

The Association between Betel Quid Chewing and Metabolic Syndrome Among Urban Adults in Mandalay District of Myanmar

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Abstract

Background. As the prevalence of metabolic syndrome, obesity and diabetes increase worldwide, the need to identify modifiable lifestyle risk factors also increases, especially those that may be relatively unique to a specific population. To explore a possible association between betel quid chewing and metabolic syndrome, a community-based cross-sectional study was conducted.

Methodology. Three hundred ninety-one (391) adults were interviewed and the following parameters were measured: triglycerides, HDL-cholesterol, glucose, waist circumference, body mass index and blood pressure. Multiple logistic regression was used to determine the association between betel quid chewing and metabolic syndrome while controlling for confounders.

Results. The prevalence of metabolic syndrome was similar in chewers and non-chewers, 50% and 49%, respectively. After controlling for other factors, development of metabolic syndrome was positively associated with number of betel quids chewed per day, age greater than 40 years, and a positive family history of hypertension and diabetes. Regarding the duration of betel chewing, when analyzed by sex, the risk was doubled in men compared to non-chewers (OR 2.15; 95% CI = 1.21, 3.84). As a result, a man chewing more than 10 pieces (OR 2.49; 95% CI = 1.36, 4.57) of betel quids per day for more than 10 years had a two-fold increased chance of developing the metabolic syndrome.

Conclusions. Frequency and duration of betel quid chewing may represent a behavioral lifestyle target for approaches to reduce the incidence of metabolic syndrome.

Key words: betel quid chewing, metabolic syndrome

INTRODUCTION

Worldwide, studies show that betel quid (BQ) chewing increases the risk of oral cancer and esophageal cancer.¹ In a population-based study in Taiwan where prevalence of BQ use is about 15%, data showed an increased risk of metabolic disease.² Arecoline, one of the betel nut alkaloids, may contribute to the metabolic abnormalities associated with BQ use. In the 3T3-L1 adipocyte, arecoline blocks insulin signaling and lipid storage in humans,³ while in animals, it inhibits adipogenesis, induces lipolysis and interferes with insulin-induced glucose uptake.⁴ The betel nut (Areca Nut) is the fourth most widely used psychoactive stimulant around the world after nicotine, alcohol and caffeine.⁵ Though the actual global prevalence of this habit is yet to be documented, it has been estimated that approximately 600 million individuals worldwide chew betel quid on a daily basis.¹ The BQ is composed of areca nuts wrapped in a betel leaf coated with slaked lime.

The betel leaf comes from the Piper betel vine and is a mild stimulant. In Myanmar, BQ is known as “*Kwunyar*,” and is chewed with or without tobacco. The tobacco may be prepared in a variety of ways, including raw or cured (with or without drying or roasting), and other additives may include alcohol, honey, lime juice or fragrance.⁶ The use of betel quid is embedded in Myanmar culture and history,⁶ with an estimated prevalence of 30% to 52%; 85% of chewers add tobacco or smoked tobacco products.^{7,8}

The goal of this community-based study was to explore the possible association between betel quid chewing and metabolic syndrome in a Township in Myanmar. This would allow health personnel to estimate the impact of BQ chewing on health, to raise awareness regarding the risk of these serious diseases, and to encourage preventive measures, such as legislation, to decrease smokeless tobacco use.

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METHODOLOGY

This community-based cross-sectional study evaluated adults in the Chan Aye Thar Zan Township in Mandalay District, chosen because of its heterogeneous population. The study was conducted from August 1, 2018 to April 30, 2019 through the combined efforts of the Department of Endocrinology, University of Medicine, Mandalay (UMM) and the Regional Public Health and Medical Services Department, Mandalay region, Myanmar. The study was approved by the UMM Ethical Review Committee, and written informed consent was obtained from each participant.

Participants

A minimum of 385 adult residents were needed to estimate the prevalence of betel nut chewing in Chan Aye Thar Zan Township, Myanmar given the following information: 1) The estimated prevalence of betel chewing in Myanmar Dagon (East) Township is 50%;⁸ 2) Desired confidence level set at 95%; and 3) Margin of error is set at 5%. The sample size was computed using the STEPwise approach to surveillance (STEPS) Sample Size Calculator and Sampling Spreadsheet developed by the WHO.

