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Integrative traditional Chinese medicine treatment for children with obstructive sleep apnea

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A R T I C L E I N F O

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A B S T R A C T

Purpose: Obstructive sleep apnea (OSA) is a chronic disease that affects 1%–6% of children. Our study aims to explore the effectiveness and clinical characteristics of integrative Traditional Chinese Medicine (ITCM) for pediatric OSA.
Materials and methods: In this retrospective cohort study, we assessed differences of polysomnography (PSG) parameters and clinical characteristics between 2009 and 2020. Children <12 years old diagnosed with OSA (n = 508) were included and were categorized into ITCM cohort, western medicine (WM) cohort ,and surgery cohort. Outcomes were apnea-hypopnea index (AHI), respiratory disturbance index (RDI), and body mass index (BMI).
Results: There were 56 (11%), 324 (63.8%), and 128 (25.2%) patients in the ITCM, WM, and surgery cohorts. Among 17, 26, and 33 patients in the ITCM, WM, and surgery cohorts underwent follow-up PSG studies, respectively. In the ITCM follow-up cohort, AHI were significantly reduced (9.59 to 5.71, $p < 0.05$). BMI significantly increased in the WM follow-up cohort (19.46 to 20.50, $p < 0.05$) and the surgery follow-up cohort (18.04 to 18.85, $p < 0.01$). Comparing ITCM to WM cohort, a significant difference was found between the changes in RDI (ITCM: −6.78, WM: 0.51, $p < 0.05$) after treatment. Among ITCM follow-up cohort, the most prescribed TCM formula was Forsythia and Laminaria Combination. The most prescribed TCM herb was Ephedrae Herba.
Conclusions: ITCM therapy can significantly reduce RDI and control BMI. We identified potential TCM treatments for pediatric OSA. Further study of the pharmacological mechanisms and clinical efficacy is warranted.

1. Introduction

Obstructive sleep apnea (OSA) affects 1%–6% of children with the peak incidence in those between two and six years of age.[1] A definitive diagnosis of OSA is made using overnight polysomnography (PSG). The number of apneas or hypopneas per hour is recorded, providing an apnea/hypopnea index (AHI) score. In children, an AHI score of one or more is indicative of OSA. OSA not

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only disrupts sleep, but can also lead to failure to thrive, neurocognitive problems, behavioral disorders, poor school performance, enuresis, and cardiopulmonary disease. Adolescents with OSA have a higher risk of metabolic dysfunctions such as dyslipidemia, insulin resistance, and hypertension and often experience difficulty losing excess weight.[2] Pediatric OSA is a chronic disease that is underestimated, but poses a significant threat to the health. OSA has been reported as an independent risk factor for severe COVID-19 and increases the risks of neurocognitive impairment and abnormal functional pulmonary changes after the acute phase of COVID-19 infection.

The etiology of OSA is multifactorial and the condition may result from adenoid-tonsillar hypertrophy, obesity, allergic rhinitis (AR), asthma, premature birth or craniofacial anomalies.[3] Pathogeneses that contribute to OSA include obstruction or collapse of the upper airway, a low arousal threshold, ineffective pharyngeal dilator muscle function, and high loop gain in the respiratory system.[4] Enlarged tonsils and adenoid are the most common OSA trigger in children. Other conditions that result in narrowing airway including AR, turbinate hypertrophy, nasal septum deviation or maxillary constriction are also common causes in children.[5] Treatment of OSA depends on the etiology and severity of the disease. The first-line treatment for moderate to severe OSA resulting from adenoid-tonsillar hypertrophy is adenotonsillectomy. In children without adenoid-tonsillar hypertrophy or with contraindications of surgery, continuous positive airway pressure (CPAP) is required. In mild to moderate OSA, myofunctional therapy can improve mean oxygen saturation and lower AHI in children.[6] No effective drugs have been approved for OSA so far. Preliminary research suggests that the leukotriene receptor antagonist, montelukast, may improve clinical symptoms in children with mild to moderate OSA in the short term.[7] However, adverse reactions to montelukast, including neuropsychiatric symptoms, headache, nausea, and vomiting have raised concerns about this treatment.[8] Several studies have proposed intranasal corticosteroid therapy as a potential treatment for OSA with co-existing rhinitis,[9] but it is limited to patients with the symptom of nasal obstruction.

Surgery is invasive and, for children under three years of age, is a high-risk treatment. Incomplete resolution of pediatric OSA after adenotonsillectomy was observed in a prospective 3-year longitudinal study. The risk factors of recurrence of OSA include an increasing change in body mass index (BMI) after surgery, enuresis, or allergic rhinitis before surgery.[10] Besides, CPAP is difficult for children to endure and approximately 20% of children will fail in CPAP treatment.[11]

Given these limitations of the currently available treatments for OSA children, there is a critical need for safe alternative therapies for children with OSA. Traditional Chinese medicine (TCM) has been widely used in Asian countries for thousands of years and 22% of Taiwanese children have ever received TCM treatment,[12] that is highly accepted in Taiwan. However, the effectiveness and epidemiology of integrative TCM therapy in pediatric OSA have not been investigated. In this study, we aimed to disclose the epidemiology in a tertiary hospital and identify TCM prescriptions to evaluate the effectiveness in pediatric OSA.

2. Material and methods

In this retrospective cohort study, we reviewed medical charts of PSG from Jan.2009 to Jan.2020 and compared the changes in PSG parameters of surgical treatment, western medicine (WM), and integrative TCM (ITCM) treatment. We also identified the TCM prescriptions commonly used for pediatric OSA.

2.1. Data source

We included pediatric OSA patients who attended the outpatient clinic and those admitted for hospitalization from the period between January 2009 and January 2020. Claims data were collected from the electronic medical records of China Medical University Hospital (CMUH), Taichung, Taiwan. We gathered data on the clinical characteristics of the patients, the type of treatment received, reports from the PSG study, and surgical reports. CMUH is a tertiary university-affiliated medical and has a TCM research center in central Taiwan. It has offered clinical TCM clinical services since 1980 and has a dedicated TCM department staffed by 69 TCM doctors.

2.2. Participants and variables

The inclusion criteria consisted of children under 12 years old who had received a diagnosis of OSA through overnight PSG study. Exclusion criteria were only one visit to the TCM clinic; required ventilation; Prader–Willi syndrome; mucopolysaccharidosis; Down's syndrome; cleft palate; laryngomalacia; congenital muscular dystrophy; craniofacial anomalies; head and neck vascular malformations; adenotonsillectomy prior to the PSG study; and incomplete PSG studies. Of those enrolled, 51 children were excluded for the above reasons. Children treated with TCM and ordinary WM treatment were defined as the ITCM cohort. Since WM is the main type of healthcare provided in Taiwan, most of the ITCM cohort was treated with both treatments. Those children who underwent western medicine treatment were defined as the western medicine (WM) cohort. The children who underwent adenoid tonsillectomies, palatine tonsil resection, uvulopalatopharyngoplasty (UPPP), or nasal laser surgery were defined as the surgery cohort.

The clinical and demographic characteristics collected comprised sex, age, body weight (BW), body height, BMI, body size, and comorbidities when the first PSG was performed. Body sizes were classified as normal, overweight (above the 85th percentile), obese (above the 95th percentile), and underweight (below the 5th percentile) according to the child's BMI percentile on the new growth curve for Taiwanese children and adolescents.[13] This reference index for children and adolescents varies according to age and gender. Comorbidities were assigned diagnostic codes in the electronic medical records of the International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) based on the data from PSG studies and assessments during hospitalization, and/or outpatient clinic visits. Comorbidities observed in our subjects were AR (ICD-9-CM code: 477), asthma (ICD-9-CM code: 493), tonsillar and/or adenoid hypertrophy (TAH) (ICD-9-CM codes: 474.2, 474.11, 474.1, 474.9), attention deficit hyperactivity disorder (ADHD) (ICD-9-CM code: 341), and enuresis (ICD-9-CM code: 788.36, 307.6).

