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ORIGINAL ARTICLE

Mouth Breathing, Head Posture, and Prevalence of Adenoid Facies in Patients with Upper Respiratory Tract Obstruction

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ABSTRACT

Frequent upper respiratory tract infections and allergic reactions may cause upper respiratory tract obstruction (OURT). Mouth breathing (MB) occurs in individuals with nasal breathing problems. A person with MB will raise his head higher; thus, MB is a risk factor for head posture (HP) deviation. Children with MB during growth and development may exhibit dentocraniofacial (DCF) deviation. Objective: To evaluate the prevalence of MB, HP, and DCF deviation in OURT patients to know risk factors of HP deviation, morphological aberrations of DCF and DCF deviation growth and development. Methods: This cross-sectional study included 285 OURT subjects aged 9–15 years. Data obtained from cephalometric analysis, physical examination, and questionnaires were analyzed. Results: Of 285 OURT subjects, 80.4% showed MB, 44.2% HP deviation, and 66.7% DCF deviation. As risk factors for DCF deviation, MB and HP showed odds ratios of 20.45 and 8.11 and population attributable risks of 87.5% and 59.7%, respectively. Conclusion: The prevalence of MB and DCF deviation in OURT patients is high, but that of HP deviation is generally comparable. MB and deviated HP are risk factors for DCF deviation growth and development.

Keywords: dentocraniofacial deviation, head posture, mouth breathing habit, Obstruction of upper respiratory tract, prevalence

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INTRODUCTION

During growth and development, children often suffer upper respiratory tract infections and allergic reactions, often in conjunction with one another frequent upper respiratory tract infections or allergic reactions may cause upper respiratory tract obstruction (OURT), which can result in respiratory problems. Normal breathing through the nose can transition to mouth breathing (MB) or a combination of nose and mouth respiration. According to Pacheco et al., MB is an etiology for sleep-disordered breathing (SDB) during childhood. MB can be habitual or due to upper airway obstruction. The MB habit may be perpetuated even after airway clearance. Habitual and obstruction-induced MB may cause facial muscle imbalance and craniofacial changes. MB may occur in patients with problems breathing through the nose. During MB, the patient will raise the head higher, so that MB is a risk factor for head posture (HP) deviation. In children experiencing this condition during growth and development, the direction of dentocraniofacial (DCF) growth and development may be changed, causing DCF deviation. Malocclusion (protrusive upper teeth, deep anterior bite, and deep palatal arch) is one characteristic of DCF deviation, with an 80% prevalence in Indonesia. Convex profile, long face syndrome, narrow face, and short upper lip are characteristics of the DCF appearance of OURT. According to the pilot study, the population of OURT patients in Indonesia is high. Considering the prevalence of this condition, the prevalence of MB habit, HP deviation, and malocclusion in Indonesia was assumed to be relatively high.

Children with MB habit during growth and development will suffer malocclusion with DCF characteristics, called adenoid facies due to the development of adenoid enlargement caused by OURT. Intraoral characteristics...
of adenoid facies include crowding or protruding upper anterior teeth, deep and narrow palatal arch, and retruded mandibula (Figure 1.).\(^3^,^4\) Adverse impacts caused by OURT and MB are serious enough to affect the risk factors. Equally important is the early detection of MB habits and DCF irregularities. In an early detection effort of OURT, MB, and adenoid facies children, Purwanegara et al.\(^5\) developed a series of valid and reliable questionnaires, which are simple and objective, and do not require expensive tools.