Multi-stage sampling was conducted. First, ten quarters of the Township were randomly selected and a similar proportion of eligible households was identified in each quarter based on its population size. Next, a lottery was used to identify a single individual from each household. The staff (Health Assistants and Midwives) of the Chan Aye Thar Zan Township Medical Office contacted these potential subjects and evaluated their eligibility for participation.

Inclusion criteria were age 18 years and above, male or female of any ethnic group and willingness to participate. Exclusion criteria were pregnancy, inability to communicate or hear well and mental illness.

Data collection

Potential subjects were asked to report to the Dhamma Hall of the corresponding quarter at 0700h after a 10-hour fast. After consenting to the study, blood was obtained to measure triglycerides, HDL-cholesterol (HDL) and glucose using a Cobas 6000 analyzer. Waist circumference, height, weight and sitting blood pressure were also measured. A 15-minute face to face interview was performed using a structured questionnaire that included age, sex, occupation and details about health-harming risk factors (smoking, alcohol use, betel quid chewing and physical inactivity, as well as past medical history, drug history and family history of type 2 diabetes (T2DM), hypertension and cardiovascular disease). For betel quid users, the number of betel quid chewed per day, age at initial use, estimated years of chewing and the ingredients of preferred betel quid were recorded. At the conclusion of the interview, a sitting blood pressure was measured.

Definition of terms

Participants chewing one or more betel quids daily for one year were categorized as betel quid chewers and the remaining subjects were considered to be non-chewers.

Metabolic syndrome was defined as the presence of three out of five components using previously published consensus criteria.⁹

Central obesity (ethnicity-specific values for waist circumference for Asians): ≥ 90 cm in males or ≥ 80 cm in females

Raised triglycerides: ≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality

Reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in males and < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality

Raised blood pressure: Systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg or treatment of previously diagnosed hypertension (mean value of the two measurements of sitting blood pressure was used).

Raised fasting plasma glucose: FPG ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed T2DM

Smoking habits were defined as: 1) Current smoker: a person who has smoked greater than 100 cigarettes or equivalents in his/her lifetime and has smoked in the last 28 days; 2) Ex-smoker: a person who has smoked greater than 100 cigarettes or equivalents in his/her lifetime but has not smoked in the last 28 days or; 3) Non-smoker: a person who has not smoked greater than 100 cigarettes or equivalents in his/her lifetime and does not currently smoke.¹⁰

Statistical analysis

Descriptive statistics were shown as percentages for categorical variables and mean/median for continuous variables. Differences in clinical characteristics between chewers and non-chewers were evaluated using either the chi-square test (for categorical variables) or the independent t-test (for continuous variables) (Table 1). Possible confounders were identified using simple logistic regression by determining the crude association between metabolic syndrome and the following demographic and clinical factors: age, sex, smoking, alcohol use, unhealthy food intake, sedentary lifestyle, family history of T2DM, hypertension and cardiovascular disease. Factors whose crude association with metabolic syndrome resulted in a $p > 0.10$ were considered as confounders and were included in the multiple logistic regression model. Backward elimination method was then applied to determine the final model using $p \geq 0.05$ as cut-off. Sex, smoking and alcohol drinking were included in the final model regardless of p -values due to strong evidence of their association with metabolic

syndrome in related literature.¹¹⁻¹³ Multicollinearity was checked by using the variance inflation factor (VIF) >2.5 and tolerance <0.1. The final logistic regression model was used to determine the association between betel quid chewing and metabolic syndrome. Data were analyzed with Statistics Package for Social Sciences (SPSS) version 20.

RESULTS

Of the 391 individuals who participated in the study, 182 (46.6%; 95% CI = 42%, 52%) were betel quid chewers and 209 (53.5%; 95% CI = 48%, 59%) were non-chewers, with

similar proportions of men and women in each group. Most participants had completed secondary level schooling and were more than 40 years old. Chewers were more likely than non-chewers to be married, to smoke and to drink alcohol, while non-chewers were more likely to have a family history of diabetes.

The BMI (kg/m²) of the chewers was higher than that of the non-chewers (26.7 ± 17.6 vs 23.9 ± 5.0, *p*<0.05) and the waist circumference (cm) of male betel quid chewers was higher than that of male non-chewers (85.7 ± 14.6 vs 81.7 ± 14.4, *p*<0.05) (Table 2).