2.3. Polysomnography

The children in the study underwent overnight PSG at the sleep center of CMUH. PSG measures included six-channel electroencephalography, electrocardiography, electrooculography, thoracic-abdominal movements, submental and shin electromyography, nasal air pressure transduction, oronasal thermistor airflow monitoring, finger oxygen saturation (SpO2), sound recording, snore detection with a piezoelectric sensor, and video recording during sleep. Sleep stages and respiratory events were scored by certified sleep technicians using version 2.4 of the American Academy of

Sleep Medicine (AASM) scoring manual.[14] Sleep stages consist of the waking state (W), rapid eye movement sleep (REM), and the three non-rapid eye movement sleep stages (N1, N2, N3) of progressively deeper sleep. Sleep efficiency is defined as the ratio of total sleep time to time in bed. Children were determined to have poor sleep quality if their sleep efficiency was below 74%.[15] According to AASM (2007) criteria, obstructive apnea is a reduction in airflow of more than 90% for at least two respiratory cycles with paradoxical chest and abdominal movements. Hypopnea is defined as a ≥30% reduction in nasal pressure with paradoxical chest and abdominal movements resulting in at least 3% desaturation of SpO2. AHI was calculated as the average number of apneas and hypopneas per hour. The severity of OSA in children under 12 years of age is based on their AHI scores and can be mild (AHI 1–5); moderate (AHI ≥ 5–10), or severe (AHI ≥10). Arousal from sleep means abrupt changes in sleep electroencephalogram (EEG) from a deeper stage of sleep to a lighter stage of sleep or to waking state.[16] Arousal is defined as an abrupt shift in EEG frequency that includes alpha, theta, or frequencies greater than 16 Hz, sustaining at least 3 s, with at least 10 s of stable sleep preceding the change. Arousal is classified by the reasons evoked, such as respiratory event, movement of the limbs, or spontaneous nature. A series of breaths over at least 10 s associated with increased respiratory effort that results in arousal from sleep without meeting the criteria for apnea or hypopnea is defined as respiratory effort-related arousal (RERA). The respiratory disturbance index (RDI) is a measure of the average number of breathing events (apneas + hypopneas + RERAs) per hour over the total sleep time. Improvements in OSA in our subjects were evaluated based on differences of AHI and RDI between pre- and post-treatment. To compare the effectiveness of the three treatment types, these differences were compared between the ITCM, WM, and surgery groups. In addition, the differences in PSG parameters before and after the intervention were compared between the WM and ITCM groups.

2.4. Herbal formulas and single herbs

The most common primary diagnosis was determined from ICD-9-CM codes assigned at clinical visits. To explore potentially effective formulas and single herbs, we analyzed the prescriptions given to the 56 children in the ITCM cohort and the 17 children in the ITCM follow-up cohort. All herbal formulas prescribed were listed by their Latin names, Chinese names, and pin-yin names. Their ingredients were listed as Chinese name, pin-yin name, Latin name, and botanical names. Single herbs were also listed by Chinese name, pin-yin name, Latin name, and botanical names. The full botanical names used were in accordance with the rules of the International Plant Names List (IPNI; http://www.ipni.org) and the Plant List (http://www.theplantlist.org/). For all prescriptions used in the interval between their first and second PSG study, the mean duration for which they were to be taken, the number of prescriptions, and the average daily doses were calculated.

2.5. Adverse effect

To assess the potential adverse effects of traditional Chinese medicine (TCM) usage in our study participants, we conducted a comprehensive review of the integrative TCM cohort's medical records and the Taiwan Adverse Drug Reaction Reporting System for Herbal Medicine (TADRRS-HM) established by the Ministry of Health and Welfare, Taiwan.[17]

2.6. Statistical analysis

The clinical characteristics of the three cohorts, the primary diagnosis of those in the ITCM group, and the most frequently prescribed herbal formulas and single herbs for OSA treatment were analyzed. Shapiro-Wilk test was used to assess normal distribution at first. Comparison of clinical characteristics and baseline polysomnography parameters between ITCM, WM, and surgery cohorts before treatment was analyzed by the Kruskal-Wallis test because the claims data do not follow a normal distribution. Categorical variables were presented as absolute numbers and percentages and compared using chi-square tests. Continuous variables were presented as means ± standard deviations (SDs) and compared using Kruskal–Wallis tests. The baseline clinical characteristics and differences in PSG parameters between the ITCM cohort and the Western medicine cohort were analyzed using the Mann-Whitney test and the chi-square test. Differences were calculated by subtracting the values for each variable before treatment from their values after treatment. Results with p-values of <0.05 were considered statistically significant. All of the statistical analyses were performed using SAS v. 9.4 (SAS Institute, Inc, Cary, NC) software.

3. Results

Fig. 1 presents a flow chart of the recruitment process that led to our final study subjects of 508 children under 12 years of age with OSA. There were 56 (11%), 324 (63.8%), and 128 (25.2%) patients in the ITCM, WM, and surgery cohorts. The clinical characteristics and baseline PSG parameters of these three cohorts are shown in Table 1. Males were predominant in all three cohorts; however, male-to-female ratios differed significantly between the three cohorts (ITCM: 2.11, WM: 2.72, surgery: 4.8, $p < 0.01$). In the surgery cohort, male to female ratio was twice that of the other two groups. The mean age at the time of OSA diagnosis was between 6.6 ± 2.45 and 7.21 ± 2.57. This was not significantly different between groups. The mean BW and body size were significantly different between these three cohorts ($p < 0.01$). Over 40% of the children in the WM and surgery groups were overweight or obese. In all three groups, more than 50% of the children were of normal body size. OSA severity was also significantly different between the three cohorts ($p < 0.05$). The percentages of those with mild, moderate, and severe OSA were 58.93%, 17.86%, and 23.21% in the ITCM cohort; 60.8%, 20.68%, and 18.52% in the WM cohort; and 28.91%, 22.66%, and 48.44% in the surgery cohort. The prevalence of comorbidities also differed between cohorts. The prevalence of AR was significantly higher in the ITCM cohort than in the other two ($p < 0.05$). The prevalence of ADHD was significantly higher in the WM cohort than in the other two ($p < 0.05$). And the prevalence of adenoid and/or tonsillar hypertrophy was significantly higher in the surgery cohort than in the other two ($p < 0.05$).

The baseline PSG parameters compared among three cohorts are shown in Table 1. Mean AHI scores, mean obstructive apnea counts, mean hypopnea counts, RERA, and RDI were significantly different ($p < 0.05$) among the three cohorts. For all PSG parameters, mean AHI scores (24.72, 9.64, 9.59), mean obstructive apnea counts (28.63, 9.85, 9.68), mean hypopnea counts (64.44, 29.28, 27.04), and RDI (18.97, 8.02, 7.70) were highest in the surgery cohort, second highest in the WM cohort, and lowest in the ITCM cohort. The mean RERA scores (3.88,1.89,1.67) were highest in the surgery cohort, second highest in the ITCM cohort, and lowest in the WM cohort. The surgery cohort had the lowest SpO2 trough (82.26 ± 10.66), followed by the WM cohort (85.51 ± 9.78), then the ITCM cohort (87.82 ± 5.01).

Of the patients in each group, 17, 26, and 33 of those in the ITCM, WM, and surgery groups, respectively, underwent a follow-up-PSG study. Table 2 shows a comparison of the clinical variables and PSG parameters before and after intervention for each of the three

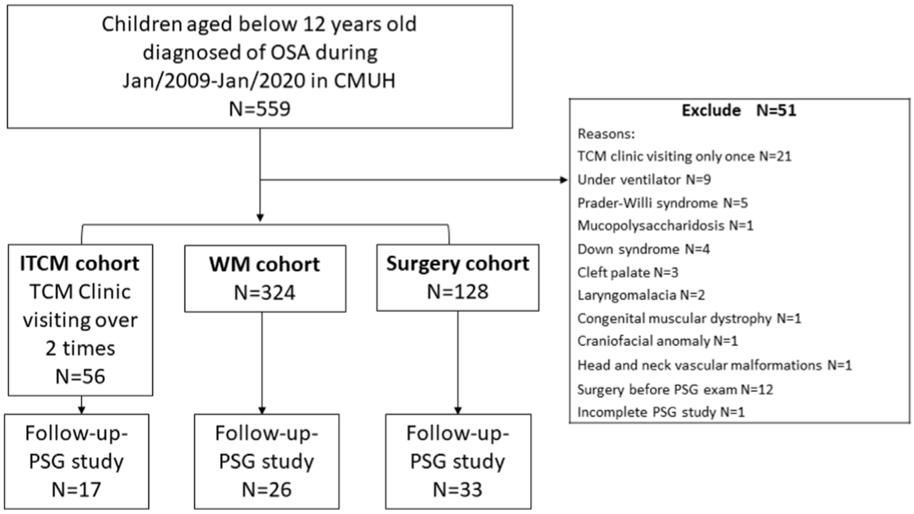

Fig. 1. Flow chart of obstructive sleep apnea (OSA) children recruitment. Abbreviation: CMUH, China Medical University Hospital; ITCM, Integrative Traditional Chinese Medicine; WM, Western Medicine; PSG, Polysomnography; TCM, Traditional Chinese Medicine.

