BMJ Open Comorbidity patterns and associated characteristics in children with obstructive sleep apnoea-hypopnoea syndrome in Shanghai, China: a cross-sectional study

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ABSTRACT

Objectives Paediatric obstructive sleep apnoea-hypopnoea syndrome (OSAHS), which usually cooccurs with various diseases, significantly impacts health and social resources. Domestic paediatric OSAHS studies have not included comorbidity patterns or distribution characteristics. Thus, we investigated the comorbid characteristics of paediatric OSAHS in Shanghai, China.

Design Large hospital-based cross-sectional study.

Setting Paediatric ward medical data from the Pudong New Area, Shanghai, China from 2013 to 2016.

Participants 4045 Chinese children aged 0–18 years.

Primary and secondary outcome measures Paediatric OSAHS was diagnosed using the Paediatric Sleep Questionnaire with a cut-off score of 8 points. The outcomes were comorbidity patterns and their characteristics. χ^2 tests were performed to compare differences among the top comorbidity patterns.

Results Major comorbidities were otolaryngological morbidities. Among one-comorbidity patterns, OSAHS+chronic rhinitis (37.53%) and OSAHS+allergic rhinitis (28.13%) were most common. Among two-comorbidity patterns, OSAHS+chronic rhinitis+chronic exudative otitis media (10.88%), OSAHS+allergic rhinitis+chronic exudative otitis media (7.94%), OSAHS+allergic rhinitis+chronic tonsillitis (4.43%) and OSAHS+chronic rhinitis+chronic tonsillitis (4.23%) were most common. Males predominated in all comorbidity groups. Age differences for the top five patterns in both the one-comorbidity ($p=0.035$) and two comorbidities ($p<0.001$) groups were statistically significant. In the one-comorbidity group, patients were more likely to have one operation ($p<0.001$), and in the two comorbidities group, patterns of 'OSAHS+chronic rhinitis+chronic exudative otitis media' and 'OSAHS+allergic rhinitis+chronic exudative otitis media' were more common in the ≥ 2 operations group ($p<0.001$). Notably, the top five patterns of the 2-comorbidities group were significantly associated with the length of stay (LOS) ($p<0.001$), while those in the one-comorbidity group were not.

Conclusion OSAHS+rinitis (chronic rhinitis or allergic rhinitis) was the most common diagnosis. Age, number

Strengths and limitations of this study

- Characteristics and comorbidity patterns in paediatric obstructive sleep apnoea-hypopnoea syndrome (OSAHS) were examined in a large sample from Shanghai, China.
- Baseline information was provided for further research and policymaking on paediatric OSAHS, especially regarding complex otolaryngological comorbidities.
- Participants in this study were restricted to inpatients; thus, the cases included may be more severe.

of operations, and LOS are significantly associated with the patterns. This emphasises the importance of better understanding complex otolaryngological comorbidity diagnoses and treatments in paediatric OSAHS to reverse clinical outcomes and save health resources.

INTRODUCTION

Paediatric obstructive sleep apnoea-hypopnoea syndrome (OSAHS) is characterised by recurrent partial or complete upper airway obstruction events (hypopnoea, obstructive or mixed apnoeas) with disruption of normal oxygenation, ventilation and sleep patterns.¹ It is a common respiratory disease with a high prevalence in children, ranging from 1.2% to 5.7%, and the peak age of onset is between 2 and 8 years.²

Paediatric OSAHS has a significant impact on physical health and has been associated with nocturnal enuresis³ and pulmonary hypertension.⁴ Psychological health can also be affected, as patients with paediatric OSAHS may develop excessive daytime sleepiness,¹ inattention or hyperactivity⁵ and behavioural problems (aggressivity, poor social skills and poor communication and/