Table 1. Demographic and clinical characteristics of betel quid chewers and non-chewers (n = 391). Statistically significant results are shown in bold font

Characteristics	Chewers	Non-chewers	<i>p</i>
Total participants, n (%)	182 (46.6%, CI: 0.42-0.52)	209 (53.5%, CI: 0.48-0.59)	
Male sex, n (%)	120 (65.9%)	140 (67.0%)	0.826
Female sex, n (%)	62 (34.1%)	69 (33.0%)	
Age (yrs.), mean (SD)	44.1 ± 14.1	41.27 ± 15.9	0.061
Age, n (%)			<0.05
<19	6 (3.3%)	26 (12.4%)	
20-29	27 (14.8%)	33 (15.8%)	
30-39	34 (18.7%)	33 (15.8%)	
40-49	43 (23.6%)	49 (23.4%)	
50-59	42 (23.1%)	37 (17.7%)	
≥60	30 (16.5%)	31 (14.8%)	
Education, n (%)			<0.001
Illiterate	6 (3.3%)	1 (0.4%)	
Read & write	14 (7.7%)	3 (1.4%)	
Primary school	43 (23.6%)	30 (14.4%)	
Secondary school	56 (30.8%)	53 (25.4%)	
High school	34 (18.7%)	52 (24.9%)	
University	14 (7.7%)	18 (8.6%)	
Graduate	15 (8.2%)	52 (24.9%)	
Occupation, n (%)			<0.001
Government servant	14 (7.6%)	23 (11.0%)	
Company employee	7 (3.8%)	36 (17.2%)	
Own business	64 (35.2%)	77 (36.8%)	
Students	5 (2.8%)	4 (1.9%)	
Unemployed	5 (2.8%)	3 (1.4%)	
Labourer	23 (12.6%)	17 (8.1%)	
Farmer	2 (1.1%)	1 (0.5%)	
Pensioner	12 (6.6%)	12 (5.7%)	
Driver	36 (19.8%)	35 (16.8%)	
Others	14 (7.7%)	1 (0.5%)	
Marital status, n (%)			<0.001
Married	126 (69.2%)	113 (54.0%)	
Single	38 (20.9%)	84 (40.2%)	
Divorced	4 (2.2%)	1 (0.5%)	
Widow/Widower	14 (7.7%)	11 (5.3%)	
Family history, n (%)			
Diabetes mellitus	11 (6%)	20 (11.0%)	<0.05
Hypertension	34 (18.7%)	44 (21.1%)	0.558
Cardiovascular disease	3 (1.6%)	8 (3.8%)	0.194
Smoking, n (%)			<0.05
Current smoker	46 (25.3%)	38 (18.1%)	
Ex-smoker	17 (9.3%)	11 (5.3%)	
Non-smoker	119 (65.4%)	160 (76.6%)	
Alcohol drinking, n (%)			<0.001
Current drinker	70 (38.4%)	41 (19.6%)	
Ex-drinker	26 (14.3%)	16 (7.7%)	
Non-drinker	86 (47.3%)	152 (72.7%)	
Exercise, n (%)	79 (43.4%)	86 (41.2%)	0.652

*NS=not significant

The metabolic syndrome was present in 131 participants (33.5%; 95% CI = 28%, 38%) and was more common in people who were more than 40 years old (80.2% vs 19.9%, $p < 0.001$) (Table 3). The youngest age of a participant with metabolic syndrome was 21 years. While the proportion of women with metabolic syndrome (38.2%) was higher than

those without (31.2%), it was not statistically significant ($p = 0.165$)

Overall, the prevalence of the metabolic syndrome was similar in chewers and non-chewers, 50% (95% CI = 41%, 59%) and 49% (95% CI = 41%, 58%), respectively. However,

Table 2. Values for components of the metabolic syndrome in betel quid chewers and non-chewers. Statistically significant results are shown in bold font.

