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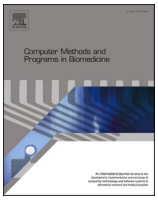

A subject-based association network defines new pediatric sleep apnea phenotypes with different odds of recovery after treatment

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ABSTRACT

Background and objectives: Timely treatment of pediatric obstructive sleep apnea (OSA) can prevent or reverse neurocognitive and cardiovascular morbidities. However, whether distinct phenotypes exist and account for divergent treatment effectiveness remains unknown. In this study, our goal is threefold: i) to define new data-driven pediatric OSA phenotypes, ii) to evaluate possible treatment effectiveness differences among them, and iii) to assess phenotypic information in predicting OSA resolution.

Methods: We involved 22 sociodemographic, anthropometric, and clinical data from 464 children (5–10 years old) from the Childhood Adenotonsillectomy Trial (CHAT) database. Baseline information was used to automatically define pediatric OSA phenotypes using a new unsupervised subject-based association network. Follow-up data (7 months later) were used to evaluate the effects of the therapeutic intervention in terms of changes in the obstructive apnea-hypopnea index (OAHI) and the resolution of OSA (OAHI $<$ 1 event per hour). An explainable artificial intelligence (XAI) approach was also developed to assess phenotypic information as OSA resolution predictor at baseline.

Results: Our approach identified three OSA phenotypes (PH_{OSA1}-PH_{OSA3}), with PH_{OSA2} showing significantly lower odds of OSA recovery than PH_{OSA1} and PH_{OSA3} when treatment information was not considered (odds ratios, OR: 1.64 and 1.66, 95 % confidence intervals, CI: 1.03–2.62 and 1.01–2.69, respectively). The odds of OSA recovery were also significantly lower in PH_{OSA2} than in PH_{OSA3} when adenotonsillectomy was adopted as treatment (OR: 2.60, 95 % CI: 1.26–5.39). Our XAI approach identified 79.4 % (CI: 69.9–88.0 %) of children reaching OSA resolution after adenotonsillectomy, with a positive predictive value of 77.8 % (CI: 70.3 %-86.0 %).

Conclusions: Our new subject-based association network successfully identified three clinically useful pediatric OSA phenotypes with different odds of therapeutic intervention effectiveness. Specifically, we found that children of any sex, >6 years old, overweight or obese, and with enlarged neck and waist circumference (PH_{OSA2}) have less odds of recovering from OSA. Similarly, younger female children with no enlarged neck (PH_{OSA3}) have higher odds of benefiting from adenotonsillectomy.

1. Introduction

Obstructive sleep apnea (OSA) affects up to 5 % of children by increasing upper airway collapsibility, resulting in complete or partial respiratory events (apneas and hypopneas, respectively) during sleep [1–5]. These events lead to inadequate gas exchange and sleep fragmentation, triggering oxidative stress and inflammatory processes that elevate the risk of cardiovascular, metabolic, and neurocognitive

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morbidities in these children [1,2]. These adverse effects can diminish health and quality of life in childhood and may have lifelong consequences [1].

Adenotonsillectomy (AT) is the primary treatment for pediatric OSA and effectively reduces the number of obstructive apneic events per hour of sleep (obstructive apnea-hypopnea index, OAHI), reversing other OSA-related consequences [2,6]. However, treatment effectiveness varies based on patient attributes such as body mass index [2,7–9]. Additionally, inconsistencies arise between OAHI -regularly used to establish OSA and its severity- and the actual symptoms and morbidity profiles of affected children [10]. These observations suggest different pediatric OSA phenotypic clusters with shared clinical and treatment response characteristics [10]. Accordingly, relying solely on a variable like OAHI may obscure important clinically relevant sub-group characteristics, making the identification of such phenotypes essential for timely, accurate, and tailored diagnosis and treatment.

OSA phenotype identification has been extensively reviewed in adult patients [11]. Data-driven methods enabling hierarchical unbiased clustering have been effectively implemented [11–16]. Nonetheless, similar efforts for pediatric OSA phenotypes are limited. Principal component analysis and *k*-means were used with clinical variables from polysomnography (PSG) to support a continuum in pediatric OSA severity [17]. Another study applied *k*-means and PSG data to identify characteristics of two fixed clusters for AT candidates among OSA patients [18]. Similarly, *k*-medoids clustering, alongside anthropometric and respiratory variables, has aimed to objectivize pediatric OSA severity groups [19]. Other studies focused on very specific pediatric OSA-related issues such as neurocognitive or asthma phenotypes [20,21]. Despite the advances achieved in these works, two main research gaps have been identified. First, all these partition-based clustering methods (*k*-means, *k*-modes, *k*-medoids) suffer from limitations such as the *a priori* need to fix the number of subgroups (*k*), the assumption of spherically shaped clusters, and sensitivity to outliers [22–24]. Second, none of these studies evaluated the clinical usefulness of new phenotypes in terms of the odds of treatment effectiveness.

