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Association of betel nut chewing with chronic kidney disease: A retrospective 7-year study in Taiwan

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SUMMARY AT A GLANCE

This paper details a population-based study in Taiwan aimed at determining a possible association between Betel nut chewing and chronic kidney disease. Much larger than previous studies in the area, the authors have determined that an association exists in some subgroups of their large cohort.

ABSTRACT:

Aim: **Only few studies have reported that betel nut (BN) chewing is independently associated with chronic kidney disease (CKD); however, the sample size was relatively small. This study was to explore further the association between BN chewing and CKD using a larger case series.**

Methods: **We retrospectively reviewed the records of a health check-up program from 2003 to 2009. Laboratory tests, medical history and status of cigarette smoking, alcohol drinking and BN chewing were compared between CKD and non-CKD groups. We checked interaction effects between BN chewing and all other covariates, and conducted multivariate logistic regression analysis to explore the risk of CKD with BN chewing.**

Results: **A total of 27 482 participants (15 491 females and 11 991 males, mean age 58.02 ± 11.85 years) were included in the study, of whom 4519 (16.4%) had CKD and 1608 (5.9%) chewed BN. CKD prevalence in the chewers was higher than in the non-chewers in all age groups per decade. BN chewing was significantly associated with CKD in overall subjects (odds ratio (OR) = 1.23, $P = 0.027$) and also in the male (OR = 1.23, $P = 0.035$), non-drinking (OR = 1.62, $P = 0.000$), non-diabetic (OR = 1.27, $P = 0.021$), and non-proteinuric groups (OR = 1.30, $P = 0.013$). This relationship was insignificant in female, drinking, diabetic and proteinuric groups.**

Conclusion: **The association between BN chewing and CKD seemed conditional on demographics, health behaviours, and underlying co-morbidities. This association should be interpreted cautiously.**

INTRODUCTION

The incidence of end-stage renal disease (ESRD) has increased rapidly worldwide.[1] Taiwan has the highest ESRD incidence and prevalence in the world,[2] leading to heavy burdens on health care resources and national finance. Early detection of potential risk factors and early treatment of chronic kidney disease (CKD) may slow the decline of renal function and prevent the development of severe cardiovascular complications.[3] In addition to well-established CKD risk factors, such as age, hypertension, diabetes, obesity and metabolic syndrome, there are still other potentially modifiable risk factors to be identified for the prevention and management of CKD.

Betel nut (BN) is the fourth most widely used addictive substance in the world, and BN chewers make up over 10% of the world's population.[4] The prevalence of BN use has increased gradually in Taiwan, especially in rural areas.[5] In addition to the associations with oral cancer,[6] cardiovascular disorders,[7] hyperglycemia,[8,9] obesity,[10] metabolic syndrome,[8] type 2 diabetes mellitus,[9] liver cirrhosis[11] and increase in urinary albumin excretion,[12] BN chewing has also been reported to be associated with CKD.[13,14] However, the number of CKD patients recruited in previous studies[13,14]

was relatively small ($n = 677$) and the adjustment factors included were limited. In the present study, we conducted a retrospective analysis with the currently largest available series (27 482 participants, 4519 CKD) to explore the in-depth relationship between BN chewing and CKD in Taiwan.

METHODS

Participants

From 2003 to 2009, a total of 34 372 people attended a national health insurance health check-up program (NHI-CP) in Chia-Yi Christian Hospital, with 36 577 records in total; 1481 people attended the program more than once in different years with a total of 2205 extra visits. All of the participants were enrolled in this retrospective record-review study. For those receiving more than one health check-up, only the first was included. Participants with incomplete data ($n = 6890$) were excluded from the analysis, and a total of 27 482 participants were included. The study was approved by the Institutional Review Board of this hospital.

Methods

The NHI-CP is a formally designed physical check-up package for adults at or over the age of 40, issued by the Bureau of National Health Insurance (BNHI), Taiwan. It contains a standard lab test package, a brief questionnaire for basic demographic data (age, sex, address), health behaviours (status of cigarette smoking, alcohol drinking and BN chewing), personal medical history (including diabetes, hypertension, and hyperlipidemia), and a physical examination (PE). The participants were asked to report three aforementioned health behaviours in the last 6 months as a non-user, social user or regular user. PE data include body height, body weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP), and body mass index (BMI) was derived from the PE data. The standard laboratory studies include serum creatinine (Scr), total cholesterol (TC), triglycerides (TG), uric acid (UA), fasting blood sugar (FBS), alanine aminotransferase (ALT), hemoglobin (Hb) and urinalysis (including bio-chemical and sediment microscopic exams), which were all measured with standard automated technology. In addition, we also calculated estimated glomerular filtration rates (eGFR) for all included participants using the Modification of Diet in Renal Disease (MDRD) formula.[3] Participants fasted for 12 h overnight before blood sampling in the morning.