Characteristics	Chewers (182, 46.6%)	Non chewers (209, 53.5%)	p
	(mean ± SD)	(mean ± SD)	
BMI	26.7 ± 17.6	23.9 ± 5.0	<0.05
Waist circumference, Male (≥90 cm)	85.7 ± 14.6	81.7 ± 14.4	<0.05
Female (≥80 cm)	82.4 ± 16.1	83.6 ± 11.4	0.64
Systolic blood pressure (≥130 mm Hg)	126.2 ± 21.2	129.5 ± 18.5	0.102
Diastolic blood pressure (≥85 mmHg)	81.1 ± 13.2	81.7 ± 11.6	0.769
HDL ** Male (<40 mg/dL)	49.0 ± 15.8	47.3 ± 10.2	0.288
Female (<50 mg/dL)	52.0 ± 10.9	52.9 ± 10.8	0.631
TG (≥150 mg/dL)	147.3 ± 109.6	128.9 ± 86.9	0.065
Fasting Blood glucose (≥100 mg/dL)	108.9 ± 51.6	102.7 ± 41.8	0.184

*TG – triglycerides; **HDL – High density lipoprotein cholesterol

Table 3. Factors associated with the presence or absence of metabolic syndrome. Statistically significant results are shown in bold font. Chi square test was used.

Variables	Metabolic syndrome		p
	Positive (131, 33.50%)	Negative (260, 66.50%)	
Duration of betel quid chewing			
Non-chewers	65 (49.62%)	144 (55.38%)	0.067
<10 years	19 (14.50%)	51 (19.62%)	
≥10 years	47 (35.88%)	65 (25.00%)	
Sex			
Male	81 (61.83%)	179 (68.85%)	0.165
Female	50 (38.17%)	81 (31.15%)	
Age			
≤40 yr.	26 (19.85%)	133 (51.15%)	<0.001
>40 yr.	105 (80.15%)	127 (48.85%)	
Education			
Up to Secondary school	70 (53.44%)	136 (52.31%)	0.833
More than Secondary school	61 (46.56%)	124 (47.69%)	
Occupation			0.135
Govt servant/Company employee / Own business	67 (51.15%)	154 (59.23%)	
Others (Laborer /Unemployed/ /Farmer/Driver)	60 (45.80%)	93 (35.77%)	
Students	4 (3.05%)	13 (5.00%)	
Marital status			
Married	90 (68.70%)	149 (57.31%)	<0.05
Single/other	41 (31.30%)	111 (42.69%)	
Smoking			
Current smoker	26 (19.85%)	58 (22.31%)	0.842
Ex-smoker	10 (7.63%)	18 (6.92%)	
Non-smoker	95 (72.52%)	184 (70.77%)	
Alcohol drinking			
Current drinker	37 (28.24%)	74 (28.46%)	0.998
Ex-drinker	14 (10.69%)	28 (10.77%)	
Non-drinker	80 (61.07%)	158 (60.77%)	
Exercise			
Doing exercise	59 (45.04%)	106 (40.77%)	0.42
Not doing exercise	72 (54.96%)	154 (59.23%)	
Family history of hypertension			
Yes	48 (36.64%)	30 (11.54%)	<0.001
No	83 (63.36%)	230 (88.46%)	
Family history of diabetes mellitus			
Yes	27 (20.61%)	4 (1.54%)	<0.001
No	104 (79.39%)	256 (98.46%)	
Family history of CVD			
Yes	5 (3.82%)	6 (2.31%)	0.394
No	126 (96.18%)	254 (97.69%)	

there was a positive association between the number of betel quids chewed each day and the presence of metabolic syndrome. There was also an increase in metabolic syndrome in those with more than 10 years of chewing. The rates of smoking, alcohol use and exercise were similar in individuals with and without metabolic syndrome. Among the participants with metabolic syndrome, most have a family history of hypertension and DM.

The betel chewers who consumed more than 10 pieces per day have 1.91 times higher risk of developing MS compared to non-betel chewers. Participants older than 40 years have 2.23 times higher risk of metabolic syndrome compared to younger individuals. Participants who are single have 39% lower risk for metabolic syndrome.

Family history of hypertension and diabetes have influence on metabolic syndrome risk (Table 4). After controlling for other variables, the predisposing factors for development of metabolic syndrome among betel chewers are number of betel quids per day, age and positive family history of hypertension and DM. Participants who chewed more than 10 pieces per day of betel quid have higher risk of metabolic syndrome compared to non-chewers (AOR 1.47; 95% CI = 1.10, 3.30). Participants who are 40 years and older have 2.23 odds of developing MS (AOR 2.23; 95%CI = 1.28, 3.92). Participants who do not have a family history of hypertension have 62% lower risk of developing MS compare to its reference group (AOR 0.38; 95% CI = 0.21,0.68). Similarly, participants who do not have family history of DM, have 90% risk reduction for MS compare to those with a family history of DM (AOR 0.10; 95% CI = 0.03, 0.32).

