Unhealthy Dietary Patterns Increased Risks of Incident Obesity: A Prospective Cohort Study in Southwest China

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Purpose: Few studies have explored the associations between diet patterns and incident obesity in China. This study aimed to explore associations between dietary patterns and incident obesity in a prospective community-population cohort in Southwest China.

Patients and Methods: Totally, 5742 adult residents from Guizhou province were eligible for this analysis. Demographic characteristics, lifestyle, history of chronic diseases, and dietary patterns measured by hundred-item food frequency questionnaires (FFQs) were collected at the baseline study. Four dietary patterns were identified using factor analysis. Cox proportional hazard models stratified by physical activity were used to explore the association and estimate adjusted hazard ratio (aHR) and 95% confidence interval (CI).

Results: Among 5742 subjects, the average age was 45.06 ± 15.21 years old and more than half were women. During the follow-up of 40,524.15 person years (PYs), the overall incidence rate of obesity was 10.54/1000PYs. After the adjustment for possible confounding factors, subjects with the third (aHR: 1.51, 95% CI: 1.14–2.00) and the fourth quartile (aHR: 1.46, 95% CI: 1.10–1.94) of junk food patterns had statistically increased risk of incident obesity compared to those with the first quartile. Also, subjects with the third quartile of the western pattern had significantly higher risk of incident obesity (aHR: 1.33, 95% CI: 1.01–1.75) than those with the first quartile.

Conclusion: There was a high risk in incident obesity among Chinese community population of Southwest China and unhealthy diet significantly increased risk of developing obesity. The findings indicated that effective and targeted measures to improve dietary patterns need to be undertaken urgently in Southwest China.

Keywords: dietary patterns, obesity, cohort study, factor analysis, China

Introduction

Obesity is one of the important challenges in public health worldwide. It may cause damage to the function of human organs and systems and ultimately lead to other chronic non-communicable diseases (NCDs) including cardiovascular disease, type 2 diabetes, dyslipidemia, chronic kidney disease, osteoarthritis, and cancer.1–8 Over the last decades, the global prevalence of obesity has increased rapidly, approximately 11% of men and 15% of women were obese in the world.9 In 2015, the prevalence of overweight and obesity among Chinese adults were 41.3% and 15.7%, respectively.10 Obesity-related NCDs brought a huge economic burden in China, and obesity and overweight accounted for 11.1% of deaths associated with NCDs in 2019.11

The root cause of obesity is that the body’s energy intake is greater than the body’s energy expenditure, resulting in excess energy being stored in the form of fat although lots of risk factors for obesity were explored and identified...
including genetics, diet, physical exercise, and psychological factors in previous studies.\textsuperscript{11} Thus, dietary factors still play a key role in the process of developing obesity even though some previous findings were controversial over countries or populations.\textsuperscript{12,13}

The traditional nutritional epidemiology researches generally explore relationships between one or several foods or nutrients and health outcomes. Recently, dietary patterns of the overall diet were occupied to assess the comprehensive effects of food or nutrients on human health, and they showed more effectively and precisely than traditional those.\textsuperscript{14} However, different dietary patterns varied widely over countries, races, and research methods.\textsuperscript{15} Previous studies showed that western and junk food dietary patterns increased energy intake and risk of obesity,\textsuperscript{16} while Mediterranean dietary pattern was considered to reduce triglyceride levels.\textsuperscript{17} Also, an association between Chinese traditional dietary pattern and obesity was reported in one research.\textsuperscript{18} However, most of previous studies were cross-sectional studies between dietary patterns and obesity,\textsuperscript{18–20} and it was rare to explore prospective associations between dietary patterns and obesity with community population cohorts in China.

There were huge differences in food culture and diet behaviors over different regions, even in China, due to the geographical features and ethnic diversity.\textsuperscript{21} Thus, based on a prospective community-based population cohort in Guizhou province, this study aimed to explore associations between dietary patterns and incident obesity in Southwest China.