groups. The mean (±SD) follow-up-intervals (in years) for the three groups were 0.66 ± 0.64 in ITCM cohort, 1.29 ± 1.50 in WM cohort, and 0.96 ± 1.22 in surgery cohort. The pre and post-intervention differences in AHI, RDI, and BMI were compared between cohorts in Table 2. In the ITCM follow-up cohort and the surgery follow-up cohort, there was a significant reduction in the mean AHI, which was 9.59 to 5.71, $p < 0.05$ in the ITCM follow-up cohort and 24.72 to 4.14, $p < 0.01$ in the surgery follow-up cohort. The percentages of the follow-up cohorts with severe OSA showed considerable decreases from the pre-treatment percentages in both the ITCM follow-up cohort (35.29%–17.65%) and the surgery follow-up cohort (63.64%–6.06%). RDI was significantly reduced postoperatively in the surgery follow-up cohort ($p < 0.01$). In both the WM (19.46–20.50, $p < 0.05$) and the surgery (18.04–18.85, $p < 0.01$) follow-up cohorts, there was a significant post-treatment increase in the mean BMI. In addition to sleep structure, the duration of sleep stage N2 and N3 showed a significantly longer duration after surgery. The mean number of arousals due to movement of the limb was significantly higher after intervention in both the ITCM and surgery follow-up cohorts, but significantly lower in the WM follow-up cohort.

The comparison of baseline clinical characteristics between the ITCM follow-up cohort and the WM follow-up cohort is shown in Table A1. The BMI in the WM follow-up cohort (19.46 ± 5.73) showed a significantly higher compared to the ITCM follow-up cohort (16.69 ± 2.43). The proportion of AR in the ITCM follow-up cohort (N = 16, 94.12%) was significantly higher compared to the WM follow-up cohort (N = 14, 53.85%). The confounders of sex, age, weight, body size, and comorbidities of tonsillar adenoid hypertrophy and asthma between the ITCM follow-up cohort and the WM follow-up cohort did not meet significantly different. The comparison of the difference between the ITCM and WM cohorts before and after the intervention is shown in Table A2. The change in RDI was significantly different (ITCM: 6.78 ± 19.03; WM: 0.51 ± 14.31, $p = 0.05$). The changes in AHI (ITCM: 5.88 ± 13.33, WM: 1.13 ± 8.53, $p = 0.05$) and BMI (ITCM: 0.08 ± 1.41, WM: 0.80 ± 1.53, p = 0.07) were different, albeit not statistically significant. After treatment, the ITCM follow-up cohort (△Stage N2:13.22%) showed a significant prolongation of the N2 stage duration compared to the WM follow-up cohort (△Stage N2:0.93%).

The ten most common primary diagnoses received by the children in the ITCM cohort who attended the TCM clinic for OSA treatment are listed in Table 3. AR (ICD-9-CM code of 477.9) was the most common primary diagnosis (26%), followed by sleep disturbance (13%), insomnia with sleep apnea (11%), nocturnal enuresis (11%), and adenoid vegetation (8%). Among ITCM cohorts, TCM treatment included oral concentrated herbal extract granules, which were manufactured from Chinese herbal formulas and single herbs according to the standards of good manufacturing practices in Taiwan. The ten most Chinese herbal formulas and single herbs prescribed to the ITCM group (n = 56) are shown in Table A3 And Table A4. To explore the potential effective prescriptions, we focused on the prescriptions of the 17 children in the ITCM follow-up cohort. In the ten most prescribed Chinese herbal formulas and single herbs, we summarized the possible pharmacological effects of the ingredients (Tables 4 and 5). The most prescribed Chinese herbal formula (Chinese name, Pin-Yin name, average daily dose) was Forsythia & Laminaria Combination (散腫潰堅湯, sàn zhǒng kuì jiān tang, 8.49 g), followed by Magnolia Flower Lung-Clearing Decoction (辛夷清肺湯, xīn yí qīng fèi tang, 11.5 g), Xanthium Powder (蒼耳子散,cāng ěr zǐ sàn, 9.16 g), Honeysuckle & Forsythia Formula (銀翹散,yín qiào sàn, 2.96 g), and Tea-Mix and Chuanxiong Powder (川芎茶調散,chuān xiōng chá diào sǎn, 1.17 g). The most prescribed single herb (Chinese name, Pin-Yin name, average daily dose) was Ephedrae Herba (麻黃,má huáng, 9.67 g), followed by Glycyrrhizae Radix et Rhizoma (甘草,gān cǎo, 2.24 g), Salviae Miltiorrhizae Radix et Rhizoma (丹參,dān shēn, 0.60 g), Platycodonis Radix (桔梗,jié gěng, 0.56 g), and Atractylodis Macrocephalae Rhizoma (白朮,bái zhú, 1.09 g).

After thoroughly reviewing the medical records and the Taiwan Adverse Drug Reaction Reporting System for Herbal Medicine (TADRRS-HM) of the integrative traditional Chinese medicine (ITCM) cohort at China Medical University Hospital, no significant adverse effects were reported in our study.

4. Discussion

Untreated OSA can cause serious health problems in children. Due to the multiple factors that contribute to OSA, no effective drug has yet been approved for its treatment in children. Currently, the main treatments are surgery or lifelong CPAP to keep airways

Table 1
Comparison of clinical characteristics and baseline polysomnography parameters in integrated with traditional Chinese Medicine (ITCM), Western Medicine (WM), and surgery cohorts.

Variables	ITCM (N = 56)		WM (N = 324)		Surgery (N = 128)		*P*-value
Sex							0.043[a]
Female [n, %]	18	32.14	87	26.85	22	17.19	
Male [n, %]	38	67.86	237	73.15	106	82.81	
Age [mean, ±SD]	7.21	2.57	7.03	2.64	6.60	2.45	0.203[b]
Height [mean, ±SD]	123.33	15.14	123.79	16.43	122.60	16.36	0.781[b]
Weight [mean, ±SD]	26.31	9.19	29.63	13.58	29.58	13.54	0.017[b]
BMI [mean, ±SD]	16.78	3.02	18.38	4.46	18.65	4.13	0.525[b]
Neck [mean, ±SD]	28.47	13.52	27.42	4.94	27.53	4.57	0.525[b]
Waist [mean, ±SD]	56.74	10.63	61.54	13.39	60.89	15.04	0.051[b]
Body size							0.003[a]
normal [n, %]	38	67.86	169	52.16	66	51.56	
obesity [n, %]	5	8.93	82	25.31	42	32.81	
overweight [n, %]	5	8.93	49	15.12	16	12.5	
Underweight [n, %]	8	14.29	24	7.41	4	3.13	
Comorbidities							
AR [n, %]	57	44.53	118	36.42	35	27.34	0.001[a]
Enuresis [n, %]	2	3.57	20	6.17	4	3.13	0.356[a]
ADHD [n, %]	1	1.79	25	7.72	2	1.56	0.015[a]
TAH [n, %]	10	17.86	55	16.98	39	30.47	0.005[a]
Asthma [n, %]	5	8.93	32	9.88	9	7.03	0.637[a]
PSG parameter							
NREM							
Stage_N1% [mean, ±SD]	8.59	6.12	11.05	8.76	10.68	6.90	0.398[b]
Stage_N2% [mean, ±SD]	32.64	7.85	40.62	13.83	36.71	10.89	0.216[b]
Stage_N3% [mean, ±SD]	36.98	8.56	30.70	13.69	31.47	10.54	0.392[b]
REM % [mean, ±SD]	21.85	5.33	17.63	10.12	20.54	7.64	0.795[b]
TST, hours [mean, ±SD]	6.27	1.02	6.36	0.80	6.26	0.77	0.461[b]
Sleep efficiency % [mean, ±SD]	88.50	11.50	89.17	10.89	89.47	11.17	0.860[b]
AHI [mean, ±SD]	9.59	8.67	9.64	10.98	24.72	24.75	<.0001[b]
RDI [mean, ±SD]	7.70	8.97	8.02	11.67	18.97	22.55	0.000[b]
RERA [mean, ±SD]	1.89	3.16	1.67	3.97	3.88	7.87	0.002[b]
Severity of OSA							0.038[a]
mild (<5) [n, %]	33	58.93	197	60.8	37	28.91	
moderate (5–10) [n, %]	10	17.86	67	20.68	29	22.66	
severe (>10) [n, %]	13	23.21	60	18.52	62	48.44	
Obstructive apneas [mean, ±SD]	9.68	15.91	9.85	23.68	28.63	53.01	<.0001[b]
Central apneas [mean, ±SD]	3.34	6.48	2.81	6.37	7.25	39.88	0.120[b]
Mixed apneas [mean, ±SD]	0.88	2.68	0.56	3.37	1.18	3.61	0.208[b]
Hypopneas [mean, ±SD]	27.04	31.65	29.28	38.98	64.44	71.60	<.0001[b]
Arousal by respiratory events [mean, ±SD]	12.23	20.88	10.52	24.47	23.56	46.80	0.000[b]
Arousal by spontaneous nature [mean, ±SD]	78.89	63.68	78.04	71.52	89.27	101.93	0.393[b]
Arousal by limb movements [mean, ±SD]	2.25	10.86	5.32	29.16	4.73	18.51	0.704[b]
Nadir SpO2 [mean, ±SD]	87.82	5.01	85.51	9.78	82.26	10.66	<.0001[b]