Age appeared to be an effect modifier in the association between betel quid chewing and metabolic syndrome. Therefore, age was used to stratify participants according to the duration of betel chewing (Table 5). Without stratification by age, a participant who chewed more than 10 pieces of betel quids per day had a 69% greater chance

Table 4. Multivariate analysis of metabolic syndrome in betel quid chewers and non-chewers

Variables	OR (CI)	AOR (CI)
No of betel quid		
Non-chewers	1	1
<10 pieces/day	0.79 (0.43-1.42)	0.71 (0.37-1.37)
≥10 pieces/day	1.69 (1.04-2.75) *	1.47 (1.10-3.30) *
Age		
≤40 yr.	1	1
>40 yr.	4.23 (2.51-7.09) **	2.23 (1.28-3.92) *
Marital status		
Married	1	1
Single/other	0.61 (0.39-0.95) *	0.81 (0.48-1.35)
Family history of hypertension		
Yes	1	1
No	0.22 (0.13-0.39) **	0.38 (0.21-0.68) *
Family history of diabetes mellitus		
Yes	1	1
No	0.06 (0.02-0.19) **	0.10 (0.03-0.32) **

**p<0.001, *p<0.05

of developing metabolic syndrome (OR 1.69; 95% CI = 1.04, 2.76) compared to the reference group. When a cut-off threshold of 40 years was used to stratify the analysis of the number of betel quids chewed or the duration of chewing, the odds of developing metabolic syndrome changed but the 95% confidence interval crossed one.

The prevalence of metabolic syndrome was almost double in men compared to women. When all participants were analyzed, those who chewed more than 10 pieces of betel quids per day had 1.69 times higher risk for metabolic syndrome (OR 1.69; 95% CI = 1.04, 2.76) compared to the non-chewers. When sex was considered in this analysis (Table 5), the odds in men increased to 2.49 (OR 2.49; 95% CI = 1.36, 4.57). While the risk of metabolic syndrome was decreased in women (OR 0.76; 95% CI = 0.32, 1.85), this finding was not statistically significant.

Table 5. Association of stratified age and sex with the presence of metabolic syndrome in betel quid chewers and non-chewers. Statistically significant results are shown in bold font.

Stratified factors	Independent variables	Odd ratio (95% CI) for MS
Age		
All age groups	No. of betel quid pieces/day	1
	Non-chewer	1
	<10	0.79 (0.43-1.43)
	≥10	1.69 (1.04-2.76) *
≤40 year	Non-chewer	1
	<10	0.78 (0.38-1.59)
	≥10	1.64 (0.89-3.00)
>40 year	Non-chewer	1
	<10	0.57 (0.15-2.14)
	≥10	1.42 (0.53-3.71)
Age		
All age groups	Years of betel quid chewing	1
	Non-chewer	1
	<10	0.82 (0.45-1.51)
	≥10	1.60 (0.99-2.58)
≤40 year	Non-chewer	1
	<10	1.54 (0.67-3.56)
	≥10	1.14 (0.65-1.99)
>40 year	Non-chewer	1
	<10	0.54 (0.16-1.75)
	≥10	1.99 (0.70-5.68)
Sex		
All subjects	No. of betel quid pieces/day	1
	Non-chewer	1
	<10	0.79 (0.43-1.42)
	≥10	1.69 (1.04-2.76) *
Male	Non-chewer	1
	<10	0.67 (0.29-1.54)
	≥10	2.49 (1.36-4.57) **
Female	Non-chewer	1
	<10	0.84 (0.35-2.06)
	≥10	0.76 (0.32-1.85)
Sex		
All subjects	Years of betel quid chewing	1
	Non-chewer	1
	<10	0.82 (0.45-1.51)
	≥10	1.60 (0.99-2.58)
Male	Non-chewer	1
	<10	0.62 (0.23-1.62)
	≥10	2.15 (1.21-3.84) **
Female	Non-chewer	1
	<10	0.79 (0.34-1.82)
	≥10	0.82 (0.32-2.13)

**p<0.001, *p<0.05

Regarding the duration of betel chewing, when analyzed by sex, the risk increased in men to more than twice that of non-chewers (OR 2.15; 95% CI = 1.21, 3.84). As a result, a man chewing more than 10 pieces of betel quids per day for more than 10 years had a two-fold increased chance of developing the metabolic syndrome.