or adaptability).⁵ As patients develop, health and social risks become even more severe and include stroke, arrhythmias, myocardial infarction, hypertension, hyperlipidaemia, glucose intolerance, diabetes, and depression.⁶ As a result, paediatric OSAHS reduces quality of life in children,¹ placing a great burden on families and society.^{7,8} Tarasiuk *et al* compared patients with paediatric OSAHS and healthy children and found that paediatric OSAHS patients' medical expenses in the year prior to diagnosis were 215% higher than those in the control group, and the average annual cost for patients with paediatric OSAHS was 160%–190% higher than that in the control group between the ages of 1–4 years.⁷ Remarkably, paediatric OSAHS is rarely an isolated disease, and multiple comorbidities are usually present at the time of consultation. This phenomenon is noted in multiple guidelines emphasising the importance of clinical examinations, but the focal points of these guidelines are quite different.^{19,10} Some studies have begun to analyse comorbidities in paediatric OSAHS patients. For instance, Qubty *et al* studied the coexistence of paediatric OSAHS with multiple diseases among 139 patients with paediatric OSAHS aged 0–17 months. Multiple comorbidities, such as gastro-oesophageal reflux (68%), periodic limb movement in sleep (PLMS) (42%), craniofacial abnormalities (37%), neuromuscular abnormalities (34%), and prematurity (29%), were identified. Moreover, prematurity, genetic syndromes and neuromuscular abnormalities were found to lead to severe paediatric OSAHS.¹¹

However, compared with studies on comorbidities associated with other diseases, studies on paediatric OSAHS have the following defects: the focus is usually on only a single pattern or class of comorbidities (Down syndrome,^{12–16} obesity,¹⁷ neurological diseases,¹⁸ type 1 narcolepsy,¹⁹ etc), and relevant guidelines are not well outlined. Therefore, existing studies lack descriptions of comorbidity distributions and characteristics in paediatric OSAHS patients across a wide age range, causing great inconvenience in clinical practice. In China, the number of studies on paediatric OSAHS is continuously increasing.²⁰ For instance, Li *et al*, who diagnosed paediatric OSAHS by polysomnography in Hong Kong, found that the prevalence rate was 4.8%.²⁰ A study (2014) in Shanghai described the prevalence rate in children aged 4–7 years old as 3.91%.²¹ However, domestic studies on paediatric OSAHS have not included comorbidity patterns or their distribution characteristics.

The objective of our study was to describe the patterns and characteristics of comorbidities associated with paediatric OSAHS among inpatients in the Pudong New Area of Shanghai. This study provides a better understanding of the diagnoses and treatments of complex otolaryngological comorbidities in paediatric OSAHS to reverse clinical outcomes and save health resources.

METHODS

Data source

We used the retrospective hospitalisation data of children who were hospitalised between 2013 and 2016, which were obtained from electronic health record systems. We studied 17 institutions with paediatric wards in the Pudong New Area, which is the largest district in Shanghai, incorporating both rural and urban areas. From 2013 to 2016, the average population was approximately 5.50 million (22% of the total population of Shanghai).²² A total of 193 432 inpatients were included in this database. The detailed information of these patients included the treatment department, admission method, admission time, admission ward, length of stay (LOS), International Classification of Diseases 10th edition code, diagnosis, comorbidities, operations (type and number) and basic information (sex, age, place of birth, number of admissions, etc).

Selection of inpatients

We identified inpatients with paediatric OSAHS based on the Paediatric Sleep Questionnaire developed by Chervin *et al* with a cut-off score of 8 points.²³ Overall, the data of 4045 patients with paediatric OSAHS were confirmed. All diagnoses of comorbidities were based on Chinese guidelines for specific diseases.

Outcomes

The outcomes of our study were comorbidity patterns, including those with only OSAHS (0 comorbidities), one comorbidity (OSAHS +disease A), two comorbidities (OSAHS +disease A+disease B) and three comorbidities (OSAHS +disease A+disease B+disease C). Then, the distributions of comorbidities under different characteristics, including sex, age, number of admissions, number of admissions, number of operations and LOS, were analysed. Since the frequency distribution of ≥ 3 -comorbidities subgroups was uniform and the numbers were small, we did not compare differences among the ≥ 3 comorbidities subgroups. The LOS was defined as the total period of hospitalisation. LOS values over the 50th percentile were considered prolonged LOSs.

Statistical analyses

The characteristics of inpatients with paediatric OSAHS, including sex, age, number of admissions, number of operations and LOS, were analysed first. Then, the numbers and percentages of the four groups (0 comorbidities, 1 comorbidity, 2 comorbidities and ≥ 3 comorbidities) were visualised. We then performed χ^2 tests to compare the top five patterns with the highest frequencies relative to age, sex, number of admissions, number of operations and LOS in the OSAHS groups with one comorbidity and two comorbidities. Continuous variables are expressed as medians (IQRs) or means (SD). Categorical variables are expressed as numbers and percentages.