On clinical observation, almost all patients with Class II Angle type 1 and Class I Angle type 2 malocclusion showed MB. The narrowing nasal cavities (accompanied by a narrowing tooth arch) could be seen in most of the posteroanterior and panoramic radiographs of malocclusion patients. DCF deviation due to OURT and MB habit, leading to adenoid facies, causes a less attractive appearance. Certain children with adenoid facies can experience socialization barriers, such as derogatory nicknames, which can impact against their personality and cause low self-esteem.\(^6\) Snoring and sleep apnea syndrome occur in patients with OURT and MB habit. These symptoms are harmful (even fatal) and can cause heart abnormalities. According to Primhak,\(^7\) upper airway obstruction may cause clinical problems. The obstruction may be acute glottic or subglottic, and management consists of a rapid assessment and secure airway establishment. The symptoms of supraglottic obstruction should be recognized. In severe obstruction causing sleep-disordered breathing, the treatment of choice is adenotonsillectomy; otherwise noninvasive continuous positive airway pressure (CPAP) or ventilation may be necessary.\(^7\) Early detection in OURT and MB is important and prevention of HP and DCF deviation is necessary. We evaluated data on the prevalence of MB habit, HP deviation, and DCF morphology deviation in OURT patients. Odds ratios (ORs) for OURT patients and population attributable risk (PAR; i.e., large prevalence in the total population of DCF cases preventable when risk factors are eliminated) were calculated. There were three hypotheses: (1) MB risk factor has a role in HP deviation, (2) HP risk factor in OURT patients has a role in DCF deviation, and (3) MB and deviated HP risk factors have a role in DCF deviation during growth and development.

**METHODS**

A cross-sectional study was conducted to identify the deviation in DCF morphology, the pattern of the OURT population that may lead to MB, and the prevalence of the MB habit that may lead to deviation of HP and DCF morphology. OURT was an independent variable, and the prospective subjects were OURT patients with nasal, nasopharyngeal, and oropharynx obstruction diagnosed by an ENT specialist. Calculation of the prevalence was conducted by percentages (%). Bivariate analysis was used to determine differences. The occurrence of deviated DCF morphology was affected by HP and MB risk factors. Logistic regression unconditional analysis was used to determine which risk factors were more influential toward the DCF deviation.

A series of questionnaires developed by Purwanegara et al.\(^3\) was used to diagnose OURT patients with
MB habit. They developed a valid and reliable series of questionnaires before this study so they could obtain information regarding whether a person has experienced OURT and MB for a long time and whether DCF deviation (adenoid facies) could be detected with the questionnaires. Moreover, the questionnaires provide early detection in an easy, inexpensive, and rapid manner.5

HP is the position of the head toward the neck, and was measured using the lateral cephalogram, i.e., craniofacial angle, angle related to HP against a line that represents the cervical columna (NSL/OPT).8 The Mitutoyo® caliper with 0.05 mm precision was used. Normal value of HP based on research by Purwanegara was 94.317 ± 7.265 for 12- to 15-year-old and 91.817 ± 4.613 for 9- to 11-year-old (Figure. 2.) children.

Normal DCF features and adenoid facies were determined by assessing the subject’s frontal and profile facial appearances from visual clinical examination and facial photographs. Facial assessment referred to the characteristics of adenoid facies, such as long face syndrome, appearance of the steep angle between the ramus and mandibular corpus, convex facial profile (Schwarz’ facial profile analysis), unbalanced facial ratio (Simon analysis, one-third lower face height greater than one-third middle face height), narrow face, and incompetent lip. Normal facial appearance included an oval face, straight profile/favorable convex face, balanced facial ratio, and competent lip (Figure. 3.). We determined whether DCF characteristics were normal.3

The results of the assessment of frontal and profile photographs were used as the gold standard for determining DCF characteristics. Three orthodontists (two senior orthodontists and a researcher as orthodontist) verified the reliability, with 90.5% to 92.3% agreement among them regarding the results of the photographs. Sensitivity and positive predictive value were above 90%. The κ index as a measurement of reliability was 0.789 – 0.819 and statistically significant.

Inclusion and exclusion criteria were as follows: The OURT subjects were chosen from Jakarta and its vicinity population (Bekasi, Bogor, Tangerang, Depok), and were of Deutro-Malay race, 9 – 15 years old, all sexes, and in good general health. The subjects did not have any other poor oral habit except MB and MB accompanied by “tongue thrust,” had never undergone tonsillectomy and adenoidectomy, did not have asthma, and had never received orthodontic treatment.