**Materials and Methods**

**Participants and Design**

Data for this study were from the Guizhou Population Health Cohort Study (GPHCS), a prospective community-based cohort in Guizhou province, China.\textsuperscript{22} The baseline survey was conducted between November 2010 and December 2012, and it was followed up between December 2016 and June 2020. The inclusion criteria for subjects in this study included followings: (1) aged 18 years or above; (2) lived in these communities and had no plan to move; (3) completed the questionnaire and blood sample collection; (4) signed written informed consent before data collection. A total of 9280 participants were recruited at the baseline. Those who had obesity at baseline (n = 644), who lost to follow-up (n = 1045), and who had missing data (n = 1634) or incomplete dietary survey (n = 215) were excluded. Finally, the remaining 5742 participants were eligible for the analysis (Figure 1). This study was approved by the Institutional Review Board of Guizhou Province Centre for Disease Control and Prevention (No. S2017-02).

![Flow chart of participants in this cohort study.](https://doi.org/10.2147/DMSO.S377901)
Data Collection and Measurements
A structured questionnaire was done through a face-to-face interview by local trained health professionals. The baseline and follow-up questionnaire included demographic characteristics (age, sex, ethnicity, educational level, marriage status, and occupation), lifestyle (smoking status, alcohol use, and physical activity), history of chronic diseases, and dietary factors. Current smokers referred to smoking tobacco products including manufactured or locally produced in a month. Alcohol drinkers referred to drinking alcohol more than once every month within the last 12 months. Physical activity was defined as meeting WHO recommendations on physical activity according to the global physical activity questionnaire (GPAQ). Dietary data including frequencies and quantities of 16 food items (fermented bean curd, bean paste, pickles, oil, legumes, meat, fruits, milk, eggs, fish, potatoes, grains, vegetables, beverages, desserts, and fried food) consumed during the recent 12 months before the study recruitment were collected by a simplified Food Frequency Questionnaire (FFQ). Anthropometric measurements including height, body weight, and blood pressure were measured. BMI was calculated as body weight in kilograms divided by height in meters squared (kg/m²). Obesity was defined as BMI ≥30kg/m² based on the WHO BMI classification standard.

Statistical Analysis
In this study, factor analysis with eigenvalues >1 and varimax rotation was occupied to aggregate 16 food items into factors with food patterns. Four factors that explained most of the variances were determined based on scree plots and their loadings for the initial food items. The factor-loading matrix for the four dietary patterns and their food or food groups is shown in Table S1. Factor 1, named high-salt and high-oil pattern, was characterized by a high factor load of fermented bean curd, bean paste, pickles, and oil. Factor 2, named western pattern, was characterized by a high factor load of legumes, meat, fruits, milk, eggs, fish, and potatoes. Factor 3, named grain-vegetable pattern, was characterized by a high factor load of grains and vegetables. Factor 4, named junk food pattern, was characterized by a high factor load of beverages, desserts, and fried food. A summary score for each pattern was then derived and categorized into quartiles (Quartile 0–25th, Q1; 26th-50th, Q2; 51st-75th, Q3; 76th-100th, Q4) for further analysis.

The Student’s t-test and the Chi-square test were used for continuous variables and categorical variables, respectively. Person-years (PYs) of follow-up were calculated from the date of enrolling the cohort until the date of diagnosis of obesity, death, or follow-up, whichever came first. Because physical activity violated the proportional hazards assumption, the multivariable Cox proportional hazards regression models stratified by physical activity were employed to determine the association between dietary patterns and incident obesity and to estimate hazard risk (HR), adjusted HR (aHR), and their 95% confidence intervals (CIs). Several variables were adjusted and controlled in the multivariable models: age (18–29, 30–64, ≥65 years), sex (male/female), Han Chinese (no/yes), education years (≥9/<9), current smokers (no/yes), alcohol drinkers (no/yes), diabetes mellitus (no/yes), hypertension (no/yes). Tests for linear trends across increasing quartiles of dietary pattern were performed by assigning median value to each quartile of dietary pattern. The sensitivity analysis was conducted after exclusion of participants with overweight at baseline. All statistical tests were two-sided and P < 0.05 was considered statistically significant. All analyses were performed in R software (Version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria).