Table 1 Demographic data of inpatients with paediatric OSAHS

Variable classification	No	%
Sex		
Male	2732	67.54
Female	1313	32.46
Age (years)		
0–3	1213	29.99
4–7	2413	59.65
8–18	419	10.36
No of admissions		
1	3612	89.30
≥2	433	10.70
No of operations		
0	78	1.93
1	3307	81.76
≥2	660	16.32
LOS (days)		
Median (IQR)	2.00 (2.00–2.00)	

LOS, length of stay; OSAHS, obstructive sleep apnoea–hypopnoea syndrome.

All statistical analyses were performed using SPSS software V.22.0 (SPSS). A two-sided $p < 0.05$ was deemed to indicate statistical significance in all analyses.

Patient and public involvement

No patients or public were involved in the design, outcome measures, recruitment or execution of this study. All individual information was removed in this study; thus, there was no requirement to disseminate the information to patients.

RESULTS

Demographics of paediatric OSAHS inpatients

As shown in table 1, 4045 inpatients with paediatric OSAHS were included. The patients had an average age of 4.81 years, and more than 50% were ≥4 years old. Male inpatients were predominant (67.54%). The average LOS of these inpatients was 2.04 days.

Distributions of comorbidities with different factors

As shown in figure 1 and table 2, paediatric OSAHS was usually comorbid with various conditions. The major comorbidities were chronic rhinitis, allergic rhinitis, chronic tonsillitis, adenoidal hypertrophy and chronic sinusitis. Thirty patients (0.74%) had 0 comorbidities (figure 1A). In the one-comorbidity group, the top five comorbidity patterns were OSAHS +chronic rhinitis, OSAHS +allergic rhinitis, OSAHS +chronic tonsillitis, OSAHS +adenoidal hypertrophy and OSAHS +chronic sinusitis (37.53%, 28.13%, 0.37%, 0.35% and 0.20%, respectively) (figure 1B), while the top five patterns in

Figure 1 Distributions of different comorbidity patterns. OSAHS, obstructive sleep apnoea–hypopnoea syndrome.

the two-comorbidities group were OSAHS +chronic rhinitis +chronic exudative otitis media, OSAHS +allergic rhinitis +chronic exudative otitis media, OSAHS +allergic rhinitis +chronic tonsillitis, OSAHS +chronic rhinitis +chronic tonsillitis and OSAHS +adenoidal hypertrophy +tonsil hypertrophy (10.88%, 7.94%, 4.43%, 4.23% and 0.47%, respectively) (figure 1C). Additionally, the ≥3 comorbidities group contained 96 patients, accounting for 2.37% (figure 1D).

As shown in table 2, males predominated in all comorbidity groups. However, among the comorbidity groups, there were no statistically significant differences in comorbidity patterns in either the one-comorbidity group or two comorbidities group ($p = 0.688$; $p = 0.254$). Regarding age, the difference between the top five patterns in both the one-comorbidity group ($p = 0.035$) and two comorbidities group ($p < 0.001$) was statistically significant. The largest number of inpatients were those between 4 and 7 years old. A similar result was obtained for the number of operations. In the one-comorbidity group, patients were more likely to have one operation ($p < 0.001$), and in the two comorbidities group, patterns of ‘OSAHS+chronic rhinitis +chronic exudative otitis media’ and ‘OSAHS+allergic rhinitis +chronic exudative otitis media’ were more common in the ≥2 operations group, while patients with the remaining patterns were more likely to have one operation ($p < 0.001$). However, no statistically significant differences were found in the number of admissions among the top five patterns in various comorbidity groups. Notably,

Table 2 Distribution of comorbidities and their associations with different factors