The study population included visitors to the ENT Clinic in the Cipto Mangunkusumo Central Hospital, Faculty of Medicine Universitas Indonesia Sub Department of Larynxpharyx, Orthodontic Clinic and Pediatric Dentistry Clinic of Tooth and Mouth Hospital, Faculty of Dentistry Universitas Indonesia.

| Table 1. Distribution of OURT research subjects based on age and sex |
|-----------------|-----------------|-----------------|-----------------|
| Age             | Deviated DCF ($N = 190$) | Normal DCF ($N = 95$) | $P$            |
|                 | $n$ | %      | $n$ | %      |     |
| 9–11 years      | 96  | 73.7   | 25  | 26.3   | 0.000* |
| 12–15 years     | 94  | 50.5   | 70  | 49.5   |       |
| Sex             |     |        |     |        |       |
| ♂               | 92  | 61.1   | 37  | 38.9   | 0.130 |
| ♀               | 98  | 51.6   | 58  | 48.4   |       |

*P < 0.05

| Table 2. Prevalence of MB, HP, and DCF OURT patients |
|-----------|-----------|-----------|
| Dependent Variable | Category | $n$ | %      |
| a. MB         | No        | 56  | 19.6   |
|               | Yes       | 229 | 80.4   |
| b. HP         | Normal    | 159 | 55.8   |
|               | No        | 126 | 44.2   |
| c. DCF        | Normal    | 95  | 33.3   |
|               | No        | 190 | 66.7   |

The subjects were new cases and those first diagnosed by ENT specialists. In addition, subject data were also obtained from medical records of patients diagnosed with OURT by ENT specialists. Ethical approval was achieved from the Faculty of Medicine Universitas Indonesia.

RESULTS

MB, HPm and DCF Deviation Prevalence in OURT Subjects

Depending of the major research, 285 subjects (121 were 9–11 and 164 were 12–15 years old) were included in the study. Prevalence (percentage), number of patients with OURT based on the dependent variable, and distribution of OURT subjects with normal DCF and DCF deviation based on age group and sex are shown in Table 1. There were significant differences ($p < 0.05$) between the number of OURT subjects with normal DCF features and DCF deviation based on age group, but the difference in number based on sex was not significant. The prevalence of MB (80.4%), HP deviation (44.2%), and DCF deviation (66.7%) among 285 OURT subjects is shown in Table 2. No MB was noted in 19.7% of the patients, and HP and DCF features were normal in 55.8% and 33.3%, respectively.

OR and PAR value of MB, HP and DCF Deviation Prevalence in OURT Subjects

To obtain OR and PAR values in OURT patients, bivariate and multivariate analyses were used. MB as a risk factor for deviated HP was analyzed by bivariate analysis (significance, $p < 0.25$) and the results are
presented in Table 3. The OURT subjects with MB had a 2.08 (OR) times risk of HP deviation compared to those without MB. The PAR value of independent MB variable was 46.5%, meaning that HP deviation can be prevented in 46.5% of cases if the MB risk factors are eliminated. Therefore, the first hypothesis (MB risk factor has a role in HP deviation) was proved. The rates HP deviation were 86.5% (109 subjects) and 13.5% (17 subjects) in OURT patients with and without MB, respectively.

Risk Factors of HP Related to DCF Features
Risk factors of HP associated with the DCF variable were analyzed by bivariate analysis (Table 4). Subjects with a deviated HP had 4.35 (OR) times the risk of DCF deviation compared to those with a normal HP. The PAR value of independent variable HP was 59.7%, meaning that DCF deviation can be prevented in 59.7% of cases if HP deviation risk factors are eliminated. Therefore, the second hypothesis (risk factor of HP in OURT patients has a role in the occurrence of DCF deviation) was proven. The rate of DCF deviation was 55.3% (105 subjects) and 44.7% (85 subjects) in OURT subjects with and without a deviated HP, respectively.