Variable definition

Chronic kidney disease was defined as an eGFR less than 60 mL/min per 1.73 m^2 as calculated by the MDRD formula, and then further stratified into CKD stage 3, 4 and 5 if the eGFR was 30–59 mL/min per 1.73 m^2, 15–29 mL/min per 1.73 m^2 and <15 mL/min per 1.73 m^2, respectively.[3] Hypertension (HTN) was defined as having a past personal history (regardless of whether or not they were taking medications), or a blood pressure of at least 140/90 mmHg.[15] Diabetes mellitus (DM) was defined as a fasting plasma glucose level of 126 mg/dL or higher, or a history of DM with or without medication.[16] Hyperlipidemia was defined as having a serum total cholesterol level of 200 mg/dL or higher, or a triglyceride level of 200 mg/dL or higher, or a past personal history of high TC or TG with or without medication.[17] Participants were defined as non-smokers if they did not smoke and as smokers if they smoked socially or regularly regardless of the amount they smoked. Participants were defined as non-chewers if they did not consume any BN at all; as chewers if they consumed BN socially or regularly. Likewise, participants were defined as non-drinkers if they did not consume any alcohol and as drinkers if they consumed alcohol socially or regularly. Proteinuria was defined as having +/− or heavier protein response (including + to 4+) in a urine dipstick test. Liver dysfunction was defined as an ALT level >44 IU/L according to the upper limits of the automated technology in this hospital, and anaemia was defined as an Hb level <13 g/dL in males, and <12 g/dL in females.[18] Hyperuricemia was defined as a serum UA level >7.0 mg/dL according to domestic guidelines.[19]

Laboratory methodology

Biochemistry tests including ALT, TC, TG, UA, and Scr were measured by an automatic analyzer (Hitachi 7170, Hitachi High Technologies Co, Tokyo, Japan). The test reagent for ALT was manufactured by Roche Diagnostics GmbH, Germany, and the reagents for all other biochemical tests were manufactured by Wako Pure Chemical Industries, Ltd, Japan. Hb analysis was measured by an automatic analyzer (Sysmex XE-2100/5000, Sysmex Co., Japan), and dipstick urinalysis was performed by an automated chemical analyzer (URISYS 2400, Roche Diagnostics, Germany).

Statistical analysis

Data were presented in a case-control manner, according to the status of being with and without CKD, and were reported as means and standard deviations or numbers and percentages as appropriate. Demographics, clinical characteristics and co-morbidities were analyzed by the Student's *t*-test or the Mann–Whitney U-test (as appropriate) for continuous variables, and by the χ^2 test for categorical variables.

Since age is significantly related to the decline of eGFR, we assessed the CKD prevalence of chewers versus non-chewers in different age groups (per decade until 70 years or older). The differences of CKD prevalence were compared by the χ^2 test.

To determine the association between BN chewing and CKD, we performed a multivariate logistic regression analysis (MLRA), choosing adjustment factors based on the following rationales: (i) factors that might influence CKD development, either contributing to or protecting from; (ii) potential confounding factors for CKD; and (iii) factors being both contributing factors and results of CKD. The chosen covariates included age, gender, BMI, drinking, smoking, HTN, DM, hyperlipidemia, hyperuricemia, anaemia, and proteinuria.

To test whether interaction effects (IE) existed among BN chewing and other variables, we conducted IE analyses between BN chewing and all other covariates selected for MLRA. We created a dummy variable as (BN × variable) and conducted separate multivariable regression analyses to test individual IE. For the covariates with significant IE, the odds ratios (OR) of CKD development related to BN chewing were estimated separately according to the statuses of these covariates.