Results
Baseline Characteristics of Participants
The baseline characteristics of participants are presented in Table 1. Of all subjects, the average age was 45.06 ± 15.21 years old and more than half were women. Most of them were Han Chinese and had 9 education years or longer. The prevalence of current smoking and alcohol drinking was around one-third, while the proportion of physical activity was more than four-fifths. There were significant differences in education level, physical activity, current smokers, alcohol drinkers, hypertension, and diabetes between men and women (detailed in Table 1).
Distribution of Dietary Patterns
As shown in Table 2, four dietary patterns statistically varied over different age groups and physical activity groups. Men (53.6%) had higher grain-vegetable pattern scores than women (46.4%). Han Chinese had more chances to have western pattern and junk food pattern. Participants with less than 9 education years had lower proportions of high-salt and high-oil pattern, western pattern, and junk food pattern. Those subjects with hypertension or diabetes tended to have high-salt and high-oil pattern and junk food pattern. There were also significant differences in high-salt and high-oil patterns and western pattern among participants who were current smokers or alcohol drinkers.

Incidence Rates of Obesity Over Different Sex and Age Groups
During the follow-up of 40,524.15 PYs, 427 new obesity cases were identified and the incidence rate of obesity was 10.54/1000PYs overall. There were significant sex differences in the incidence rate (9.36/1000PYs for men vs 11.64/1000PYs for women, p = 0.004). The incidence rate increased with age and the age-specific incidence rates of obesity are displayed over sex in Figure 2. Similar sex differences were observed among those aged 30 to 64 years old (p = 0.010) or elders (p = 0.031). Also, the highest incidence rate of obesity reached 12.27/1000PYs and 9.8/1000PYs in both women and men aged 30 to 64 years, respectively.

Associations Between Dietary Patterns and Obesity Incidence
In the Cox regression model stratified by physical activity, associations between dietary patterns and incident obesity are presented in Table 3. Participants in the higher quartile of junk food pattern score were more likely to develop obese with the HR (95% CI) of 1.54 (1.16–2.02) and 1.44 (1.09–1.89) for the third and fourth quartiles, respectively. After the adjustment for covariates, both aHRs in the Q3 and Q4 group of junk food pattern increased slightly and were still significant. Also, the risk of incident obesity significantly increased with the score of junk food pattern (p for trend = 0.040). In addition, subjects in the Q3 group of western pattern had a significantly higher risk of incident obesity (aHR: 1.33, 95% CI: 1.01–1.75) compared to those in the Q1 group, and there was a marginally raised trend in the risk of incident obesity as western pattern scores (p for trend = 0.087). It was not found that there were any significant associations between high-salt and high oil

<table>
<thead>
<tr>
<th>Table 1 Baseline Characteristics of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>18–29</td>
</tr>
<tr>
<td>30–64</td>
</tr>
<tr>
<td>≥65</td>
</tr>
<tr>
<td>Han Chinese, n (%)</td>
</tr>
<tr>
<td>Education years, n (%)</td>
</tr>
<tr>
<td>≥9</td>
</tr>
<tr>
<td>&lt;9</td>
</tr>
<tr>
<td>Physical activity, n (%)</td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
</tr>
<tr>
<td>Alcohol drinking, n (%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
</tr>
<tr>
<td>DM, n (%)</td>
</tr>
</tbody>
</table>

**Abbreviations:** DM, diabetes mellitus; SD, standard deviation.
Table 2 Participants’ Characteristics According to Quartiles of Four Dietary Patterns