MB and HP Risk Factors Related to Occurrence of DCF Deviation
The occurrence of DCF deviation was affected by HP and MB risk factors. To determine which risk factors were more influential toward DCF, multivariate analysis was performed (Table 5). Results indicated that: (1) MB subjects had a 9.95 (OR) times risk of DCF deviation compared to those without MB and (2) subjects with HP deviation had a 4.35 (OR) times risk of DCF deviation compared to those with a normal HP. The most dominant determinant role in the occurrence of DCF deviation was MB risk factor. The logistic regression equation was: Logit (DCF) = -1.652 + (2.298 x MB) + (1.470 x deviated HP)

Table 3. Bivariate analysis results of MB against HP in OURT subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Normal HP (N=159)</th>
<th>Deviation HP (N=126)</th>
<th>Total</th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
<th>PAR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MB</td>
<td>No</td>
<td>39</td>
<td>24.5</td>
<td>17</td>
<td>13.5</td>
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<td>1.00</td>
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<tr>
<td></td>
<td>Yes</td>
<td>120</td>
<td>75.5</td>
<td>109</td>
<td>86.5</td>
<td>229</td>
<td>0.021*</td>
<td>2.08</td>
</tr>
</tbody>
</table>

*p < 0.05

Table 4. Bivariate Analysis HP against DCF on the OURT subject.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Control (N = 95)</th>
<th>DCF case (N = 190)</th>
<th>Total</th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
<th>PAR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
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<tr>
<td>HP</td>
<td>Normal</td>
<td>74</td>
<td>77.9</td>
<td>85</td>
<td>44.7</td>
<td>159</td>
<td>1.00</td>
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</tr>
<tr>
<td></td>
<td>Deviation</td>
<td>21</td>
<td>22.1</td>
<td>105</td>
<td>55.3</td>
<td>126</td>
<td>0.000*</td>
<td>4.35</td>
</tr>
</tbody>
</table>

*p < 0.05

Table 5. The final results of the logistic regression unconditional analysis of risk factors against DCF in OURT subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Coeff.</th>
<th>SE</th>
<th>p Value</th>
<th>OR</th>
<th>95% CI OR</th>
<th>PAR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MB</td>
<td>No</td>
<td>1.00</td>
<td></td>
<td></td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2.298</td>
<td>0.367</td>
<td>0.000</td>
<td>9.95</td>
<td>4.84-20.45</td>
<td>87.8</td>
</tr>
<tr>
<td>HP</td>
<td>Normal</td>
<td>1.00</td>
<td></td>
<td></td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Deviation</td>
<td>1.470</td>
<td>0.318</td>
<td>0.000</td>
<td>4.35</td>
<td>2.33-8.11</td>
<td>59.7</td>
</tr>
<tr>
<td>Constanta</td>
<td></td>
<td>-1.652</td>
<td>0.354</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05. Log likelihood = -143.36; Pseudo R2 = 0.21; N = 285

The occurrence of DCF deviation was affected by HP and MB risk factors. To determine which risk factors were more influential toward DCF, multivariate analysis was performed (Table 5). Results indicated that: (1) MB subjects had a 9.95 (OR) times risk of DCF deviation compared to those without MB and (2) subjects with HP deviation had a 4.35 (OR) times risk of DCF deviation compared to those with a normal HP. The most dominant determinant role in the occurrence of DCF deviation was MB risk factor. The logistic regression equation was: Logit (DCF) = -1.652 + (2.298 x MB) + (1.470 x deviated HP). Therefore, the third hypothesis (MB and deviated HP risk factors have a role in the occurrence of DCF deviation during growth and development) was proven.
DISCUSSION

Martin et al.\textsuperscript{10} concluded that there was a lack of studies on the prevalence of MB. Prevalence of MB is important with respect to analysis of etiology and treatment. More sensitive health professionals are needed for early recognition and detection of MB syndrome in these patients.\textsuperscript{10} Just as important, our study was conducted to determine the mapping of OURT cases, MB, HP, and DCF deviation to determine policies in this country.