No of comorbidities	No (%)	Sex		Age (Years)		
		Male (%)	Female (%)	0-3 (%)	4-7 (%)	8-18 (%)
No comorbidities	30 (0.74)	20 (66.67)	10 (33.33)	6 (20.00)	13 (43.33)	11 (36.67)
One comorbidity	2709 (66.97)	1833 (67.66)	876 (32.34)	814 (30.05)	1591 (58.73)	304 (11.22)
Top five patterns of one comorbidity:						
OSAHS +chronic rhinitis	1518 (37.53)	1025 (67.52)	493 (32.48)	442 (29.12)	905 (59.62)	171 (11.26)
OSAHS +allergic rhinitis	1138 (28.13)	770 (67.66)	368 (32.34)	359 (31.55)	655 (57.56)	124 (10.90)
OSAHS +chronic tonsillitis	15 (0.37)	8 (53.33)	7 (46.67)	2 (13.33)	7 (46.67)	6 (40.00)
OSAHS +adenoidal hypertrophy	14 (0.35)	11 (78.57)	3 (21.43)	3 (21.43)	9 (64.29)	2 (14.29)
OSAHS +chronic sinusitis	8 (0.20)	5 (62.50)	3 (37.50)	2 (25.00)	6 (75.00)	0 (00.00)
P value		0.688		0.035		
Two comorbidities	1210 (29.91)	817 (67.52)	393 (32.48)	363 (30.00)	748 (61.82)	99 (8.18)
Top five patterns of two comorbidities:						
OSAHS +chronic rhinitis +chronic exudative otitis media	440 (10.88)	292 (66.36)	148 (33.64)	173 (39.32)	247 (56.14)	20 (4.55)
OSAHS +allergic rhinitis +chronic exudative otitis media	321 (7.94)	218 (67.91)	103 (32.09)	113 (35.20)	196 (61.06)	12 (3.74)
OSAHS +allergic rhinitis +chronic tonsillitis	179 (4.43)	112 (62.57)	67 (37.43)	32 (17.88)	122 (68.16)	25 (13.97)
OSAHS +chronic rhinitis +chronic tonsillitis	171 (4.23)	124 (72.51)	47 (27.49)	28 (16.37)	122 (71.35)	21 (12.28)
OSAHS +adenoidal hypertrophy +tonsil hypertrophy	19 (0.47)	15 (78.95)	4 (21.05)	1 (5.26)	12 (63.16)	6 (31.58)
P value		0.254		<0.001		
≥3 comorbidities*	96 (2.37)	62 (64.58)	34 (35.42)	30 (31.25)	61 (63.54)	5 (5.21)
No of comorbidities	No of admissions		No of operations		LOS	
	1 (%)	≥2 (%)	0 (%)	1 (%)	≥2 (%)	Median (IQR)
No comorbidities	26 (86.67)	4 (13.33)	12 (40.00)	18 (60.00)	0 (00.00)	2.00 (1.00–2.00)
One comorbidity	2416 (89.18)	293 (10.82)	38 (1.40)	2640 (97.45)	31 (1.14)	2.00 (2.00–2.00)
Top five patterns of one comorbidity:						
OSAHS +chronic rhinitis	1356 (89.33)	162 (10.67)	16 (1.05)	1492 (98.29)	10 (0.66)	2.00 (2.00–2.00)
OSAHS +allergic rhinitis	1013 (89.02)	125 (10.98)	12 (1.05)	1119 (98.33)	7 (0.62)	2.00 (2.00–2.00)
OSAHS +chronic tonsillitis	11 (73.33)	4 (26.67)	1 (6.67)	14 (93.33)	0 (0.00)	2.00 (2.00–3.00)
OSAHS +adenoidal hypertrophy	13 (92.86)	1 (7.14)	8 (57.14)	1 (7.14)	5 (35.71)	1.00 (1.00–3.00)
OSAHS +chronic sinusitis	8 (100.00)	0 (00.00)	1 (12.50)	7 (87.50)	0 (0.00)	2.00 (1.00–3.00)
P value		0.275		<0.001		0.491
Two comorbidities	1089 (90.00)	121 (10.00)	24 (1.98)	628 (51.90)	558 (46.12)	2.00 (2.00–2.00)
Top five patterns of two comorbidities:						
OSAHS +chronic rhinitis +chronic exudative otitis media	393 (89.32)	47 (10.68)	8 (1.82)	167 (37.95)	265 (60.23)	2.00 (2.00–3.00)
OSAHS +allergic rhinitis +chronic exudative otitis media	292 (90.97)	29 (9.03)	1 (0.31)	74 (23.05)	246 (76.64)	2.00 (2.00–2.00)