Abbreviations: BMI, body mass index; TST, total sleep time; AR, allergic rhinitis; ADHD, attention deficit hyperactivity disorder; TAH, tonsillar-adenoid hypertrophy; PSG, polysomnography; NREM, non-rapid-eye-movement; REM, rapid-eye-movement; AHI, apnea-hypopnea index; RERA, respiratory effort-related arousal; RDI, respiratory disturbance index.
[a] Chi-square test.
[b] Kruskal-Wallis test.

patent during sleep. TCM formulas and herbs are natural products containing multiple bioactive components. They offer potential treatment for this disease due to their safety and diverse pharmaceutical effects. This is the first study to explore the effectiveness of integrating TCM therapy with WM to treat OSA in children. Our study has also identified the clinical characteristic of OSA children treated with TCM, WM, and surgery in a tertiary medical center.

We found an uneven gender distribution with a higher proportion of male patients in our subjects. The mean age at the time of OSA diagnosis was 6–7 years old. This is compatible with findings from previous studies in other countries.[3,18] Our study revealed a particularly high male-to-female ratio (82.8%: 17.2%) in the surgery cohort. This is consistent with Kang et al.'s[19] finding that, in terms of AHI scores, male adolescents exhibit more severe OSA than females with the condition. Therefore, male gender is a risk for greater severity of OSA and a consequent greater need for surgical intervention. Of the children with OSA treated at CMUH, 11% sought TCM treatment. This roughly corresponds to the overall percentage of pediatric TCM users in Taiwan.[20] CPAP is not commonly used with children in our institution. Only nine children have received CPAP therapy in the past ten years. In the ITCM cohort, five children (8.9%) were obese, five (8.9%) were overweight, 38 (67.9%) were of normal weight, and eight (14.3%) were underweight. The distribution of body size and the comorbidity of AR in the ITCM cohort were significantly different from those in the WM and surgery cohorts. This is likely to be related to parental decisions when seeking healthcare in Taiwan. Children with AR, dyspepsia, or short stature would likely favor TCM.[12] OSA was most severe in the surgery cohort, followed by the ITCM cohort, and then the WM cohort. Most of the ITCM cohort had mild OSA, but severe OSA was the second most frequent level in this group. We speculated that this may be because parents of children with mild OSA and no indications for surgery may be more inclined to seek TCM treatment, as would those of children with severe OSA who were hesitant about surgery.

The most common reason children with OSA were brought to the TCM clinic was AR. AR is among the diseases that aggravate OSA in children and, in Taiwan, a high proportion of children with AR are

Table 2
Comparison of variables and polysomnography parameters in integrated with TCM (ITCM), western medicine (WM), and surgery cohorts before and after intervention.

	ITCM					WM					Surgery				
	before (N = 17)		after (N = 17)			before (N = 26)		after (N = 26)			before (N = 33)		after (N = 33)		
PSG follow-up interval [mean, ±SD]/year	[0.66, 0.64]					[1.29, 1.50]					[0.96, 1.22]				
Variables					*P*-value					*P*-value					*P*-value
Height [mean, ±SD]	124.51	12.76	128.78	14.04	0.0034[d]	120.55	18.51	128.53	18.02	0.0004[d]	117.59	17.31	124.08	17.98	<.0001[d]
Weight [mean, ±SD]	26.49	7.61	28.25	8.13	0.0263[d]	30.75	19.00	36.43	20.23	<.0001[d]	26.48	13.24	31.15	16.85	<.0001[d]
BMI [mean, ±SD]	16.69	2.43	16.64	2.16	0.8177[d]	19.46	5.73	20.50	6.08	0.0172[d]	18.04	3.84	18.85	4.41	0.0017[d]
Neck [mean, ±SD]	26.86	2.14	29.26	6.27	0.0176[d]	27.10	4.96	28.26	4.54	0.0659[d]	26.50	3.76	27.95	3.90	0.0008[d]
Waist [mean, ±SD]	57.47	7.26	56.23	10.91	0.9012[d]	63.23	16.41	67.45	17.39	0.0105[d]	57.66	16.47	63.95	13.29	<.0001[d]
PSG parameter															
NREM															
Stage_N1 [%,±SD]	8.59	6.12	6.34	4.01	0.1172[d]	11.05	8.76	10.47	7.17	0.4954[d]	10.68	6.90	6.99	3.81	0.0182[d]
Stage_N2 [%,±SD]	32.64	7.85	41.36	7.00	0.0003[d]	40.62	13.83	41.82	11.42	<.0001[d]	36.71	10.89	41.37	10.66	<.0001[d]
Stage_N3 [%,±SD]	36.98	8.56	32.04	8.41	0.2292[d]	30.70	13.69	30.89	12.08	0.9688[d]	31.47	10.54	32.21	10.95	<.0001[d]
REM [%,±SD]	21.85	5.33	19.69	5.62	0.1004[d]	17.63	10.12	16.83	7.87	0.6742[d]	20.54	7.64	19.44	6.92	0.5173[d]
TST/hours [mean, ±SD]	6.55	0.69	6.50	0.65	0.784[d]	6.23	1.05	6.07	1.49	0.4306[d]	6.25	0.59	6.67	0.62	0.0057[d]
Sleep efficiency % [mean, ±SD]	90.32	5.93	90.72	7.00	0.8626[d]	89.02	11.60	86.79	14.51	0.3277[d]	88.52	16.96	92.05	6.23	0.1088[d]
AHI [mean, ±SD]	9.59	8.64	5.71	6.33	0.0159[d]	9.64	10.98	8.18	11.37	0.5468[d]	24.72	24.75	4.14	4.78	<.0001[d]
RDI [mean, ±SD]	11.26	12.07	6.79	7.46	0.0984[d]	11.03	13.61	11.68	19.23	0.7639[d]	29.61	31.33	8.15	21.33	<.0001[d]
Severity of OSA					0.391[c]					0.572[c]					<0.001[c]
Mild (<5) [n, %]	6	35	9	52.94		13	50	13	50.00		5	15	22	66.67	
Moderate (5–10) [n, %]	5	29.41	5	29.41		5	19.23	7	26.92		7	21.21	9	27.27	
Severe (>10) [n, %]	6	35.29	3	17.65		8	30.77	6	23.08		21	63.64	2	6.06	
Obstructive apneas [mean, ±SD]	17.18	22.65	7.76	13.27	0.0369[d]	14.27	35.05	9.81	23.30	0.1144[d]	52.15	82.73	5.91	11.14	<.0001[d]
Central apneas [mean, ±SD]	4.12	7.24	2.12	2.93	0.46[d]	2.35	3.96	3.19	6.31	0.5764[d]	3.67	6.09	3.30	5.36	0.5529[d]
Mixed apneas [mean, ±SD]	1.71	3.92	1.06	2.86	0.25[d]	0.58	1.36	0.46	1.24	0.7207[d]	1.30	3.41	0.21	0.65	0.0371[d]
Hypopneas [mean, ±SD]	38.65	43.16	25.29	31.76	0.1017[d]	40.69	55.59	36.69	55.22	0.9688[d]	95.55	95.50	31.82	75.27	<.0001[d]
Arousal by respiratory events [mean, ±SD]	19.18	30.10	10.29	11.56	0.3524[d]	10.19	19.14	24.96	51.79	0.1063[d]	35.03	64.15	14.94	54.73	0.0451[d]
Arousal by spontaneous nature [mean, ±SD]	78.71	59.87	74.18	36.51	0.8632[d]	68.46	38.45	144.15	175.48	0.2175[d]	110.39	136.67	69.94	69.49	0.1812[d]
Arousal by limb movements [mean, ±SD]	0.71	0.92	2.47	4.35	<.0001[d]	4.08	13.15	3.50	7.84	<.0001[d]	3.64	14.37	5.36	17.84	<.0001[d]
Nadir SpO2 [mean, ±SD]	87.94	3.99	89.24	4.13	0.3129[d]	83.35	8.75	86.23	7.92	0.0432[d]	77.15	17.43	86.42	6.67	0.0002[d]

