Transgenerational effects of betel-quid chewing on the development of the metabolic syndrome in the Keelung Community-based Integrated Screening Program\(^1\)\(^-\)\(^4\)

Tony H-Hsi Chen, Yueh-H Chiu, and Barbara J Boucher

ABSTRACT

Background: The transgenerational metabolic effects of betel-quid chewing have been reported in mice but not in humans.

Objective: This study aimed to determine whether exposure to paternal chewing of betel nut quids led to an increased risk of early manifestation of the metabolic syndrome (MetS) in human offspring.

Design: The subjects were selected from 66,971 residents aged \(>19\) years who attended a community-based Integrated Screening Program in Taiwan and who were identified as parent-child trios \((n = 5037)\). Using a population-based, parent-child study design, we compared the mean ages of offspring with MetS at entry between those who were exposed and those who were unexposed to paternal chewing of quids containing betel nut. Cox proportional hazards regression models were used to estimate adjusted hazard ratios and to assess dose-response relations for paternal betel-quid exposure.

Results: The offspring who were exposed to paternal betel-quid chewing were younger than those who were not exposed, regardless of MetS status; they also had a 2.14-fold increase in the risk of early manifestation of MetS (adjusted hazard ratio = 2.14; 95% CI: 1.25, 3.66) after control for environmental and other risk factors, including personal betel chewing. Significant dose-response relations were found between the risk of early MetS and the quantity and duration of paternal exposure to betel quids. In the absence of MetS in either parent and of betel-quid consumption by the offspring, paternal exposure to betel quids increased the risk of early manifestation of MetS in offspring 2.53-fold (95% CI: 1.03, 2.64) compared with paternal nonexposure.

Conclusion: Our findings suggest that exposure to paternal betel-quid chewing increases the risk of early manifestation of MetS in human offspring in a dose-dependent manner. Am J Clin Nutr 2006;83:688–92.

KEY WORDS Areca catechu, betel, metabolic syndrome, transgenerational effect, Taiwan, paternal, humans

INTRODUCTION

In addition to the established causal relation between betel-quid (paan) chewing and oral cancer, which is independent of chewing tobacco use \((1)\), the effect of this habit on chronic diseases has gained increasing attention over the past decade. Evidence suggesting an independent role of betel-quid chewing in the development of type 2 diabetes has been shown in 2 population-based studies conducted in humans, one conducted in Taiwan \((2)\) and the other conducted in Papua New Guinea \((3)\). In addition to type 2 diabetes, betel-quid use has also been associated with increases in heart rate, blood pressure, waist size, cholesterol and triacylglycerol concentrations, and body weight \((4–7)\). A previous experimental study in CD1 mice showed that paternal exposure to betel nut \((Areca catechu)\) transmits an increased risk of hyperglycemia to non–betel fed first generation offspring, especially male offspring. Furthermore, this effect was independent of paternal or maternal hyperglycemia \((8)\). However, no studies have, to date, investigated the possibility of similar inheritance of betel-quid diabetogenicity in humans. Whether the inheritance of betel-quid effects is limited to diabetes or may also apply to other features of the metabolic syndrome (MetS) associated with cardiovascular disease remains in question \((4, 6)\).

We recently found strong associations between betel-quid consumption (independent of tobacco use) and features of MetS, including its diabetogenicity, in a community-based study \((2)\). This led us to test the hypothesis of whether exposure to paternal betel-quid chewing increases the risk of early development of features of MetS in human offspring.

SUBJECTS AND METHODS

Study subjects and design

Data used in the present study were obtained from an on-going community-based multiple screening program named the Keelung community-based integrated screening (KCIS) program, which is conducted in Keelung, the northernmost county of Taiwan. The KCIS study, which is run by the Health Bureau of Keelung City, has been in progress from the beginning of 1999 and has ethical approval from the local health committee. The KCIS paper no. 8.

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2 KCIS paper no. 8.