DISCUSSION

Although a variety of definitions and criteria have been used to characterize the metabolic syndrome, it remains a useful marker of a two-fold increased risk for cardiovascular disease and a five-fold increased risk of type 2 diabetes.⁹ Moreover, as the prevalence of the metabolic syndrome, obesity and diabetes increases worldwide, the need to identify and mitigate risk factors increases, especially those that may be relatively unique to a specific population.

Amidst concerns that the metabolic syndrome is becoming a worldwide epidemic, a number of studies have considered whether there are modifiable lifestyle factors that might reduce this trend. A previous study in the Yangon region demonstrated significantly greater rates of components of the metabolic syndrome in urban dwellers compared to rural inhabitants.¹⁴ In men, rates of hypercholesterolemia and hypertriglyceridemia were higher, and in both sexes, obesity (12.3% vs. 7.7%; $p = 0.019$) and diabetes (17.2% vs. 9.2%; $p = 0.024$) were more common in urban residents.

Using the Modified ATP III criteria, up to 26.4% of adults in the Yangon region of Myanmar had one or more components of the metabolic syndrome: obesity (5.5%), diabetes (10.5%), overweight (16.9%), prediabetes (19.7%) and hypertension (26.4%).¹⁵ In the Yangon study, metabolic syndrome was present in 16.6% of men and 20.5% of women. By contrast, in the current study in Mandalay, metabolic syndrome was found in 33.5% of participants, with 38.2% being men and 31.2% were women. Whether this reflects different behaviors in the two areas or a general increase in risk factors over time cannot be determined.

This study found that men who chewed betel quid more than 10 pieces per day for more than 10 years had a two-fold increased chance of developing metabolic syndrome. These data suggest that betel quid chewing is an important modifiable factor for the development of metabolic syndrome, particularly with long-term and heavy use. The risk for MS in addition to the increased risk for development of oral, pharyngeal and esophageal cancers, indicates the need for an urgent intervention at the community level to reduce BQ chewing, in the hope of significantly reducing cardiovascular and oncologic morbidity and mortality. Use of areca nut and betel quid is especially common in the entire Asia-Pacific region, including Myanmar. A 2016 Policy Review from a meeting of scientific and public health leaders representing 21 countries called for action to reduce use of this agent.¹⁶

Although we have shown that betel quid chewing is associated with development of metabolic syndrome, there are several limitations to this study. First, this study is cross-sectional, so causality cannot be demonstrated, and future prospective cohort studies would be necessary to validate these conclusions. Second, because self-report questionnaires were used to estimate the exposure to betel quid, misclassification may have occurred. However, using the cumulative exposure of betel quid chewing to assess the relationship to metabolic syndrome likely minimizes the residual confounding. Furthermore, we show dose-response effects between betel quid chewing and metabolic syndrome. While this reduces the possibility of a biased result, the true strength of association may be weakened.

CONCLUSION

The amount of betel quid chewed per day is associated with the development of metabolic syndrome in the Mandalay region of Myanmar. This finding provides a target for intervention at the community level. However, a number of factors may pose a challenge to any campaign to reduce betel quid use. These include the following: psychoactive effects of the areca nut, development of dependence, widespread cultural acceptance of this practice, an association with masculinity in men and a perception that the practice enhances interpersonal relationships.¹⁷ It is our hope that identification and public awareness of these risks associated with betel quid use will lead to worldwide policies aimed at reducing its use and improving population health.

Statement of Authorship

The authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement

AAA: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **SNSZ:** Methodology, Validation, Investigation, Resources, Data Curation, Writing – original draft preparation, Visualization; **AKK:** Software, Validation, Formal analysis, Investigation, Resources, Data Curation; **ACT:** Software, Validation, Investigation, Resources.

Author Disclosure

The authors declared no conflict of interest.

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