Abbreviations: BMI, body mass index; TST, total sleep time; PSG, polysomnography; NREM, non-rapid-eye-movement; REM, rapid-eye-movement; AHI, apnea-hypopnea index; RDI, respiratory disturbance index.
[c] McNemar's test.
[d] Wilcoxon signed-rank test.

Table 3
The ten most common primary diagnosis visiting traditional Chinese medicine (TCM) clinic in integrated TCM cohort (N = 56).

ICD-9 code	Primary diagnosis visiting TCM clinic	Frequency (%)
477.9	Allergic rhinitis	26%
780.51	Insomnia with sleep apnea	11%
788.36	Nocturnal enuresis	11%
780.5/780.591	Sleep disturbance	13%
474.2	Adenoid vegetations	8%
474.9	Chronic disease of tonsils and adenoids.	6%
780.57	Unspecified sleep apnea.	6%
691.8	Atopic dermatitis	4%
780.53	Hypersomnia with sleep apnea	4%
307.4	Nonorganic sleep disorder	2%

brought for TCM treatment).[21] Other common reasons that children with OSA were brought to the TCM clinic were nocturnal enuresis and adenoid hypertrophy. These two diseases are common comorbidities of pediatric OSA. Nocturnal enuresis may be related to nocturnal respiratory events. OSA-induced changes in intra-abdominal pressure and systemic blood pressure may alter circulatory levels of atrial and cerebral natriuretic peptides and the antidiuretic hormone, vasopressin, and this, in turn, could induce natriuresis and polyuria.[22] The common comorbidity of these conditions means that TCM physicians need to consider the possible coexistence of OSA in children with adenoid hypertrophy or enuresis.

In our study, Forsythia & Laminaria Combination (散腫潰堅湯 sàn zhǒng kuì jiān tāng) (SZ), (English: Forsythia and Laminaria Combination; Japanese: Sanshu Kaigen To), was the most prescribed herbal formula for children with OSA in this study. The formula consists of 17 species of herbs: (*Scutellariae baicalensis* (黃芩huáng qín), *Gentiana radix* (龍膽草lóng dǎn cǎo), *Trichosanthes radix* (瓜蔞根guā lóu gēn), *Phellodendri cortex* (黃柏huáng bò), *Anemarrhena asphodeloides* (知母zhī mǔ), *Platycodonis radix* (桔梗jié gěng), *Laminaria thallus* (昆布kūn bù), *Bupleuri radix* (柴胡chái hú), *Glycyrrhizae* (甘草gān cǎo) (*Glycyrrhizae*), *Sparganii rhizoma* (荊三棱jīng sān léng), *Curcumae rhizome* (莪朮é zhú), *Forsythia fructus* (連翹lián qiáo), *Pueraria lobatae radix* (葛根gé gēn), *Paeonia radix alba* (白芍bái sháo), *Angelica sinensis radix* (當歸尾dāng guī wěi), *Coptidis rhizoma* (黃連huáng lián), and *Cimicifuga rhizoma* (升麻shēng má). According to TCM theory, SZ can clear heat, relieve toxicity, disperse stagnation, and soften hardness. It has been used in the treatment of lymphadenitis since the Jin-Yuan Dynasty. A retrospective study by Wu et al. found that the combination of concentrated herbal granules in SZ can reduce snoring and improve the quality of life[23] of adults with sleep-disordered breathing. SZ has also demonstrated anti-cancer effects and appears to inhibit the proliferation of human breast cancer cells by the induction of p21/WAF1 and activation of the mitochondrial apoptotic system.[24]

Magnolia Flower Lung-Clearing Decoction (辛夷清肺湯xīn yí qīng fèi tāng) (XYQFT), Xanthium Powder (蒼耳子散cāng ěr zǐ sàn), Pueraria Combination or Kudzu Relaxe (葛根湯gé gēn tāng), and Minor Green Blue Dragon Decoction (小青龍湯xiǎo qīng lóng tāng) (XQLT) are the most frequently prescribed TCM formulations for pediatric AR in Taiwan.[21] In our study, they were also in the top ten most prescribed formulas for pediatric OSA (Table 4). XYQFT by Shih-Gong Chen (1617 AD) and Xanthium Powder (蒼耳子散cāng ěr zǐ sàn) by Yong-He Yan (1253 AD) have been widely used in East

Table 4
Top ten common Chinese herbal formulas prescribed and possible pharmacological effects for patients with obstructive sleep apnea in integrative Traditional Chinese medicine follow-up cohort (n = 17).

Herbal Formula Chinese name Pin-Yin name	English name	Ingredient of herbal formula Chinese name, Pin-yin name (Latin name; botanical plant name)	Possible pharmacological effects of the ingredients	Average daily dose(g)	Number of prescriptions N (%)	Average duration for prescription (days)	Reference
散腫潰堅湯 sàn zhǒng kuì jiān tāng	Forsythia and Laminaria Combination	黃芩huáng qín (Scutellariae Radix; *Scutellaria baicalensis* Georgi) 龍膽草lóng dǎn cǎo (Gentianae Radix et Rhizoma; *Gentiana manshurica* Kitag/Gentiana scabra *Bunge/Gentiana triflora Pall./Gentiana rigescens* Franch) 瓜蔞根guā lóu gēn (Trichosanthis Radix; *Trichosanthes kirilowii* Maxim) 黃柏huáng bò Phellodendri Chinensis Cortex; *Phellodendron chinense* C·K.Schneid) 知母zhī mǔ (Anemarrhenae Rhizoma; *Anemarrhena asphodeloides* Bunge 桔梗jié gěng (Platycodonis Radix; *Platycodon grandiflorus* (Jacq.) A.DC.) 昆布kūn bù 昆布kūn bù(*Laminariae Thallus/ Eckloniae Thallus*) 柴胡chái hú (Bupleuri Radix; *Bupleurum chinense* DC.) 炙甘草zhì gān cǎo (Glycyrrhizae Radix et Rhizoma; *Glycyrrhiza uralensis* Fisch. ex DC.) 荊三稜jīng sān léng (Sparganii Rhizoma; *Sparganium stoloniferum* Buch.-Ham) 莪朮é zhú (Curcumae Rhizoma; *Curcuma phaeocaulis* Valeton) 連翹lián qiáo (Forsythiae Fructus; *Forsythia suspensa* Thunb. Vahl) 葛根gé gēn (Puerariae Lobatae Radix*; Pueraria lobata* (Willd.) Ohwi) 白芍bái sháo (Paeoniae Radix Alba; *Paeonia lactiflora* Pall) 當歸尾dāng guī wěi (Angelicae Sinensis Radix; *Angelica sinensis* (Oliv.) Diels) 黃連huáng lián (Coptidis Rhizoma; *Coptis chinensis* Franch.) 升麻shēng má (Cimicifugae Rhizoma; *Cimicifuga foetida* L;*Cimicifuga heracleifolia* Kom;*Cimicifuga dahurica* (Turcz.) Maxim.)	Anti-cancer effect Inhibit the proliferation of human breast cancer cell by induction of p21/WAF1 and activity of the mitochondrial apoptotic system.	8.49	90 (12.53%)	12.13	26
辛夷清肺湯 xīn yí qīng fèi tāng	Magnolia Flower Lung-Clearing Decoction	辛夷xīn yí (*Magnoliae* Flos;*Magnolia biondii* Pamp./*Magnolia denudata* Desr./*Magnolia sprengeri* Pamp.*)* 黃芩huáng qín (Scutellariae Radix;*Scutellaria baicalensis* Georgi) 山梔子shān zhī zi (Gardeniae Fructus;*Gardenia jasminoides* J.Ellis) 麥門冬mài mén dōng (Ophiopogonis Radix;*Ophiopogon japonicus* Ker Gawl.) 百合bǎi hé (Lilii Bulbus;*Lilium lancifolium* Thunb./*Lilium brownii* F.E.Br. ex Miellez/*Lilium pumilum* Delile) 石膏shí gāo (Gypsum Fibrosum) 知母zhī mǔ (Anemarrhenae Rhizoma;*Anemarrhena asphodeloides* Bunge) 甘草gān cǎo (Glycyrrhizae Radix et Rhizoma;*Glycyrrhiza uralensis* Fisch. ex DC.) 枇杷葉pí pá yè (Eriobotryae Folium;*Eriobotrya japonica* (Thunb.) Lindl) 升麻shēng má (Cimicifugae Rhizoma;*Cimicifuga foetida* L./*Cimicifuga heracleifolia* Kom./*Cimicifuga dahurica* (Turcz.) Maxim.)	Anti-allergy effect by reducing IL-4, IL-6, and TNF-α levels. Anti-inflammation by suppressing NF-κB, JNK, and ERK1/2 signaling pathways. Antibacterial effect by activating macrophage in murine sinusitis model.	11.50	77 (10.72%)	12.82	28–30
蒼耳子散 cāng ěr zǐ sàn	Xanthium Powder	辛夷xīn yí (Magnoliae Flos;*Magnolia biondii* Pamp./*Magnolia denudate*) 蒼耳子cāng ěr zǐ(Xanthii Fructus;*Xanthium sibiricum* Patrin ex Widder) 白芷bái zhǐ (Angelicae Dahuricae Radix;*Angelica dahurica* (Hoffm.) Benth. & Hook.f. ex Franch. & Sav.)	Clinical application in treating chronic rhinitis, paranasal sinusitis, and allergic rhinitis	9.16	61 (8.50%)	12.18	27