<table>
<thead>
<tr>
<th>Variable</th>
<th>High-Salt and High-Oil (n=1436)</th>
<th></th>
<th>Western (n=1436)</th>
<th></th>
<th>Grain-Vegetable (n=1436)</th>
<th></th>
<th>Junk Food (n=1436)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1*</td>
<td>Q4*</td>
<td>P value</td>
<td>Q1*</td>
<td>Q4*</td>
<td>P value</td>
<td>Q1*</td>
<td>Q4*</td>
</tr>
<tr>
<td>Age, years</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.058</td>
<td>&lt;0.001</td>
<td>0.058</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>18–29</td>
<td>388 (27.0)</td>
<td>256 (17.8)</td>
<td></td>
<td>189 (13.2)</td>
<td>380 (26.5)</td>
<td></td>
<td>280 (19.5)</td>
<td>250 (17.4)</td>
</tr>
<tr>
<td>30–64</td>
<td>932 (64.9)</td>
<td>1009 (70.3)</td>
<td></td>
<td>1001 (69.7)</td>
<td>950 (66.2)</td>
<td></td>
<td>914 (63.6)</td>
<td>1073 (74.7)</td>
</tr>
<tr>
<td>≥65</td>
<td>116 (8.1)</td>
<td>171 (11.9)</td>
<td></td>
<td>246 (17.1)</td>
<td>106 (7.4)</td>
<td></td>
<td>242 (16.9)</td>
<td>113 (7.9)</td>
</tr>
</tbody>
</table>
| Women, n (%)              | 733 (51.0)                       | 760 (52.9)| 0.792            | 771 (53.7) | 746 (51.9)               | 0.403    | 853 (59.4)       | 666 (46.4)|<0.001
| Han Chinese, n (%)        | 1014 (70.6)                      | 799 (55.6)| <0.001           | 704 (49.0) | 939 (65.4)               | <0.001   | 996 (69.4)       | 704 (49.0)|<0.001
| Education years, n (%)    | ≥9                                | 944 (65.7) | 945 (65.8)       | 680 (47.4) | 1119 (77.9)              | <0.001   | 870 (60.6)       | 922 (64.2)|<0.001
|                           | <9                                | 492 (34.3) | 491 (34.2)       | 756 (52.6) | 317 (22.1)               |         | 566 (39.4)       | 514 (35.8)|0.058
| Physical activity, n (%)  | ≥9                                | 1194 (83.4) | 1226 (85.7)      | 1085 (75.8) | 1202 (84.0)              | <0.001   | 1136 (79.4)      | 1207 (84.2)|0.001
|                           | <9                                | 465 (32.4) | 376 (26.2)       | 339 (23.6) | 463 (32.2)               | <0.001   | 358 (24.9)       | 460 (32.0)|<0.001
| Current smoker, n (%)     | 465 (32.4)                       | 376 (26.2)|                | 339 (23.6) | 463 (32.2)               | <0.001   | 358 (24.9)       | 460 (32.0)|<0.001
| Alcohol drinking, n (%)   | ≥9                                | 433 (30.2) | 544 (37.9)       | 390 (27.2) | 576 (40.1)               | <0.001   | 398 (27.7)       | 508 (35.4)|<0.001
|                           | <9                                | 320 (22.3) | 386 (26.9)       | 408 (28.4) | 313 (21.8)               | <0.001   | 391 (27.2)       | 371 (25.8)|0.187
| Hypertension, n (%)       | ≥9                                | 108 (7.5)  | 143 (10.0)       | 131 (9.1)  | 110 (7.7)                | 0.309    | 130 (9.1)        | 124 (8.6)|0.330
| DM, n (%)                 | <0.001                           | <0.001   | 0.013            | 0.013     | 0.013                    |         | 0.013            | 0.013    |

Notes: *Q1*, quartile 1 (lowest); *Q4*, quartile 4 (highest).
Abbreviation: DM, diabetes mellitus.
No significant interactions were observed between dietary pattern and main covariates, either. In the sensitivity analysis, the main results remained robust after exclusion of participants with overweight at baseline (seen in Figure S1).