The distribution of OURT subjects in this study according to sex in either age group (9–11 or 12–15 years) demonstrated more female than male subjects. According to age group, more subjects were 12–15 than were 9–11 years old. In contrast, in a study by Abreu et al.,\textsuperscript{11} on patients diagnosed with MB (but not OURT), of 370 total patients (193 boys and 177 girls; mean age, 5.9 ± 1.9 years), 55% (204) were diagnosed with MB. They concluded that this prevalence was high enough, but there was no statistical correlation between MB and sex, socioeconomic condition, or age group. They also suggested validating a questionnaire for clinical diagnosis of MB in primary care children, while Purwanegara developed a series of questionnaires for use to diagnose MB.\textsuperscript{5,11}

Of our OURT subjects, 80.4% had a MB habit. This prevalence is relatively high considering the fact that MB affects DCF morphology and causes clinical and psychological disturbances. Our results were almost the same as those of Li et al.,\textsuperscript{12} who concluded that habitual snoring (HS) was a sleep-related breathing symptom, and also a significant and prevalent problem in primary school children. The efforts at prevention and care were indispensable for significant risk factors, such as male sex, obesity, parental HS, atopic symptoms, and history of upper respiratory infections. HS also was associated with sleep-disordered breathing symptoms and adverse neurobehavioral outcomes.\textsuperscript{13}

Purwanegara et al.\textsuperscript{13} had proven the significant correlation between OURT and snoring in the 12–15-year age group. They measured the McNamara modification line to diagnose the nasopharyngeal lumen as an indicator of upper airway tract obstruction. A healthy and clear pharynx is important for good sleep. According to Purwanegara et al.,\textsuperscript{13} snoring and apnea are symptoms of sleep-disordered breathing. Wang\textsuperscript{14} also concluded that children diagnosed with OURT and MB might suffer from sleep-disordered breathing, snoring, and apnea. Certain children might experience other symptoms, such as hypertension, headache, and psychological disorders. Various cardiovascular diseases could occur in severe cases. Early detection of OURT and MB is important.\textsuperscript{14} Alabi et al.\textsuperscript{15} concluded that snoring was an important health problem among pupils, most of whom were between the third and sixth years of life.\textsuperscript{15}

In this research, 18.7% of our OURT patients did not have a MB habit, even though nasal resistance was quite significant. However, if there was no neuromuscular response from the neck and facial muscles, there would not be any downward-backward changes in the posture of the mandible. The tongue would not slide down anteriorly, and the HP would not straighten up in certain children, so the MB habit would not develop. What is important here is the person’s reaction toward nasal obstructions.

Given its high prevalence, patients with MB must be treated more intensively. The community must be aware of the negative effects of a poor MB habit. In our study, the prevalence of OURT patients with MB was 80.4%, which also proved that MB was a risk factor for HP deviation.\textsuperscript{3} In our study, 44.2% of the subjects had HP deviation, while 55.8% had a normal HP. Each person has a different adaptation capability toward any nasal obstructions. Some open their mouths and raise their heads, so that oral respiration replaces nasal respiration.

Cuccia et al.\textsuperscript{16} analyzed lateral cephalograms taken in natural head posture in 35 MB patients (mean age, 8.8 ± 2.2 years; standard deviation, 5–13 years) and 35 patients with varied malocclusions and physiological breathing. They reported that, compared to physiological breathing subjects, MB children showed greater extension of the head to the cervical spine, which was related to reduced cervical lordosis and more skeletal divergence.\textsuperscript{16} Bolzan et al.\textsuperscript{17} analyzed the facial type in nasal and mouth breathers, and also HP by physical and photographic examination in 59 subjects 8 to 10 years 10 months old and verified the relationship among facial type and breathing mode (predominantly short face or brachyfacial type in nasal breathers, and long face or dolicofacial type in MB patients). There was no correlation between morphological facial index and HP.\textsuperscript{17} Flutter\textsuperscript{18} reported that in patients with chronic MB, the poor HP sometimes arose in the cranium, which is referred to as the ascending pattern. There was no distorted body part or distortion reflected throughout the body. Body distortions could be either ascending or descending problems. Flutter established that in nasal breathing there was an improvement in the entire body posture and head levels.\textsuperscript{18}

Major et al.\textsuperscript{19} reported that pediatric sleep-disordered breathing was common in children with chronic adenoid hypertrophy. The strong implication of this condition was deviation of the craniofacial growth pattern, called adenoid facies. The characteristics of adenoid facies included long face, maxillary constriction with an associated dental crossbite, increased overjet, and weak chin projection. Therefore, according to Major et al.,\textsuperscript{19}
the best care solution for pediatric sleep-disordered breathing is adenotonsillectomy.