(continued on next page)

Table 4 (*continued*)

Herbal Formula Chinese name Pin-Yin name	English name	Ingredient of herbal formula Chinese name, Pin-yin name (Latin name; botanical plant name)	Possible pharmacological effects of the ingredients	Average daily dose(g)	Number of prescriptions N (%)	Average duration for prescription (days)	Reference
銀翹散 yín qiào sàn	Honeysuckle & Forsythia Formula	薄荷bò hé (Menthae Haplocalycis Herba;*Mentha haplocalyx* Briq) 蔥白cōng bái (*Allium fistulosum* L.) 細茶xì chá (*Camellia sinensis* (L.) Kuntze) 連翹lián qiáo (Forsythiae Fructus;*Forsythia suspensa* (Thunb.) Vahl) 金银花jīn yín huā (Lonicerae Japonicae Flos;*Lonicera japonica* Thunb.) 桔梗jié gěng (Platycodonis Radix;*Platycodon grandiflorus* (Jacq.) A.DC.) 薄荷bò hé (Menthae Haplocalycis Herba;*Mentha haplocalyx* Briq) 淡竹叶dàn zhú yè (Lophatheri Herba;*Lophatherum gracile* Brongn) 甘草gān cǎo (Glycyrrhizae Radix et Rhizoma;*Glycyrrhiza uralensis* Fisch. ex DC) 荆芥jīng jiè (Schizonepetae Herba;*Schizonepeta tenuifolia* Briq.) 淡豆豉dàn dòu chǐ (*Schizonepeta tenuifolia* Briq.;*Glycine* max (L.) Merr) 牛蒡子niú bàng zi (Arctii Fructus;*Arctium lappa* L.) 蘆根lú gēn (Phragmitis Rhizoma;*Phragmites communis* Trin.)	Antipyretic and anti-inflammatory effects by inhibition of prostaglandin E2 and free radical scavenging.	2.96	57 (7.94%)	15.39	34,35
川芎茶調散 chuān xiōng chá diào sǎn	Tea-Blended and Chuanxiong Powder	川芎chuān xiōng (Chuanxiong Rhizoma;*Ligusticum chuanxiong* S·H.Qiu; Y.Q.Zeng; K·Y.Pan; Y·C.Tang & J.M.Xu) 細辛xì xīn (Asari Radix et Rhizoma;*Asarum heterotropoides* F.Schmidt/*Asarum mandshuricum* (Maxim.) M.Kim & S.So/*Asarum sieboldii* Miq./*Asarum sieboldii* var. *seoulense* Nakai) 白芷bái zhǐ (Angelicae Dahuricae Radix;*Angelica dahurica* (Hoffm.) Benth. & Hook.f. ex Franch. & Sav.) 羌活qiāng huó, (Notopterygii Rhizoma et Radix;*Notopterygium incisum* Ting ex H.T.Chang) 防風fáng fēng (Saposhnikoviae Radix;*Saposhnikovia divaricata* (Turcz.) Schischk) 薄荷bò hé (Menthae Haplocalycis Herba;*Mentha haplocalyx* Briq) 荆芥jīng jiè(Schizonepetae Herba;*Schizonepeta tenuifolia* Briq.) 甘草gān cǎo (Glycyrrhizae Radix et Rhizoma;*Glycyrrhiza uralensis* Fisch. ex DC)	Disperse Wind Heat or Wind Cold and alleviate headache	1.17	53 (7.38%)	11.50	43
葛根湯 gé gēn tāng	Pueraria Combination or Kudzu Relaxe	葛根gé gēn (Puerariae Lobatae Radix;*Pueraria lobata* (Willd.) Ohwi) 桂枝guì zhī (Cinnamomi Ramulus;*Cinnamomum cassia* (L.) J.Presl) 麻黃má huáng (Ephedrae Herba;*Ephedra sinica* Stapf) 白芍bái sháo (Paeoniae Radix Alba;*Paeonia lactiflora* Pall) 大棗dà zǎo (Jujubae Fructus;*Ziziphus jujuba* Mill.) 生薑shēng jiāng (Zingiberis Rhizoma Recens;*Zingiber officinale* Roscoe) 甘草gān cǎo (Glycyrrhizae Radix et Rhizoma;*Glycyrrhiza uralensis* Fisch. ex DC)	Anti-viral activity	4.17	51 (7.10%)	12.95	37–39
小青龍湯 xiǎo qīng lóng tāng	Minor Green Blue Dragon Decoction	麻黃má huáng (Ephedrae Herba;*Ephedra sinica* Stapf) 白芍bái sháo (Paeoniae Radix Alba;*Paeonia lactiflora* Pall.) 細辛xì xīn (Asari Radix et Rhizoma;*Asarum heterotropoides* F.Schmidt/*Asarum mandshuricum* (Maxim.) M.Kim & S.So/ Asarum sieboldii Miq./*Asarum sieboldii* var. *seoulense* Nakai)	Antihistamine and anti-inflammatory effects Diminish inflammatory cells infiltrating in the nasal mucosa, and help the structural integrity of the nasal mucosa recovering. Immunomodulation Th1/Th2 balance effect by downregulating the levels of thymic stromal lymphopoietin and reducing Th2-type inflammation involving serum IgE, IL-4, IL-5, and IL-13.	4.25	49 (6.82%)	9.92	57–59

Table 4 (*continued*)