Table 1 Characteristics of age, sex, blood pressure and laboratory profiles of the 27 482 participants stratified by chronic kidney disease (CKD) status

	Overall subjects (n = 27 482)	CKD(–) (n = 22 963, 83.6%)	CKD(+) (n = 4519, 16.4%)
Age (years)	58.02 ± 11.85	56.00 ± 11.80	68.32 ± 10.19***
Male gender	11991 (43.6%)	9826 (42.8%)	2165 (47.9%)***
eGFR (mL/min/1.73 m^2)	76.33 ± 17.75	81.51 ± 13.95	50.01 ± 9.93***
BMI (kg/m^2)	25.01 ± 4.15	24.97 ± 4.24	25.22 ± 3.62***
Systolic BP (mmHg)	131.66 ± 20.63	130.00 ± 19.86	140.11 ± 22.37***
Diastolic BP (mmHg)	76.95 ± 12.23	76.69 ± 12.03	78.27 ± 13.16***
Creatinine (mg/dL)	0.98 ± 0.37	0.90 ± 0.18	1.41 ± 0.69***
Cholesterol (mg/dL)	210.69 ± 41.41	210.20 ± 40.58	213.21 ± 45.33***
Triglyceride (mg/dL)	139.43 ± 132.25	137.00 ± 133.48	151.78 ± 125.10***
Uric acid (mg/dL)	6.03 ± 1.68	5.81 ± 1.53	7.17 ± 1.91***
Fasting blood glucose (mg/dL)	104.67 ± 38.10	103.72 ± 36.57	109.46 ± 44.77***
ALT (IU/L)	32.45 ± 40.60	32.72 ± 41.48	31.05 ± 35.77*
Hemoglobin (g/dL)	14.14 ± 1.67	14.20 ± 1.63	13.79 ± 1.80***

*P-value < 0.05; **P-value < 0.01; ***P-value < 0.001. Results are expressed as n (%) or means ± standard deviation (SD). The conversion factors from Conventional Units to Standard International (S.I.) Units were: creatinine 88.4; cholesterol, 0.026; triglyceride, 0.01129; uric acid, 59.48; fasting sugar, 0.056; alanine aminotransferase, 1.0; hemoglobin, 10. ALT, alanine aminotransferase; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

All analyses were carried out using the SPSS for Windows statistical software package version 18 (SPSS Inc., Chicago, IL, USA). P-values < 0.05 were considered to be statistically significant.

RESULTS

In total, 27 482 participants (15 491 females, 11 991 males, mean age 58.02 ± 11.85 years) were included in the analysis. Of all participants, 4519 (16.4%) had CKD and 1608 (5.9%) chewed BN. The prevalence of CKD in the BN chewers was 12.4%, and 16.7% in the non-chewers. The proportions of chewers in CKD stage 3, 4, and 5 were 4.5%, 3.7% and 1.7%, respectively. Of the participants with CKD, 4.4% chewed BN, and in the non-CKD participants, 6.1% chewed BN (P < 0.001).

As seen in Table 1, those who were found to have CKD tended to be older, with a higher proportion of males, higher BMI, higher SBP and DBP, higher Scr, TC, TG, UA, and FBS, but lower eGFR, ALT and Hb levels. In the analysis of health behaviours and co-morbidities, those who were found to have CKD tended to have a higher prevalence of DM, HTN, hyperlipidemia, proteinuria, anaemia and hyperuricemia, but a lower proportion of BN chewing, smoking, drinking and liver dysfunction (Table 2).

The analysis of CKD prevalence of those who chewed BN versus non-chewers in the different age groups revealed that in all age groups, BN chewers had a higher CKD prevalence, although all P-values were >0.05 in the comparisons (Table 3).

In the MLRA models, the adjusted OR of CKD for BN use was 1.23 (95% confidence interval (CI) 1.02–1.48, P = 0.027) (Table 4). IE analysis revealed that significant IE were present among BN chewing, gender, drinking, DM and proteinuria. For these four covariates, we conducted eight further MLRA stratified by the level of each interacting factor. When stratified by gender, the adjusted OR of CKD for male BN users was 1.23 (95% CI 1.02–1.48, P = 0.035) (Table 5). When stratified by drinking status, the adjusted OR of CKD for non-drinking BN users was 1.62 (95% CI 1.26–

Table 2 Personal behaviours and co-morbidities of the 27 482 participants stratified by chronic kidney disease (CKD) status