**Table 3:** Associations Between Baseline Dietary Patterns and Incident Obesity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quartiles of Four Dietary Patterns</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1</td>
<td>Q2</td>
</tr>
<tr>
<td>High-salt and high-oil</td>
<td>10,399.85</td>
<td>10,400.84</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>9.69</td>
<td>10.38</td>
</tr>
<tr>
<td>Incidence rate (/1000PYs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td>1.00 (ref)</td>
<td>0.89 (0.69–1.15)</td>
</tr>
<tr>
<td>aHR (95%CI)</td>
<td>1.00 (ref)</td>
<td>0.91 (0.70–1.18)</td>
</tr>
<tr>
<td>Western</td>
<td>10,186.75</td>
<td>10,186.75</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>9.52</td>
<td>9.23</td>
</tr>
<tr>
<td>Incidence rate/1000PYs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td>1.00 (ref)</td>
<td>0.95 (0.72–1.26)</td>
</tr>
<tr>
<td>aHR (95%CI)</td>
<td>1.00 (ref)</td>
<td>0.95 (0.71–1.26)</td>
</tr>
<tr>
<td>Grain-vegetable</td>
<td>10,036.44</td>
<td>10,245.74</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>9.96</td>
<td>10.25</td>
</tr>
<tr>
<td>Incidence rate/1000PYs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td>1.00 (ref)</td>
<td>0.93 (0.70–1.21)</td>
</tr>
<tr>
<td>aHR (95%CI)</td>
<td>1.00 (ref)</td>
<td>0.94 (0.71–1.24)</td>
</tr>
<tr>
<td>Junk food</td>
<td>10,023.32</td>
<td>10,153.19</td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>8.88</td>
<td>9.85</td>
</tr>
<tr>
<td>Incidence rate/1000PYs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td>1.00 (ref)</td>
<td>1.29 (0.97–1.71)</td>
</tr>
<tr>
<td>aHR (95%CI)</td>
<td>1.00 (ref)</td>
<td>1.25 (0.94–1.66)</td>
</tr>
</tbody>
</table>

**Notes:** Adjusted for age, gender, ethnicity, education years, current smoker, alcohol drinker, diabetes mellitus; hypertension; Multivariable Cox proportional hazards regression models stratified by physical activity; **P < 0.01, *P < 0.05; Q1, quartile 1 (lowest); Q2, quartile 2; Q3 quartile 3; Q4, quartile 4 (highest).**

**Abbreviations:** PYs, person years of follow-up; HR, hazard ratio; aHR, adjusted hazard ratio; 95% CI, 95% confidence interval.
Discussion

The prevalence of obesity has been increasing dramatically worldwide. As a leading risk factor for obesity, unhealthy dietary habits have been prevalent in China. During the follow-up of 40,524.15 PYs, the incidence rate of obesity was estimated at 10.54/1000PYs in this study population overall with a significant sex difference. The highest incidence rate of obesity reached at 12.27/1000PYs and 9.80/1000PYs in both women and men aged 30–64 years, respectively. Those findings indicated that there was a high risk of developing obesity in this study population, especially for women, which called for the development and implementation of specific intervention for the prevention and control of obesity.

In the present study, four major dietary patterns were identified and then associations between four dietary patterns and incident obesity were explored among adult residents in Southwest China. The junk food pattern consisted of high consumption of beverages, desserts, and fried food. Likewise, the western pattern was characterized by high consumption of legumes, meat, fruits, milk, eggs, fish, and potatoes. We found that junk food pattern and western pattern were positively associated with the increased risk of developing obesity, while no significant associations between high-oil and high-salt pattern, grain-vegetable pattern and incident obesity were observed in this study. The results were consistent with the South Asian consensus on Nutritional Medical Treatment of Diabesity, which advocated for a hypocaloric diet and reducing intake of carbohydrates and saturated fats. Meanwhile, among Iranian women, it was reported that a low-carbohydrate diet was not associated with overweight and obesity.