Herbal Formula Chinese name Pin-Yin name	English name	Ingredient of herbal formula Chinese name, Pin-yin name (Latin name; botanical plant name)	Possible pharmacological effects of the ingredients	Average daily dose(g)	Number of prescriptions N (%)	Average duration for prescription (days)	Reference
		乾薑 gàn jiāng (Zingiberis Rhizoma Recens;*Zingiber officinale* Roscoe) 甘草gān cǎo (Glycyrrhizae Radix et Rhizoma;*Glycyrrhiza uralensis* Fisch. ex DC) 桂枝guì zhī (Cinnamomi Ramulus;*Cinnamomum cassia* (L.) J.Presl) 半夏bàn xià (Pinelliae Rhizoma;*Pinellia ternata* Ten. ex Breitenb) 五味子wǔ wèi zi (Schisandrae Chinensis Fructus;*Schisandra chinensis* (Turcz.) Baill.)	Regulate Th17/Treg balance by one active ingredient, catechins, decreasing RoRγ t mRNA in the nasal mucosa but increased the expression level of Foxp3 mRNA				
麻杏石甘湯 má xìng shí gān tāng	麻黃má huáng & Apricot Seed Combination	麻黃má huáng (Ephedrae Herba;*Ephedra sinica* Stapf) 杏仁xìng rén (Armeniacae Semen Amarum;*Prunus armeniaca* L./*Prunus ansu* (Maxim.) Komarov/*Prunus sibirica* L./*Prunus mandshurica* (Maxim.) Koehne) 石膏shí gāo (Gypsum Fibrosum) 甘草gān cǎo (Glycyrrhizae Radix et Rhizoma;*Glycyrrhiza uralensis* Fisch. ex DC.)	Antipyretic effect on LPS-induced fever Anti-inflammatory effect by inhibiting neutrophils to enter the airway Antitussive mechanism is related to the partial relaxation of bronchial smooth muscle by blocking the acetylcholinergic receptor and histaminergic receptor. Stimulating sympathetic a- and b-adrenoceptors activated by ephedrine alkaloids and amygdalin inhibit the central cough center	2.66	45 (6.27%)	15	60–62
香砂六君子 xiāng shā liù jūn zǐ	Costusroot and Amomum Six Gentlemen Decoction	人參rén shēn (Ginseng Radix et Rhizoma;*Panax ginseng* C.A.Mey.) 白朮bái zhú(Atractylodis Macrocephalae Rhizoma;*Atractylodes macrocephala* Koidz). 茯苓fú líng (Poria; *Poria cocos* (Schw.)Wolf) 甘草gān cǎo (Glycyrrhizae Radix et Rhizoma;*Glycyrrhiza uralensis* Fisch. ex DC.) 陳皮chén pí (Pericarpium Citir Reticulatae; *Citrus reticulata* Blanco) 半夏bàn xià (Pinelliae Rhizoma;*Pinellia ternata* Ten. ex Breitenb) 砂仁shā rén (Fructus Amomi;*Amomum villosum* Lour.) 木香mù xiāng (Aucklandiae Radix;*Aucklandia* lappa (Decne.) Decne). 生薑shēng jiāng (Zingiberis Rhizoma Recens;*Zingiber officinale* Roscoe)	Improvement of electrogastrogram Promotion of gastrointestinal motility and gastric emptying Regulation of gastrointestinal hormone	4.19	44 (6.13%)	11.62	63
補中益氣湯 Bǔ zhōng yì qì tāng	Tonify the Middle and Augment the Qi Decoction	黃耆huáng qí; Astragali Radix;*Astragalus membranaceus* Bunge/*Astragalus mongholicus* Bunge 人參rén shēn; Ginseng Radix et Rhizoma;*Panax ginseng* C.A.Mey. 白朮bái zhú; Atractylodis Macrocephalae Rhizoma;*Atractylodes macrocephala* Koidz. 甘草gān cǎo Glycyrrhizae Radix et Rhizoma;*Glycyrrhiza uralensis* Fisch. ex DC. 當歸尾dāng guī wěi; Angelicae Sinensis Radix;*Angelica sinensis* (Oliv.) Diels 陳皮chén pí; Citri Reticulatae Pericarpium;*Citrus reticulata* Blanco 升麻shēng má; Cimicifugae Rhizoma;*Cimicifuga foetida* L./*Cimicifuga heracleifolia* Kom./*Cimicifuga dahurica* (Turcz.) Maxim. 柴胡chái hú; Bupleuri Radix;*Bupleurum chinense* DC. 生薑shēng jiāng; Zingiberis Rhizoma Recens;*Zingiber officinale* Roscoe 大棗dà zǎo; Jujubae Fructus;*Ziziphus jujuba* Mill.	Suppressed nasal inflammation by an antiinflammatory effect. Suppressed serum IgE and the IL-4-stimulated production of PGE(2) and LTC (4) by polymorphonuclear neutrophils Suppressed COX-2 mRNA expression in IL-4-stimulated polymorphonuclear neutrophils	4.99	37 (5.15%)	11.56	64

Asia to treat chronic rhinitis, paranasal sinusitis, and AR.[25] Animal experiments have shown XYQFT to have anti-allergenic effects through the reduction of IL-4, IL-6, and TNF-α levels[26]; anti-inflammatory effects through the suppression of NF-κB, JNK, and ERK1/2 signaling pathways[27]; and, in a murine sinusitis model, antibacterial effects through the activation of macrophages.[28] However, XYQFT has not been evaluated in a high-quality clinical trial. In an animal study, Shi-Bi-Lin, a modified form of Xanthium Powder (蒼耳子散cāng ěr zǐ sàn) has been found to suppress eosinophilic infiltration of nasal tissue and inhibit the expression of endothelial nitric oxide synthase and the release of thromboxane B2 [29]. It also relieves blocked nose symptoms in perennial AR. XQLT

Table 5
Top ten common single herbs prescribed for patients with obstructive sleep apnea in integrative traditional Chinese medicine follow up cohort (n = 17).

Single herb Chinese name Pin-Yin name	Latin name	Botanical plant name	Possible pharmacological effects of the ingredients	Average daily dose (g)	Number of prescriptions N (%)	Average duration for prescription (days)	Reference
麻黃 má huáng	Herba Ephedrae	*Ephedra sinica* Stapf	Alleviate airway epithelial injury by inhibit abnormal changes in airway epithelial structure and apoptosis of airway epithelial cells. Inhibitory activity on hypoxia signaling through reduction of HIF-1α protein levels and Glut1 mRNA. Anti-histamine effect Anti-obesity effect by gut microbiota modulation Prevent hyperlipidemia via managing DNA repairing and energy metabolism-related genes and proteins expressing. Enhance lipid metabolism.	0.94	35 (4.87)	9.67	46,48, 51-53
甘草 gān cǎo	Glycyrrhizae Radix et Rhizoma	*Glycyrrhiza uralensis* Fisch. ex DC.	Anti-inflammation activity: (1) suppress proinflammatory cytokine COX-2, iNOS, TNF-α, HMGP 1, PGE2, myeloperoxidase, DPPH radicals, IL-6, IL-10, TGF-β, and NF-κB (2) inhibit the translocation of toll-like receptor 4 (3) inhibition of COX, PGE2, cytokines and their receptors, and nuclear transcription factor. Anti-allergy Anti-tumor Antioxidant Antimicrobial and anti-viral activity Anti-diabetes Anti-obesity	2.24	30 (4.18)	12.43	41,56,65
丹參 dān shēn	Salviae Miltiorrhizae Radix et Rhizoma	*Salvia miltiorrhiza* Bge.	Anti-inflammation Anti-oxidation Anti-tumor Anti-atherogenesis Anti-diabetes	0.60	23 (3.20)	21	66
桔梗 jié gěng	Platycodonis Radix	*Platycodon grandiflorus* (Jacq.) A.DC.	Reduce airway inflammation and cough reflex by diminishing proinflammatory cytokines such as TNF-α, IL-6, and IL-1β, and inducing nitric oxide synthases. (iNOS). Inhibits interleukin-13-induced the expression of inflammatory cytokines and mucus in nasal epithelial cells.	0.56	22 (3.06)	10.5	65,67
白朮 bái zhú	Atractylodis Macrocephalae Rhizoma	*Atractylodes macrocephala* Koidz.	Antitumor activities Neuroprotective effect Anti-hepatotoxicity Anti-inflammatory activity	1.09	20 (2.79)	14	68
夏枯草 xià kū cǎo	Prunellae Spica	Prunella vulgaris L.	Antiviral and antibacterial function Anti-inflammatory Immunoregulatory Anti-oxidative Anti-tumor Antihypertensive and hypoglycemic functions.	2.80	19 (2.65)	15.32	69
玄參 xuán shēn	Scrophulariae Radix	*Scrophularia ningpoensis* Hemsl.	Anti-Inflammatory Effects by inhibiting TNF-α, IL-6, and MMP-9 mRNA expression levels in vitro study. Immune-enhancing effects in lymphocytes Neuroprotective Effects Anti-Apoptotic Effects Anti-Allergic Effects	0.72	18 (2.51)	12.7	70
防風 fáng fēng	Saposhnikoviae Radix	*Saposhnikovia divaricata* (Turcz.) Schischk.	Anti-inflammation by LPS indued inflammation Immune regulation by increasing CD4 + /CD8+ T cells ratio, reducing IFN-γand TNF-α, and increasing IL-4, IL-10. Reduce histamine releasing Anti-viral activity Anti-oxidative and anti-apoptotic effects	0.67	18 (2.51)	10.5	71
桃仁 táo rén	Semen Persicae	*Prunus persica* (L.) Batsch	Suppress the cellular and humoral immune response	0.68	18 (2.51)	7	72
麥門冬 mài mén dōng	Ophiopogonis Radix	*Ophiopogon japonicus* Ker Gawl.	Anti-inflammation Anti-oxidation Immunomodulation Antitussive activity Cardiovascular protection	2.57	18 (2.51)	17.5	73

has been widely used to treat asthma, bronchitis, and AR, and its efficacy has been demonstrated in a clinical trial.[30]