In this study, we hypothesized that sociodemographic, anthropometric, and clinical variables can classify OSA-affected children into distinct phenotypes that may differ in treatment response. Accordingly, our threefold objective was to i) define new data-driven pediatric OSA phenotypes, ii) evaluate treatment effects in each of the phenotypes identified, and iii) assess the new phenotypic information for predicting pediatric OSA resolution. In this context, we propose a novel subject-based association network approach to identify these phenotypic clusters. Association and correlation networks are graphical analyses that, combined with modularity algorithms, do not make prior assumptions about the number of clusters or their form [25]. Moreover, they have been successfully used to establish relationships between variables in different health-related problems like schizophrenia [26], gene interactions in breast cancer [27], spontaneous breathing prediction [28], and pediatric OSA [20]. However, we propose using association networks to analyze relationships between subjects, each of them represented by a pattern composed of the individual values of 22 clinically relevant variables, permitting the detection of associations that could lead to new OSA phenotypes. We also evaluate this potential new phenotypic information by applying odds ratios for OSA resolution after treatment, and by developing a Gentle Boost-based explainable machine-learning algorithm to predict OSA resolution. To the best of our knowledge, this approach and its application to pediatric OSA are novel. Moreover, new phenotype discovery has the potential to guide clinicians towards more tailored clinical protocols and their prompt application, thus improving the positive effects on patients' health and quality of life.

2. Dataset: the childhood adenotonsillectomy trial

The study involved 464 children (5–9.9 years old, 219 boys | 245 girls) from the Childhood Adenotonsillectomy Trial (CHAT) database (clinical trial NCT00560859) [9]. The protocol followed the Declaration of Helsinki, with written consent obtained from all parents and assent from children over 7. Participants suspected of suffering from OSA underwent a baseline overnight polysomnography (PSG) to determine OAHI and reach the diagnosis. Sociodemographic and clinical data were also collected. Of the 464 children, 453 with OSA were randomized to early adenotonsillectomy (eAT) or watchful waiting with supportive care (WWSC) to evaluate differences between the two interventions [9]. From here on, both interventions will be referred to as 'treatment'. Most children ($N = 407$) had follow-up data acquired seven months post-treatment. Detailed information on the original CHAT study design and its goals can be found in prior publications [9,29]. Beyond these initial studies, the robustness and reproducibility of the CHAT database to advance pediatric OSA knowledge have been well-demonstrated in a range of subsequent investigations [30–33]. Sociodemographic and clinical variables from children involved in the study are presented in Table 1 from Section 3.1, and a summary of baseline variables is presented in Table 2 from Section 4.1.

Table 1
Variables used to define the pediatric OSA subgroups. Mode imputation was used for all of them. Daytime sleepiness was measured through the Epworth Sleepiness Scale for Children [36] and directly obtained from the answers of children's parents to the Pediatric Sleep Questionary [37].

Variables	*Categories*	*Categorization rule*	*Imputed data (%)*
Sex	Male (M) | Female (F)	Direct from CHAT study	2.40
Age	5–6 | 7–8 | 9–10 (years old)	Age equally distributed	2.40
HT	High blood pressure | Normal blood pressure	High if systolic or diastolic blood pressure percentile $\geq$ 95 % according to age, sex, and height [38]	2.60
BMI	Underweight | Normal | Overweight | Obese	Percentile according to age and sex $<$ 5 % | 5–85 % | 85–95 % | $\geq$ 95 % [39,40]	2.40
Asthma	Yes (Y) | No (N)	Direct from CHAT study	2.60
Daytime sleepiness (ESS)	Y | N	Increased if ESS $>$ 10 [36]	2.60
Enlarged Neck Circumference	Y | N	Enlarged if $\geq$ 32.5 cm in males and $\geq$ 31 cm in females [41]	2.60
High total cholesterol level	Y | N	High if $\geq$ 200 mg/dl [42]	20.00
Morning Headaches	Y | N	Direct from CHAT study	3.70
Morning Fatigue	Y | N	Direct from CHAT study	9.90
Insomnia	Y | N	Direct from CHAT study	2.60
Daytime sleepiness (PSQ)	Y | N	Direct from CHAT study	2.80
Allergic Rhinitis	Y | N	Direct from CHAT study	2.60
Gasp and Chokes	Y | N	Direct from CHAT study	3.00
Depression	Y | N	Direct from CHAT study	3.20
Mallampati score [43,44]	I | II | III | IV	Direct from CHAT study	2.40
Irritability	Y | N	Direct from CHAT study	3.70
Race	Black | White | Other	Direct from CHAT study	2.40
Anxiety	Y | N	Direct from CHAT study	5.20
Reflux	Y | N	Direct from CHAT study	2.60
Enlarged Waist circumference	Y | N	Enlarged if percentile $\geq$ 75 % according to age and sex [45]	2.60
Restless sleep or frequent awakenings from sleep	Y | N	Direct from CHAT study	3.00