In China, the consumption of junk food such as desserts, beverages, and fried food is on the rise since the 1980s. In this study, the contribution of junk food dietary pattern to a higher risk of obesity was demonstrated, which was consistent with a Mediterranean prospective cohort design with a median 6-year follow-up. Previous studies revealed that during the frying process, excessive fat and calories tended to increase, and trans-fatty acids related to the risk of weight gain were also prone to be generated. Furthermore, the junk food pattern has a high intake of beverages and sweets, and the positive associations of sugar-sweetened beverages (SSBs) to obesity were confirmed by Framingham Heart Study. A recent meta-analysis revealed that the consumption of SSBs increased waist circumference in adult populations. Also, a cross-sectional study indicated that fruit drink intake was significantly linked with a higher risk of obesity among women. In addition, added sweet or sugar foods were positively associated with BMI in the women. Excess sugar intake among sweets and desserts was a significant contributor to the development of overweight or obesity.

Over the past decades, the socioeconomic level has changed dramatically in China, especially in the southwest region. The transition from the traditional dietary pattern characterized by a high intake of vegetables, grains, and legumes to the Western model had occurred. It was observed that western dietary pattern had a higher incident risk of obesity and there was a marginally raised trend in the incident risk of obesity as western pattern levels in this study. Several studies have demonstrated that Chinese who had a western dietary pattern were more likely to suffer from obesity. Some similar findings were also reported among children and adolescents. One of possible reasons might be that meat and meat products are rich in cholesterol and saturated fatty acids, which could increase the risk of suffering from obesity to a certain degree. However, Daneshzad et al demonstrated that there was no significant association between total meat consumption and obesity based on a meta-analysis of observational studies. Therefore, more prospective studies are needed to clarify the association between red meat and total meat, and obesity.

Moreover, given the topographical characteristics of the Guizhou region, a wide range of potato products, boiled, fried, or mashed, were widely consumed in the local area. As a staple food in the western world, potatoes, an energy-dense food, played a significant role in the western diet pattern, and contributed greater amounts of carbohydrates to the diet. Foods containing more starches and refined carbohydrates were positively associated with weight gain. A meta-analysis confirmed that weight change was positively associated with the consumption of potatoes (boiled or mashed potatoes, potato chips, and French fries). Halkjaer et al also reported that total potato intake was associated with the increase in waist circumstances in women. However, the evidence for a link between potato intake and the risk of obesity remains controversial.

Based on this 10-year community population-based cohort in Southwest China, this study extended the evidence on the association between dietary patterns and incident obesity. Also, this study collected data through FFQ rather than 24h
However, there were some main limitations in the study. First, the outcome of obesity was only assessed by BMI and did not include those measures of central obesity such as waistline in this study, which may underestimate the incidence of obesity. Second, over several years of follow-up, the daily diet measured on baseline may be time-varying to bias our findings but we did not collect detailed diet information in the follow-up of this study. Third, Cox proportional hazards regression models were employed with the strata by physical activity to meet Proportional Hazards Assumption. In addition, some possible confounding factors such as medications, family history of obesity or genetic variants related to obesity were not collected in this study, which may bias the findings from this study. Our findings in this southwest Chinese population need to be confirmed or clarified by more prospective studies over different populations. For future studies, associations between diets and obesity measured by waistline or body composition should be explored, and gene–diet interactions on developing obesity should be considered, too.

**Conclusion**

In summary, there was a high risk of incident obesity among this Chinese community population of Southwest China. Also, four dietary patterns were identified in this community population of Southwest China, and junk food and western pattern increased risks of incident obesity. The findings provided new evidence for obesity prevention and control from the dietary perspective, especially for the Chinese population. Urgent intervention is called to be developed to promote a healthy dietary pattern and prevent the becoming obesity.

**Ethical Statement**

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the center of disease control and prevention of Guizhou Province (No. S2017-02).

**Informed Consent Statement**

Written informed consent was obtained from all subjects before the data collection.

**Acknowledgments**

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**Author Contributions**

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

**Disclosure**

The authors declare no conflicts of interest in this work.

**References**