	Overall subjects (n = 27 482)	CKD(–) (n = 22 963)	CKD(+) (n = 4519)
Smoker	6921 (25.2%)	5850 (25.5%)	1071 (23.7%)*
Drinker	4594 (16.7%)	4096 (17.8%)	498 (11.0%)***
Betel nut chewer	1608 (5.9%)	1408 (6.1%)	200 (4.4%)***
Diabetes	3640 (13.2%)	2741 (11.9%)	899 (19.9%)***
Hypertension	11727 (42.7%)	8800 (38.3%)	2927 (64.8%)***
Hyperlipidemia	989 (3.6%)	746 (3.2%)	243 (5.4%)***
Proteinuria	2808 (10.2%)	1732 (7.5%)	1076 (23.8%)***
Liver dysfunction	4391 (16.0%)	3751 (16.3%)	640 (14.2%)***
Anemia	2592 (9.47%)	1816 (7.9%)	776 (17.2%)***
Hyperuricemia	6713 (24.4%)	4519 (19.7%)	2194 (48.6%)***

*P-value < 0.05; **P-value < 0.01; ***P-value < 0.001. Results are expressed as n (%). Definitions: Chewer: participants who chewed betel nut socially or regularly in the previous 6 months by self-reporting; CKD, eGFR < 60 mL/min/1.73 m^2 calculated by the Modification of Diet in Renal Disease formula; Smoker: participants who smoked socially, occasionally or regularly regardless of the amount in the previous 6 months by self-reporting; Drinker: participant who consumed alcohol socially or regularly regardless of the amount in the previous 6 months by self-reporting; Diabetes: fasting plasma glucose level equal to or over 126 mg/dL or a known history of diabetes with or without medication; Hypertension: having known past history or blood pressure of at least 140/90 mmHg with or without medication; Hyperlipidemia: having serum cholesterol level above 200 mg/dL, or triglyceride level 200 mg/dL or above or known past history with or without medication. Proteinuria, having +/– or heavier protein response (including + to 4+) in urine test; Liver dysfunction: ALT level >44 IU/L; Anemia, male Hb < 13 g/dL, female Hb < 12 g/dL; Hyperuricemia, for both genders, serum uric acid level > 7.0 mg/dL. CKD, chronic kidney disease.

Table 3 Comparison of CKD prevalence in chewers versus non-chewers stratified by age

Age range (years)	CKD+ ($n = 4519$)			*P*-value
	Gross CKD prevalence	CKD prevalence of non-chewers	CKD prevalence of chewers	
40~<50	299/8160 (3.7%)	265/7469 (3.5%)	34/691 (4.9%)	0.066
50~<60	454/7416 (6.1%)	415/6908 (6.0%)	39/508 (7.7%)	0.130
60~<70	1516/6385 (23.7%)	1443/6100 (23.7%)	73/285 (25.6%)	0.448
≥70	2250/5521 (40.8%)	2196/5397 (40.7%)	54/124 (43.5%)	0.522

Results are expressed as *n* (%).

Table 4 Multivariate logistic regression analysis for post-adjustment chronic kidney disease (CKD) odds

	Odds ratio	95% confidence interval	*P*-value
Age	1.09	1.09–1.10	0.000
Gender of male	0.82	0.76–0.89	0.000
Betel nut chewing	1.23	1.02–1.48	0.027
Smoking	1.02	0.93–1.12	0.645
Drinking	0.75	0.66–0.85	0.000
Body mass index	1.00	0.99–1.01	0.605
Hypertension	1.39	1.29–1.51	0.000
Diabetes	1.05	0.95–1.17	0.309
Hyperlipidemia	1.32	1.12–1.57	0.001
Anaemia	2.07	1.845–2.32	0.000
Proteinuria	2.43	2.19–2.69	0.000
Hyperuricemia	3.57	3.29–3.87	0.000

*P-value < 0.05; **P-value < 0.01; ***P-value < 0.001.

Table 5 Odds ratio of chronic kidney disease (CKD) with betel nut (BN) chewing, stratified by presence and absence of variables with significant interaction effect (gender, drinking, diabetes mellitus (DM), proteinuria)

	Odds ratio	95% confidence interval	*P*-value
Corporate *a*	1.23	1.02–1.48	0.027
Gender *b*			
Male	1.23	1.02–1.48	0.035
Female	0.94	0.44–2.00	0.865
Drinking *b*			
Yes	1.01	0.77–1.32	0.961
No	1.62	1.26–2.08	0.000
DM *b*			
Yes	1.11	0.73–1.69	0.621
No	1.27	1.04–1.56	0.021
Proteinuria *b*			
Yes	1.00	0.68–1.48	0.989
No	1.30	1.06–1.60	0.013

a: Multivariate logistic regression analysis conducted with all adjustment factors, including age, gender, drinking, smoking, hypertension (HTN), DM, hyperlipidemia, hyperuricemia, body mass index, anemia and proteinuria; *b*: Multivariate logistic regression analysis conducted with the rest of the variables, in addition to specific variables under stratified conditions as presence and absence.