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details of the study design, implementation, early findings, financial sources, and different committees have been described in full elsewhere (9). In brief, the KCIS program was originally designed to invite women who had not had a Pap test during the 3 y preceding the start of the program for screening for factors relating to 5 neoplastic diseases and 3 nonneoplastic diseases; other family members were also invited to participate. Of the total population of Keelung, 66 971 residents (23%) aged ≥20 y gave written informed consent, attended the KCIS program, and had been screened by December 2003.

Because the KCIS program was implemented on a family basis, the dataset provides an opportunity to explore the transgenerational effects of betel-quid consumption on MetS with the use of a family parent-offspring study design nested within the 66 971 subjects. This cohort contained 12 138 subjects with and 54 833 subjects without MetS. By linking the screening dataset with the population registry that recorded the parents’ name for each resident, we could identify 10 566 parent-child trios. After exclusion of incomplete parent-child trios (when a parent, both parents, or the offspring had not participated in the KCIS program), we confirmed 5037 parent-child trios eligible for inclusion in the planned analyses.

Exposure and outcome

Because we were interested in the transgenerational effects of parental betel-quid chewing on the risk of MetS, the definition of MetS was central to the study and was made according to the modified National Cholesterol Education Program Adult Treatment Panel III criteria (10), ie, when abnormalities were present in ≥3 of the following criteria: waist size >80 cm in women or >90 cm in men, serum triacylglycerol concentrations >150 mg/dL, HDL cholesterol <50 mg/dL (1.29 mmol/L) in women or <40 mg/dL (<1.04 mmol/L) in men, blood pressure >130 mm Hg (systolic) or >85 mm Hg (diastolic), fasting blood glucose >110 mg/dL (≥6.1 mmol/L), and a body mass index (in kg/m²) >25. Data for the 5 variables used in this definition of MetS (10) were collected during the subjects’ on-site screening. Weight, height, waist and hip circumferences, and blood pressure were measured with standard techniques by trained staff; a venous blood sample was taken after the subjects had fasted 12 h overnight for the measurement of plasma glucose, triacylglycerol, total cholesterol, HDL-cholesterol, LDL-cholesterol, and uric acid concentrations.

Information on betel-quid consumption, smoking and alcohol habits, physical activity, dietary factors, and educational levels was collected by face-to-face interviews during the on-site screening. Both duration (in y) and quantity (no. of portions chewed/d) of betel-quid usage were recorded. Two specific points should be noted. First, because few mothers had been exposed to betel quid (0.8%), only the relations of outcome to paternal exposure could be analyzed, and the effects of maternal exposure were not investigated further. Second, because fathers may have started chewing betel quids only after the birth of the index child, the duration of paternal exposure before birth of the index child was calculated as the difference between the age of the father at entry to the study (minus age at commencement of betel-quid chewing) and the age of the index offspring at entry to the study. Duration of paternal exposure to betel quid was examined in relation to age in offspring who were diagnosed with MetS after 5 male offspring were excluded from the analysis because paternal betel chewing had begun only after their birth.

The cumulative exposure of fathers to betel-nut chewing was calculated as the number of portions chewed/d × the duration of chewing.

Statistical methods

The primary outcome measurement was the age of the offspring who were found to have MetS, as defined by ≥3 of the component abnormalities, whether newly diagnosed or previously recognized. We first used multiple linear regression models to test whether there was any interaction between the differences in the mean age of offspring at recruitment (stratified by MetS status) and sex and paternal exposure to betel chewing. Because the offspring without MetS at entry may not have known whether they had MetS or when it developed (if MetS was found to be present), we used Cox proportional hazards regression models to estimate hazard ratios (HRs) and their 95% CIs, with age at entry as “survival time” and regarding the status of those who were free of MetS at entry as “censored” compared with the “uncensored” status of those found to have MetS at entry.

To assess whether the effect of exposure to paternal betel chewing as a risk factor for the development of MetS in the offspring varied with sex, an interaction assessment was performed with the use of the interaction variable (paternal exposure × offspring sex) in Cox regression modeling. The findings were then tested for independence of exposure to paternal betel consumption as a predictor of risk of development of MetS by using a univariate analysis (Cox regression model) with control for all of the confounders identified as significant (P < 0.05).