Continued

Table 2 Continued

No of comorbidities	No (%)	Sex		Age (Years)		
		Male (%)	Female (%)	0-3 (%)	4-7 (%)	8-18 (%)
OSAHS +allergic rhinitis +chronic tonsillitis	166 (92.74)	13 (7.26)	2 (1.12)	176 (98.32)	1 (0.56)	2.00 (2.00–2.00)
OSAHS +chronic rhinitis +chronic tonsillitis	146 (85.38)	25 (14.62)	2 (1.17)	166 (97.08)	3 (1.75)	2.00 (2.00–2.00)
OSAHS +adenoidal hypertrophy +tonsil hypertrophy	18 (94.74)	1 (5.26)	1 (5.26)	9 (47.37)	9 (47.37)	4.00 (3.00–4.00)
P value		0.169		<0.001		<0.001
≥3 comorbidities*	81 (84.38)	15 (15.63)	4 (4.17)	21 (21.88)	71 (73.96)	2.00 (2.00–3.00)

The p values in table 2 were used to reflect the differences in the top five patterns within the one comorbidity group and two comorbidities group.

*The subgroups of ≥3 comorbidities are not shown in this table since the frequency distribution was uniform and comorbidities varied greatly.

LOS, length of stay; OSAHS, obstructive sleep apnoea–hypopnoea syndrome.

the top five patterns in those with two comorbidities were significantly associated with LOS ($p<0.001$), while the patterns in the one-comorbidity group were not.

DISCUSSION

In this study, we discovered that comorbidity patterns with high prevalence associated with paediatric OSAHS in inpatients were mainly otolaryngological diseases, as follows: OSAHS +chronic rhinitis, OSAHS +allergic rhinitis, OSAHS +chronic rhinitis +chronic exudative otitis media, OSAHS +allergic rhinitis +chronic exudative otitis media, OSAHS +allergic rhinitis +chronic tonsillitis, and OSAHS +chronic rhinitis +chronic tonsillitis (37.53%, 28.13%, 10.88%, 7.94%, 4.43% and 4.23%, respectively). However, Qubty *et al* found that diseases in other systems, such as gastro-oesophageal reflux (95/139 patients, 68%) and PLMS (59/139 patients, 42%), were the most frequently diagnosed comorbidities.¹¹ This can be explained by the difference in age of the study populations since subjects in Qubty's study were infants aged 0–17 months, while those in this study were aged 0–18 years. The otolaryngological system and immune system usually require more time to develop; thus, more congenital morbidities will be detected in the infant period, while more otolaryngological morbidities will be detected in older children.

According to this study, the OSAHS prevalence was much higher in males (67.54%) than in females (32.46%). This result is similar to those of previous studies and may be explained by the fact that testosterone flow in boys may lead to upper-airway muscle mass enlargement, resulting in relatively small upper airways.²⁴ Additionally, boys are more likely to develop allergic rhinitis and other allergic diseases, which are additional important risk factors for OSAHS.^{25–26} Therefore, more attention should be given to snoring in boys, especially during puberty, in clinical diagnoses and treatments. In addition, we found that there were many more patients in the 4–7 years group

than in any other age group. This was consistent with a previous study in Shanghai.²¹

Patients with paediatric OSAHS were found to be prone to rhinitis in this study. OSAHS +chronic rhinitis (37.53%) and OSAHS +allergic rhinitis were the most prevalent comorbidity patterns (28.13%). Conventionally, tonsil hypertrophy and adenoid hypertrophy are considered the most common comorbidities.^{10–27} This finding may be associated with the rapid increase in youth allergic rhinitis within a short period of time in China.^{28–29} Shanghai, for instance, saw a striking increase in the prevalence of paediatric allergic rhinitis from 13.6% in 2005²⁹ to 17.6% in 2011.³⁰ A study in major cities in China found that this rapidly increasing prevalence was associated with a complex mixture of compounds (eg, SO₂, NO₂ and particles with an aerodynamic diameter of ≤10 μm (PM₁₀)) in the atmosphere.³¹ In addition, due to rapid modernisation in China, indoor environmental factors (carpeted floor, gas cooking, perceived indoor odour, perceived dryness, furry pets, cockroaches, etc) and lifestyle factors (antibiotic use, starting day care before 3 years old, shared bedrooms, printers/photocopiers at home, etc) also contributed to the increasing prevalence.³² Allergic rhinitis is likely to develop into chronic rhinitis, causing chronic rhinitis to become another highly prevalent comorbidity. Furthermore, we found that most rhinitis patients underwent one surgery for treatment of OSAHS. However, it is commonly accepted that topical steroids and topical nasal antihistamines should be administered as first-line treatments.³³ This may be related to the more severe rhinitis in hospitalised patients than in outpatients. A detailed study of the pathophysiological relationship between these two diseases may be bidirectional. Rhinitis is commonly associated with nasal mucosa oedema and thus increases nasal resistance and the risk of OSAHS. On the other hand, nocturnal intermittent hypoxia during an episode of OSAHS could lead to an increase in 5-lipoxygenase activity, which is the key enzyme of leukotriene biosynthesis, resulting in rhinitis.³⁴ As a result, more