2.08, $P = 0.000$). When stratified by diabetes, the adjusted OR of CKD for non-diabetic BN users was 1.27 (95% CI 1.04–1.56, $P = 0.021$). When stratified by proteinuria, the adjusted OR of CKD for non-proteinuric BN users was 1.30 (95% CI 1.06–1.60, $P = 0.013$). There were no significant ORs in the female, drinking, diabetes and proteinuric groups.

DISCUSSION

In this cross-sectional study, we found a conditional association of BN chewing with CKD in males, non-drinkers, and those without diabetes or proteinuria, which is unique to previous studies. In the current study, the overall prevalence of CKD in BN chewers seemed to be lower than in non-chewers (12.4% vs 16.7%). However, when the data were stratified by age per decade (Table 3), the prevalence of CKD in BN chewers became higher than in non-chewers in all age groups from 40 to over 70 years, although without statistical significance. In addition, CKD prevalence increased with age in both the BN chewers and non-chewers groups. These results seem to support the idea that BN chewers might have a higher CKD prevalence. The data also raised the possibility that other factors might be involved in the pathogenesis of CKD. BN chewing was not considered to be a main pathogenic factor of CKD. Instead, age was an obviously important contributor, and, as shown in Tables 1 and 2, participants found to have CKD also had higher prevalence of some well-established CKD pathogenic risks such as obesity, diabetes, hypertension, hyperlipidemia, proteinuria, anaemia and hyperuricemia.

The proportion of BN chewing in the CKD subjects appeared to be lower than in participants without CKD (Table 2). This observation does not coincide with our hypothesis that BN chewing might be associated with CKD. However, as also shown in Table 2, the proportion of all the modifiable variables (including smoking, drinking and BN chewing) appeared to be lower in the participants with CKD, and the prevalence of all non-modifiable risk factors (DM, HTN, hyperlipidemia) in the CKD participants was significantly higher. It seems reasonable to infer that people might change their health behaviours as they grew older or with poorer health. This hypothesis is supported by Tseng's study,[20] which reported that in older age groups, a protective behavioural pattern was more dominant. In addition, the

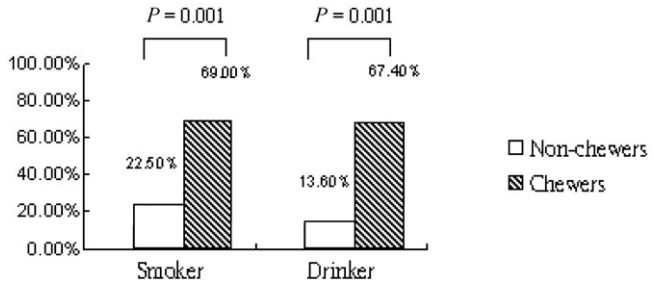

Fig. 1 Comparison of the proportion of smokers and drinkers in chewing versus non-chewing participants.

data in this study revealed that the proportion of BN chewing decreased with worsening CKD severity (for CKD stage 3, 4, and 5, the proportions of BN chewing were 4.5%, 3.7% and 1.7%, respectively). Since the questionnaire was a fixed form authorized by the BNHI, health behaviours data were obtained by self-reporting based on the situation in the past 6 months, so there was no access to information on a more detailed BN chewing history (for example, the amount consumed and as an ex-chewer). In addition, elderly people might not be able to precisely remember their BN chewing habit over the previous 5–6 months. These were potential sources of ascertainment bias and recall bias.

As seen in Figure 1, our study results revealed a significantly higher percentage of concurrent substance use. This is consistent with previous research reporting that BN chewers are more likely to use alcohol and cigarettes as well.[21] Such concurrent substance use represents certain lifestyle patterns that might exert clusters of health effects simultaneously and confer a higher health risk. Current relevant evidence has reported additive effects on chronic hepatitis B, chronic hepatitis C and hepatoma,[22] oral cavity cancer,[23] and calcium urolithiasis.[24] This should be dealt with seriously by the relevant health authorities, for example, by sponsoring more health education activities targeting all three risky behaviours at the same time.