Dose-response effects for quantity, duration, and cumulative exposure to betel chewing were each evaluated by using trend tests. Models incorporating quantity, duration, or cumulative paternal exposure as ordinal variables together with potential confounding factors [sex, vegetable consumption (≥3 or ≤3 portions/meal), exercise (sedentary or regular), paternal and maternal MetS status, and personal betel chewing by offspring] were compared with models that included only the potential confounding factors identified as significant with likelihood ratio testing. Departure from linearity was then examined with respect to quantity, duration, or cumulative paternal exposure in a comparison, in each case, of models that included quantity, duration, or cumulative exposure of paternal betel use as an ordinal variable with models that included quantity, duration, or cumulative exposure of paternal betel use as a categorical property with likelihood ratio testing. All statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

The findings for age and for the variables relevant to MetS in fathers, mothers, and offspring are shown in Table 1. Regardless of MetS status, the offspring who were exposed to paternal betel-quid chewing were younger than the offspring who were not exposed to paternal betel chewing [mean (±SD) age: 30.92 ± 8.32 compared with 38.16 ± 8.0 y]. The significant confounding factors for the presence of MetS that were identified in the offspring were vegetable consumption, personal betel chewing by the offspring, and parental MetS status; no significant interactions were found between personal betel chewing and abnormalities in any variables that were used to define MetS in the offspring. These significant confounding factors, together with paternal betel habits, were then used in a multivariate analysis to
The dose effects on consumption rates, duration of use, and cumulative exposure found for paternal betel chewing were significant. Except for cumulative exposure ($P < 0.0001$), these relations were linear (Table 3). However, the results for cumulative exposure have to be interpreted with caution because the numbers of fathers in the highest category of cumulative exposure was small and may have distorted the estimates.

Three important confounding factors (the presence of maternal MetS, the presence of paternal MetS, and the habit of chewing betel quid in the offspring) for occurrence of MetS were allowed for by additional analyses of the data after stratification by each of these variables. The offspring who were exposed to paternal betel chewing in the absence of any of these 3 confounders had a 2.53-fold (95% CI: 1.03, 2.64) increase in the risk of early development of MetS compared with those who were not exposed.

**DISCUSSION**

Our findings, which are based on a population-based, parent-child family study, strongly suggest that exposure to paternal betel-quid chewing leads to a significantly earlier appearance of MetS in human offspring. This postulate is supported by 3 major findings: 1) the 2-fold increase in the risk of early development of MetS in offspring whose fathers had chewed betel quids (after control for environmental risk factors, parental MetS, and betel-quid chewing leads to a significantly earlier appearance of MetS in offspring); 2) the significant dose-response relations for both the quantity and the duration of paternal betel-quid chewing and for cumulative paternal exposure to betel quid before the birth of the offspring; and 3) the independent 2.53-fold increase in the risk of early development of MetS in the non-betel chewing offspring of parents without MetS but with betel-chewing fathers.

The use of a parent-child family study design based on a community-based integrated screening study has several advantages, including the assessment of both parents and offspring with respect to the diagnosis of MetS at the same time rather than relying on self-reports of MetS in parents by the offspring, as is common in conventional epidemiologic studies. Similarly, the

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**TABLE 1**

Descriptive data for metabolic syndrome (MetS)–defining variables in fathers, mothers, and offspring with and without MetS at entry to the study