attention should be given to the diagnoses and treatments of rhinitis since it might indicate the onset of paediatric OSAHS. Nevertheless, there are few studies on treatment regimens for rhinitis combined with OSAHS, which still need further exploration.³⁴

As an important part of Waldeyer's ring of lymphatic tissue, tonsil and adenoid diseases still occupied a position in the statistics. Although the proportion was not high, OSAHS +chronic tonsillitis (0.37%) was still among the top five comorbidities in the 1-comorbidity group, while OSAHS +allergic rhinitis +chronic tonsillitis (4.43%) and OSAHS +chronic rhinitis +chronic tonsillitis (4.23%) were the second most common comorbidity patterns in the two comorbidities group in this study. The relationship between rhinitis and chronic tonsillitis has been demonstrated, as the tonsilla palatina are located at the entrance of the respiratory tract; thus, allergic or chronic inflammation in the nose can easily affect homeostasis in the tonsillar tissue.³⁵ For adenoidal hypertrophy, we found that OSAHS +adenoidal hypertrophy (0.35%) and OSAHS +adenoidal hypertrophy +tonsil hypertrophy (0.47%) had lower prevalence rates than tonsil diseases. For paediatric OSAHS comorbid with either tonsil diseases or adenoid hypertrophy, surgical removal is currently the recommended first-line treatment. Based on its outstanding clinical efficacy, multiple guidelines^{10 36} and the Childhood Adenotonsillectomy Trial study³⁷ have stated that tonsillectomy is a cost-effective treatment for paediatric OSAHS combined with chronic tonsillitis. Similar to our findings, almost all patients comorbid with tonsil diseases underwent surgeries. However, more attention has been given to nonsurgical treatments for adenoidal hypertrophy, causing a low proportion of inpatients with this comorbidity in recent years since more patients were treated by outpatient services, especially intranasal medication. This method is practical since the flow of drugs, including intranasal corticosteroids used to relieve symptoms and increase oxygen saturation,^{38 39} ultimately reaches the pharynx.⁴⁰ Montelukast, which targets cysteinyl leukotriene 1 receptor, is another anti-inflammatory medication commonly used for asthma. Studies have shown that montelukast has significant short-term effects on patients, but the long-term effects are also unclear.³⁸ Other novel medications target phosphatases, including phosphoserine phosphatase and dual-specificity phosphatase 1.^{41 42} These treatments still need further research and could reduce expenses and hospitalisation rates if their effects are comparable to those of surgeries.

This study is the first to carefully examine the characteristics of comorbidity patterns in paediatric OSAHS in a large sample. However, several limitations must be considered. First, participants in this study were restricted to inpatients; thus, the cases included in this study may be more severe. Additional cases of outpatients should be included in further research. Second, there were few patients with three comorbidities, making comparisons in this group difficult; therefore, future comparisons

including more inpatients are needed. Third, in our study, we included only the institutions with paediatric wards; however, some institutions without paediatric wards may also have paediatric patients. Thus, in future work we would aim to select and include more samples from other institutions to improve the representativeness of our sample.

CONCLUSION

According to this study, OSAHS+chronic rhinitis and OSAHS+allergic rhinitis had the highest distributions among all comorbidity patterns in paediatric OSAHS. The characteristics of the patterns were delineated, and significant differences in age, number of operations, and LOS were found. The findings of this study provide baseline data for further studies on paediatric OSAHS, especially in patients with complex otolaryngological comorbidities, to examine the crosstalk of otolaryngological organs and develop more effective and efficient diagnoses and treatments.

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Competing interests None declared.

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