Our results showed a 66.7% prevalence of DCF deviation in OURT subjects, while 33.3% had no deviation, meaning that the prevalence of adenoid facies was two times higher than that of normal DCF in OURT subjects. In their cross-sectional and descriptive study, Souki et al. reported that the incidence of posterior crossbite in MB children was higher than that found in the general population, and that MB children in the mixed and permanent dentition period were more likely to have an anterior open bite and class II malocclusion. Peltomäki reported that the increase in adenoid size resulted in obstruction of the nasal respiratory tract, thus causing MB in which the position of the head and tongue will change and lead to change in the DCF growth direction (adenoid facies).

Basheer et al. performed otolaryngological examinations in children 6–12 years old and found 20 MB children with adenoid enlargement and 60% with nasopharynx obstruction. Adenoid facies occurred in all MB subjects, with a significant increase in lower incisor proclination, lip incompetency, convex facial profile, and mentolabial sulcus depth. According to Viveros, although many studies analyzed the mode of breathing and sleep-disordered breathing effects on facial growth, the direct relationship between nasal obstruction and facial malformation remains unknown. The question of the influence of genetics and environment also remains unanswered. To answer and understand this question required research with a large population and a dynamic scale and three-dimensional study. In this case, the key factor in the relationship between facial growth and mode of breathing would obviously be answered. Koca et al. first reported a photographic method to analyze the effects of adenoid hypertrophy on maxillofacial development, and the reflection of skeletal deformities on soft tissue distances and angles.

Macari and Haddad concluded that orthodontists have an important role in the early detection and diagnosis of airway problems. Early treatment of the airways, whether achieved medically or surgically, was gaining more ground between ENT specialists as they became aware of the potential effect on craniofacial development. OURT subjects with MB and HP deviation tend to be at risk for DCF deviation. MB habit in OURT patients proved to be a risk factor for HP deviation (2.08 times the risk). Therefore, prevention efforts are necessary. Prevention can be begun early in children to maintain health by preventing upper respiratory tract infections as the cause of OURT. Purwanegara et al. reported that the critical age at onset of deviations in growth and DCF development in OURT patients was 8 years. Prevention efforts can be initiated in ENT clinics by treating patient with upper respiratory tract infections, which also can be integrated with orthodontic treatment. Early detection of OURT and MB is important to prevent the MB habit at an early age. These early detection efforts also can be performed in dental clinics (Clinical Pediatric Dentistry), and dentists then can collaborate with orthodontists, even in the neighborhoods, by using a series of questionnaires and physical examinations that are simple, and easy to perform by all medical personnel.

Orthodontists can perform treatment to prevent occurrence or worsening of MB habits. Myofunctional orthodontic treatments, such as removable appliances, for example the activator, twin block or fixed orthodontic appliance that, like anterior mandibular devices, are able to achieve mandibular advancement to expand the pharyngeal lumen. With other orthodontic tools, for example rapid palatal expansion, the nasal cavity could be expanded to reduce the severity of OURT. The combination of intra- and extraoral orthodontic appliances, such as a head gear appliance and face mask, can widen the upper airway in the anteroposterior and mediolateral directions.

**CONCLUSION**

The prevalence of MB and DCF deviation in OURT patients is high, but that of HP deviation is more or less comparable. If the risk factors are removed, then the occurrence of dependent variables can be prevented. If MB as a risk factor is eliminated, then HP deviation can be prevented. Similarly, if HP deviation as a risk factor is eliminated, then DCF deviation can be prevented. MB and HP deviation risk factors can adversely affect DCF growth and development, so that deviation can occur. Early detection and prevention, and public health knowledge improvement are important. It is important to encourage interdisciplinary cooperation among dentists, orthodontists, ENT specialists, and other health experts, such as psychiatrists and psychological experts, in the management and prevention of MB, HP deviation, DCF morphology deviation, through seminars, scientific forums, and workshops.

**CONFLICT OF INTEREST**

The authors have no financial interests related to the material in the manuscript. *It was a self-funded study*

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