<table>
<thead>
<tr>
<th>MetS</th>
<th>Age</th>
<th>Waist (cm)</th>
<th>BMI (kg/m²)</th>
<th>Glucose (mg/dL)</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
<th>Triacylglycerol (mg/dL)</th>
<th>HDL cholesterol (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Father (n = 940)</td>
<td>64.2 ± 8.7</td>
<td>94.0 ± 7.5</td>
<td>27.3 ± 3.0</td>
<td>121.4 ± 49.9</td>
<td>144.7 ± 19.1</td>
<td>86.4 ± 11.6</td>
<td>42.9 ± 10.3</td>
</tr>
<tr>
<td></td>
<td>Mother (n = 798)</td>
<td>62.3 ± 7.9</td>
<td>85.9 ± 8.1</td>
<td>27.3 ± 3.5</td>
<td>122.7 ± 50.2</td>
<td>141.9 ± 20.9</td>
<td>83.9 ± 12.6</td>
<td>50.0 ± 11.8</td>
</tr>
<tr>
<td></td>
<td>Offspring (n = 260)</td>
<td>37.9 ± 8.1</td>
<td>93.4 ± 8.3</td>
<td>28.4 ± 3.4</td>
<td>96.1 ± 30.8</td>
<td>139.3 ± 15.7</td>
<td>88.4 ± 13.9</td>
<td>39.3 ± 8.3</td>
</tr>
<tr>
<td></td>
<td>Female (n = 131)</td>
<td>39.6 ± 7.7</td>
<td>84.4 ± 7.7</td>
<td>28.1 ± 3.4</td>
<td>100.2 ± 29.1</td>
<td>132.2 ± 15.9</td>
<td>85.1 ± 10.7</td>
<td>44.9 ± 7.7</td>
</tr>
<tr>
<td></td>
<td>P1</td>
<td>&lt;0.0001</td>
<td>0.4961</td>
<td>0.1994</td>
<td>&lt;0.0001</td>
<td>0.0090</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MetS absent</td>
<td>Father (n = 2736)</td>
<td>63.8 ± 8.9</td>
<td>84.1 ± 8.6</td>
<td>24.2 ± 3.1</td>
<td>94.3 ± 25.5</td>
<td>134.2 ± 20.7</td>
<td>81.8 ± 12.1</td>
<td>54.5 ± 12.6</td>
</tr>
<tr>
<td></td>
<td>Mother (n = 2096)</td>
<td>57.9 ± 8.3</td>
<td>77.0 ± 8.8</td>
<td>24.6 ± 3.4</td>
<td>92.4 ± 21.9</td>
<td>126.9 ± 20.2</td>
<td>78.2 ± 11.5</td>
<td>62.2 ± 13.5</td>
</tr>
<tr>
<td></td>
<td>Offspring (n = 1956)</td>
<td>34.3 ± 8.1</td>
<td>80.3 ± 8.6</td>
<td>23.9 ± 3.4</td>
<td>85.9 ± 12.9</td>
<td>123.5 ± 16.2</td>
<td>77.9 ± 11.3</td>
<td>52.4 ± 11.0</td>
</tr>
<tr>
<td></td>
<td>Female (n = 2690)</td>
<td>33.8 ± 8.2</td>
<td>69.3 ± 7.8</td>
<td>21.9 ± 3.3</td>
<td>84.9 ± 12.1</td>
<td>110.9 ± 14.4</td>
<td>71.5 ± 9.9</td>
<td>61.9 ± 12.8</td>
</tr>
<tr>
<td>P of interaction1</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0098</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P of interaction2</td>
<td>0.0912</td>
<td>0.7398</td>
<td>0.2268</td>
<td>0.0182</td>
<td>0.1303</td>
<td>0.6089</td>
<td>0.1364</td>
<td>0.0043</td>
</tr>
<tr>
<td>P of interaction3</td>
<td>0.0256</td>
<td>&lt;0.0001</td>
<td>0.0017</td>
<td>0.0013</td>
<td>0.0101</td>
<td>0.0179</td>
<td>0.0043</td>
<td>0.0038</td>
</tr>
<tr>
<td>P of interaction4</td>
<td>0.0017</td>
<td>&lt;0.0001</td>
<td>0.2557</td>
<td>0.5407</td>
<td>0.0919</td>
<td>0.3331</td>
<td>0.0248</td>
<td>0.0043</td>
</tr>
</tbody>
</table>

1. SBP, systolic blood pressure; DBP, diastolic blood pressure.
2. ± SD (all such values).
3. * Test comparing the findings between male and female offspring with MetS.
4. † Test comparing the findings between male and female offspring without MetS.
5. Interaction in parents between sex of parent and MetS status in their offspring; identified by using linear regression modeling.
6. Interaction between sex of offspring and MetS status of offspring; identified by using linear regression modeling.
7. Interaction between MetS status, sex, and generation; identified by using linear regression modeling.