Recurrent upper airway infection is an important aggravator of upper airway obstruction in pediatric OSA. Therefore, exterior evil-releasing formulas against respiratory tract infections such as Honeysuckle & Forsythia Formula (銀翹散yín qiào sàn), Pueraria Combination or Kudzu Relaxe (葛根湯gé gēn tāng Ma Huang & Apricot Seed Combination (麻杏石甘湯má xìng shí gān tāng) (MXGST), and Tea-Mix and Chuanxiong Powder (川芎茶調散chuān xiōng chá diào sǎn)are commonly prescribed. The ingredients of Honeysuckle & Forsythia Formula (銀翹散yín qiào sàn) inhibit prostaglandin E2 and free radical scavenging, with consequent antipyretic and anti-inflammatory effects.[31,32] Honeysuckle & Forsythia Formula (銀翹散yín qiào sàn) is well tolerated in children with paracetamol and ibuprofen hypersensitivities and may effectively reduce fever resulting from upper respiratory tract infection.[33] Pueraria Combination or Kudzu Relaxe (葛根湯gé gēn tāng) can induce sweating to release the exterior and dispel wind-cold. Pueraria Combination or Kudzu Relaxe (葛根湯gé gēn tāng) has shown anti-viral effects in *vivo* studies.[34–36] MXGST is widely prescribed to treat asthma, chronic obstructive pulmonary disease, and COVID-19-induced pneumonia.[37–39] Tea-Mix and Chuanxiong Powder (川芎茶調散chuān xiōng chá diào sǎn) can dispel headache-inducing wind and is a popular formula for the treatment of migraine in Taiwan.[40] A high incidence (56%) of migraine has been observed in children with sleep-disordered breathing.

The most prescribed single herb was Ephedrae Herba (麻黃má huáng). Ephedrae Herba (麻黃má huáng) has been widely used to treat asthma, cold, flu, nasal congestion, fever, and cough in East-Asian traditional herbal medicine. It has also been used in children diagnosed with COVID-19. Animal studies indicate that Ephedrae Herba (麻黃má huáng) can alleviate airway injuries and exert anti-histamine effects.[41,42] The flavonoids in Ephedrae Herba (麻黃má huáng) have demonstrated inhibitory activity on hypoxia signaling through the reduction of HIF-1α protein levels and Glut1 mRNA and may also inhibit pancreatic cancer.[43]

Ephedrae Herba (麻黃má huáng) is also commonly used to treat obesity. The safe dose of Ephedrae Herba (麻黃má huáng) in the treatment of adult obesity is 4.5–7.5 g per day for up to 6 months.[44] In obese women, the weight loss effects of Ephedrae Herba (麻黃má huáng) may involve the modulation of gut microbiota.[45] In mice, it was found to prevent hyperlipidemia by managing DNA repair and the expression of genes and proteins to energy metabolism.[46] The main active ingredient of Ephedrae Herba (麻黃má huáng), ephedrine, can reduce weight by decreasing appetite and enhancing lipid metabolism.[47] Some adverse effects on the sympathetic nervous system, such as palpitations, insomnia, and dry mouth, have been reported[48]; however, no obvious adverse effects were reported in our ITCM cohort. The average daily dose of Ephedrae Herba (麻黃má huáng) prescribed by the TCM physicians in this study was 0.94 g, which appears to have been relatively safe for children and effective in our patients. Weight control is important in children with OSA as the risk of sleep-disordered breathing increases by 12% with each kg/m^2 of BMI above the mean.[49] In addition, Glycyrrhizae Radix et Rhizoma (甘草gān cǎo) has anti-inflammatory, anti-allergenic, anti-tumor, and anti-viral effects, and is an excellent alternative treatment for inflammatory diseases, especially in children.[50]

Our study had several limitations. Firstly, the sample size was small in the ITCM group. However, the percentage of our subjects who chose ITCM (11%) over ordinary treatment was compatible with the general percentage of pediatric TCM users in the Taiwan population.[12] Nevertheless, an evaluation of the efficacy of ITCM was still warranted given the need for alternative pediatric OSA treatments. In addition, OSA may not be diagnosed at a TCM clinic because TCM physicians cannot seek reimbursement for PSG studies from Taiwan's national health insurance. This is likely to influence the ITCM diagnosis rate and lead to an underestimation of the use of TCM services. Secondly, there was a low follow-up rate in all three of our cohorts because children have difficulty cooperating with the PSG setup and are likely to have found the initial PSG more strange, unpleasant, and restrictive than an adult would. Although the number of patients in our follow-up groups is small, the results of this retrospective observational study provide preliminary and illustrative findings, highlighting the need for further research. Our study has also identified the clinical characteristics of pediatric OSA patients in a tertiary hospital in Taiwan. Given the challenges of conducting PSG in pediatric populations, future research would greatly benefit from the utilization of a reliable and feasible home PSG. Thirdly, the treatment options for children with OSA were selected by their parents, potentially introducing selection bias into the study. Fourthly, the varying proportions of comorbidities among the three cohorts should be considered. However, it is important to note that confounding factors such as sex, age, weight, body size, tonsillar adenoid hypertrophy, and asthma comorbidities were similar between the ITCM follow-up cohort and the WM follow-up cohort, with no significant differences observed. Consequently, comparing the outcomes of the ITCM and WM cohorts after intervention would provide valuable insights for evaluating their effectiveness. Lastly, due to the retrospective nature of this cohort observational study, our results may not provide definitive efficacy regarding the effectiveness of integrative TCM therapy. However, it has identified common TCM prescriptions for OSA children in clinical practice and determined which TCM formulas and herbs warrant further research on their use in the treatment of pediatric OSA, preferably in pharmacological randomized controlled trials.

5. Conclusions

OSA is characterized by chronic inflammation and obstruction of the upper airway. We found that integrative TCM therapy was able to significantly reduce the AHI in pediatric OSA patients. Moreover, those patients treated with ITCM showed stable control in BMI than those treated with western medicine alone. The integration of traditional Chinese medicine (TCM) and Western therapies may serve as a viable alternative treatment for mild obstructive sleep apnea (OSA) in children, surgical contraindications, and/or CPAP intolerance, or children with incomplete resolution after surgery. It may also help overweight and obese pediatric OSA patients to reduce their BMI. The optimal TCM prescription for children with OSA appears to be SZ, XYQFT, Ephedrae Herba (麻黃má huáng), and Glycyrrhizae Radix et Rhizoma (甘草gān cǎo). However, further study of the pharmacological mechanisms and clinical efficacy of these TCM treatments is warranted.

Ethics statement

This study was conducted in accordance with the tenets of the 2013 version of the Declaration of Helsinki. The study was approved by the institutional review board of China Medical University Hospital, Taichung, Taiwan (CMUH110-REC2-046) on March 23, 2021.

Author contributions

WYL and HRY conceptualized the study. YHS and FWH performed the statistical analysis and interpreted of data. WYL and HRY contributed to the interpretation of TCM data. CCW, CHL, and LWH contributed to the interpretation of polysomnograms and western medicine data. WYL and CCW interpreted the pharmacological mechanisms. WYL and HRY drafted the manuscript and HRY finalized the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtcme.2023.08.002.

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