As shown in Table 4, our study results revealed a reduced CKD risk with alcohol drinking (OR, 0.75, 95% CI 0.66–0.85, $P = 0.000$). This is consistent with previous research reporting an inverse association between alcohol consumption and renal dysfunction.[25] Alcohol consumption in moderate amounts has been acknowledged to be a protective factor for cardiovascular health. For the kidneys, oxidative stress and endothelial dysfunction, which are inter-related, are considered to play a role in the pathophysiology of many renal diseases. Ethanol and non-alcoholic wine components, especially polyphenols, have been shown to influence oxidative balance and endothelial function, and exert favourable effects on kidneys in both animal and human studies.[26]

Our study found four significant interaction factors with BN chewing: gender, drinking, DM, and proteinuria. Table 5 presents the ORs of CKD with BN chewing in the different stratification groups. A thorough analysis of the intertwining interactions among these factors was beyond the scope of this article. However, as male gender constituted the majority of the BN chewers, it seems reasonable that the ORs and confidence intervals were almost identical with the overall values. For the non-drinking, non-diabetic and non-proteinuric groups, the ORs and confidence intervals were similar, implying that they might be regarded as background situations on which BN chewing exerted a similar influence. However, when different situations (drinking, diabetes, proteinuria) were involved, such significant associations disappeared. To our best knowledge, there is no available research discussing the interaction effects of BN chewing and diabetes or other health behaviours. For the diabetic patients, the disease itself is a well-known CKD risk so that the relative impacts of BN chewing on CKD seemed 'buffered' and became non-significant. For drinkers, a lower OR of CKD was associated with BN chewing, implying that drinking seemed to exert a protective effect as discussed in the previous paragraph. As such, we should be cautious about the interpretation of the results; the interacting effects of these covariates on the risk of CKD with BN chewing should be researched further.

In addition to the biases discussed earlier, there are several other limitations to this study. This was a retrospective cross-sectional study based on the results of a health check-up program in a single hospital setting. Sampling and ascertainment bias might arise from several aspects. First, lab diagnoses were made with only one urine sample and blood tests, which might not be able to validate the true renal function. Second, the participants took the initiative to undergo the health check-up program in this hospital, and they might have had a higher socio-economic position or education level, been more alert to their own health situation, or already had certain ailments, and so not be representative of the general population. These factors were sources of selection bias. Another limitation is that the questionnaire on health behaviours did not include detailed quantitative assessment (duration and amount) of BN consumption, nor did it include previous abstinence history. Under such circumstances, a substantial temporal relationship and dose-effect relationship between BN chewing and CKD cannot be concluded.

However, due to the following reasons, this study still can provide valuable information. First, this is currently the largest series studying the association of BN chewing and CKD. Second, the Chia-Yi region is an area with lower average income and a large elderly population. According to a national statistics report, the national average proportion of elderly people in Taiwan in 2009 was 10.6%, and the competing figure in the Chia-Yi region (Chia-Yi City and Chia-Yi County combined) was 14.0%.[27] The average family income in this area is approximately 20% lower than the national average.[28] The population in this study was therefore very different from the populations in previous Taiwanese

research.[29] Third, our study not only agreed with previous research in this field,[13,14] but also added more adjustment factors (hyperuricemia and proteinuria) for MLRA, opening a new field of IE due to life patterns, especially the effect of alcohol drinking on kidney disease. We also found a 'conditional' association of BN chewing and CKD, which is unique to previous studies and contributes to existing knowledge. Further investigations are needed for prospective longitudinal cohort studies, including a detailed history of BN chewing amount, duration, and previous abstinence history. Also, further analysis of life patterns and the complex interactions of the items therein, and especially the effect of alcohol drinking on renal health are needed.

In conclusion, BN chewing, as a personal life pattern, had intricate interactions with gender, drinking, DM and proteinuria. We found a significant association between BN chewing and CKD in male, non-drinking, non-diabetes and non-proteinuria; however, such results should be interpreted cautiously. Further studies should be conducted to delineate the relationship between BN chewing and those who drink alcohol, and those with diabetes or proteinuria.

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