The HRs for the risk of MetS in the offspring in relation to paternal betel use, both unadjusted and after adjustment for potential confounding factors, are shown in Table 3. The offspring who were exposed to paternal betel-quid chewing had a 2-fold (unadjusted HR = 2.08; 95% CI: 1.22, 3.56) increase in the risk of early manifestation of MetS compared with those who were not exposed. The increased risk of early manifestation of MetS in the offspring who were exposed to paternal betel-quid chewing persisted after adjustment for confounding variables (adjusted HR = 2.14; 95% CI: 1.25, 3.66). The findings for each of the MetS-defining variables were similar, except for hyperglycemia (HRs (95% CI) for abnormality in waist, triacylglycerol, HDL cholesterol, blood pressure, and glycemia were 1.77 (1.17, 2.66), 2.42 (1.7, 3.43), 2.48 (1.77, 3.46), 2.36 (1.8, 3.09), and 1.01 (0.25, 4.13), respectively).

The HRs and dose-response relations between the risk of early manifestation of MetS in offspring and the quantity, duration, and cumulative exposure of fathers to betel quid, after adjustment for significant confounders including parental MetS, are shown in Table 3. The dose effects on consumption rates, duration of use, and cumulative exposure found for paternal betel chewing were significant. Except for cumulative exposure ($P < 0.0001$), these relations were linear (Table 3). However, the results for cumulative exposure have to be interpreted with caution because the numbers of fathers in the highest category of cumulative exposure was small and may have distorted the estimates.
direct assessment of betel-quid habits in parents and offspring were made at the same time, as was the assessment of environmental factors related to the risk of MetS that were controlled for in the model.

The evidence for transmission of the risk of hyperglycemia from parents to offspring is weaker than for other features of MetS. This could reflect the relative young age (\(< 40\) y) of the offspring studied, because fasting glycemia has been shown to be

### TABLE 3

<table>
<thead>
<tr>
<th>Dose-response</th>
<th>MetS/non-MetS</th>
<th>HR (95% CI)</th>
<th>P for trend</th>
<th>P for departure from linearity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quantity (quids/d)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>377/4448</td>
<td>1.00</td>
<td>(&lt;0.0001)</td>
<td>0.6783</td>
</tr>
<tr>
<td>1–5 quids</td>
<td>4/101</td>
<td>1.44 (0.54, 3.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–15 quids</td>
<td>3/54</td>
<td>2.32 (0.95, 5.64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;15 quids</td>
<td>7/43</td>
<td>2.52 (1.04, 6.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duration of betel-quid chewing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>377/4448</td>
<td>1.00</td>
<td>(&lt;0.0001)</td>
<td>0.5491</td>
</tr>
<tr>
<td>1–5 y</td>
<td>4/86</td>
<td>1.31 (0.42, 4.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–15 y</td>
<td>7/93</td>
<td>3.41 (1.51, 7.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;15 y</td>
<td>3/19</td>
<td>6.31 (0.87, 45.57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cumulative exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>377/4448</td>
<td>1.00</td>
<td>(&lt;0.0001)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(&lt;5 \times 10^4) betel quid-d</td>
<td>4/80</td>
<td>1.74 (0.43, 7.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5–15 \times 10^4) betel quid-d</td>
<td>8/86</td>
<td>5.48 (1.72, 17.44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&gt;15 \times 10^4) betel quid-d</td>
<td>2/32</td>
<td>1.89 (0.71, 5.09)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Cox proportional hazard regression models were used to estimate adjusted HRs and their 95% CIs for quantity of quids used per day, duration of chewing, and cumulative exposure after control for other factors that significantly affected MetS risk in offspring [HR (95% CIs) for each factor—paternal MetS: 1.62 (1.32, 2.00); betel quid chewing by offspring: 1.77 (1.35, 2.52); vegetable consumption: 0.58 (0.44, 0.77); and exercise: 0.74 (0.60, 0.91)]. There were no significant sex of offspring \(\times\) chewing interactions.

