysis revealed that BQDS had three factors, which were labeled as “physical and psychological urgent need,” “increasing dose,” and “maladaptive use.” This scale had good discriminatory ability in distinguishing prisoners who had and did not have betel quid chewing exposure in the past six months. The item pool for betel quid



OR= Odds ratio; High level of biomarker was defined as the biomarker concentration greater than the highest quartile for each biomarker. (A) High arecaidine (≥16114.51 vs <16114.51 ng/mg creatinine); (B) High N-methylnipecotate (≥ 13651.08 vs <13651.08 ng/mg creatinine); (C) High Cotinine (≥ 1061.45 vs <1061.45ng/mg creatinine); Each measurement was divided into low, medium, and high groups by tertile.

Fig. 2. The external validation analysis of scores for factors of betel quid dependence instrument by using biochemical indicators of arecaidine, N-methylnipecotate, and cotinine as external variables.

dependence constructed by our study included all items in the BQDS in addition to items adopted from dependence scales of the SDS, FTND, and the Cigarette Dependence Scale. During the pilot study, several items in BQDS were excluded due to limited item discriminatory power, such as “Have you ever felt that you cannot go on without betel quid,” “Have you ever chewed betel quid nonstop,” and “Have you often found yourself chewing more betel quid than expected and/or spending more time in chewing betel quid than expected.” We found the first two items applied more to a high state of dependence. The exclusion of these two items may be due to low prevalence of high dependence in our study sample, and thus the discriminatory power of these two items was low.

This study has several strengths. First, we recruited participants who were betel quid chewers from a well-defined community with a non-probability sampling scheme. Compared to the prior study

conducted among prisoners (Lee et al., 2012), our study findings were more likely to generalize to betel quid chewers in a community. Second, the instrument developed by Lee et al. adopted the definition of DSM-IV-TR. The theoretical construct of betel quid dependence in the present study was guided by both WHO and DSM-IV-TR, which enhanced sampling validity. Third, the prior study that was conducted in prison asked participants to recall their betel quid chewing behavior and perception in the past, as these prisoners were not permitted to use BQ. Thus, recall bias could have existed. On the contrary, a recall bias was less likely in our study because we asked our participants to answer questions with reference to the past four weeks. Fourth, our study was the first to use betel quid metabolites to validate accuracy of a betel quid dependence instrument. Our results revealed that total and sub-scale scores of the BQDI had good construct validity in association with betel quid metabolites of arecaidine and N-methylnipecotate.

This study has several limitations. First, our sample size is small (n = 113) compared to prior studies that administered questionnaires only (n = 230–300) (Lee et al., 2012) (Herzog et al., 2014). Due to the need to collect urine specimens, the process of recruitment in our study was more difficult than those that utilized questionnaires alone. Nevertheless, our study had sufficient power to detect associations between BQDI score and betel quid biomarkers of arecaidine and N-methylnipecotate. Second, our study only measured betel quid biomarkers of arecaidine and N-methylnipecotate, but not arecoline. Thus, we cannot evaluate whether BQDI scores were associated with arecoline level. However, it has been reported that the arecoline level was very low with a half-life of 0.97 h after administration of betel quid extracts. Thus, arecoline may not be suitable as a biomarker of betel quid use (Hu et al., 2010) . In addition, these betel quid biomarkers of arecaidine and N-methylnipecotate weren't sensitive to type of betel quid. Thus, we cannot validate the accuracy of information for types of betel quid being used that were collected through questionnaires.

The Chinese-version BQDI included three domains for measuring betel quid dependence in residents recruited from the community. The strength of Chinese-version BQDI lies in its comprehensive coverage of content relevant to betel quid dependence and ease of administration. This study provide preliminary validation of the instrument but the limitation of our study is the small sample size and selected sample. The significant cross-sectional association between Chinese-version BQDI scores and arecaidine and N-methylnipecotate support the construct and discriminatory ability of the instrument. However, further testing for participants' sensitivity to change needs to be undertaken before this measure can be applied in clinical settings for betel quid cessation programs.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.11.027.

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