2 Significantly different from reference, \(P < 0.01\).
relatively weak for the detection of sustained hyperglycemia and type 2 diabetes in previous studies conducted in Taiwan. A comparison of impaired fasting plasma glucose (IFG) according to the American Diabetes Association criteria (5.6–7.8 mmol glucose/L) with impaired glucose tolerance (IGT) according to World Health Organization criteria showed that in 50% of subjects who were diagnosed according to the American Diabetes Association criteria will have undiagnosed diabetes and 68% will have IGT according to the World Health Organization criteria (11). Similarly, the overlap between IFG and IGT was present in only 21% of Taiwanese subjects in a study that examined the relation of IFG and of IGT to cardiovascular disease risk profiles; thus, if IFG alone was used for screening glucose tolerance, 67% of subjects with IGT and an abnormal cardiovascular disease risk profile would have been undetected (12). Similar findings, which suggested that type 2 diabetes may be a late feature of MetS in the Taiwanese population, were reported by Anand et al (13). Our study shows that the prevalence of MetS-defining increases in fasting glucose was indeed higher in parents (18% in mothers and 17.2% in fathers) than in their offspring (2.9% in males and 1.8% in females).

Several biological explanations could account for the transgenerational effect of betel-quid chewing on the risk of early development of MetS. First, genetic changes occur after damage to nuclear DNA by the specific and carcinogenic arecal nitrosamines that are formed in the nut, in the mouth, and during digestion from the alkaloids found in the betel (Areca catechu) nut (1, 14). Support for this possibility includes an increase in chromosomal aberrations and micronucleated cells in peripheral blood mononuclear cells of adult betel-quid chewers (15). Additionally, remarkable increases in abnormal sperm morphology were seen in mice that were fed arectine or pan masala (an aromatic chewing containing betel nut) and in the sperm of human pan masala consumers (14–16). Furthermore, several nitrosamines similar to the arecal nitrosamines, such as the nitrosocompound streptozocin, are known to induce type 1 diabetes experimentally and can induce non–insulin dependent diabetes at low dosages in young animals (17). Because the production of gametes is a continuous process in men during their reproductive life, and women in Taiwan rarely chew betel, the betel-related factor responsible might be expected to affect the forming spermatooza, but not oocytes, in our study population. The predominance of the transmission of MetS risk by betel chewing fathers to male offspring, rather than female offspring, in mice suggests that any betel nut–related genetic damage might be limited to the Y chromosome; but whether this applies in humans awaits additional investigation as more of the subjects in this survey develop MetS with age.

Epigenetic phenomenon, such as increased methylation of DNA as a result of exposure to the free radical cascades generated by the specific arecal nitrosamines (1), could also account for our findings. However, it may not be possible to identify the genetic or epigenetic effects that may lead to the transmission of MetS risk in a cohort of offspring as young as those whom we studied, because not all affected persons will have manifested MetS yet.

In conclusion, our study showed that exposure to paternal betel-quid chewing is associated with dose-dependent increases in the risk of developing MetS in offspring at an earlier age than is seen in the offspring of non-betel-quid chewing fathers. Ten percent of the world’s population, ~600 million people, chews

betel nut (Areca catechu) (1). Identification of the mechanisms underlying our findings is warranted because they might, similar to other epigenetic phenomena, prove to be reversible.

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TH-HC contributed to the conceptual design of the study, collection and analysis of the data, and interpretation and writing of the manuscript. Y-CH contributed to the collection of data, statistical analysis, and interpretation of the manuscript. BJB contributed intellectually to the concepts investigated and both intellectually and practically to the preparation of the final text. All authors reviewed and agreed to the final manuscript. The authors had no conflicts of interest.

REFERENCES