BMI: body mass index; *CHAT*: Childhood Adenotonsillectomy Trial; *ESS*: Epworth Sleepiness Score; *HT*: Hypertension; *PSQ*: Pediatric Sleep Questionary.

Table 2
Proportion of subjects in each phenotype for the variables showing significant differences between any pair of phenotypes and χ-square value of the comparison between each pair of them.

Variables	PH_{OSA1} (red, N =155)	PH_{OSA2} (purple, N = 168)	PH_{OSA3} (blue, N = 141)	χ-square PH_{OSA1} vs PH_{OSA2}	χ-square PH_{OSA1} vs PH_{OSA3}	χ-square PH_{OSA2} vs PH_{OSA3}
Sex	5.8 % | F	58.3 % | F	97.9 % | F	**98.0**	**246.7**	**64.3**
	(0.0 % i.d.)	*(0.0 % i.d.)*	*(7.8 % i.d. Female)*			
Age	83.9 % | 5–6 y	10.1 % | 5–6 y	80.2 % | 5–6 y	**178.4**	1.7	**158.7**
	13.5 % | 7–8 y	58.9 % | 7–8 y	18.4 % | 7–8 y			
	2.6 % | 9–10 y	31.0 % | 9–10 y	1.4 % | 9–10 y			
	(0.0 % i.d.)	*(0.0 % i.d.)*	*(7.8 % i.d. 5–6 y)*			
BMI	3.9 % | Under	0.0 % | Under	6.4 % | Under	**93.8**	7.5	**113.6**
	67.7 % | Normal	18.5 % | Normal	70.2 % | Normal			
	7.7 % | Over	20.2 % | Over	12.8 % | Over			
	20.7 % | Obese	61.3 % | Obese	10.6 % | Obese			
	(0.0 % i.d.)	*(0.0 % i.d.)*	*(7.8 % i.d. Normal)*			
Asthma	32.9 %	38.7 %	19.1 %	0.9	6.5	**13.1**
	(3.9 % i.d. No)	*(1.8 % i.d. No)*	*(8.5 % i.d., No)*			
Enlarged Neck Circumference	1.3 %	35.1 %	0.0 %	**58.0**	0.4	**58.9**
	(0.0 % i.d.)	*(0.6 % i.d. No)*	*(7.8 % i.d. No)*			
Gasp and chokes	65.2 %	49.4 %	74.5 %	7.5	2.6	**19.2**
	(0.7 % i.d. Yes)	*(0.6 % i.d. Yes)*	*(8.5 % i.d. Yes)*			
Mallampati score [43,44]	5.8 % | I	20.2 % | I	8.5 % | I	**23.9**	10.1	9.1
	36.8 % | II	45.2 % | II	52.5 % | II			
	48.4 % | III	27.4 % | III	33.3 % | III			
	9.0 % | IV	7.2 % | IV	5.7 % | IV			
	(2.5 % i.d. II)	*(0.6 % i.d. II)*	*(8.5 % i.d. II)*			
Enlarged Waist circumference	41.9 %	92.3 %	45.4 %	**91.7**	0.23	**79.3**
	(0.0 % i.d.)	*(0.6 % i.d. Yes)*	*(7.8 % i.d. Yes)*			

Italic values are the percentage of imputed data within each phenotype, as well as the category assigned as imputed data. Bold χ-square values and variables represent statistically significant at p-value 0.05 after Bonferroni's correction. *BMI:* body mass index.

3. Methods

3.1. Study design, variables, and data imputation

Fig. 1 illustrates the study design. Yellow cylinders indicate available data for phenotype definition and comparison. Light blue (baseline) and orange (follow-up) boxes are analyses conducted on these data or results. Red figures highlight key results, including newly identified subgroups, their defining characteristics, and their differences before and after treatment. Sociodemographic, anthropometric, and clinical data of the 464 children within the baseline subgroup of CHAT were used to define the pediatric OSA phenotypes. To this effect, we included the

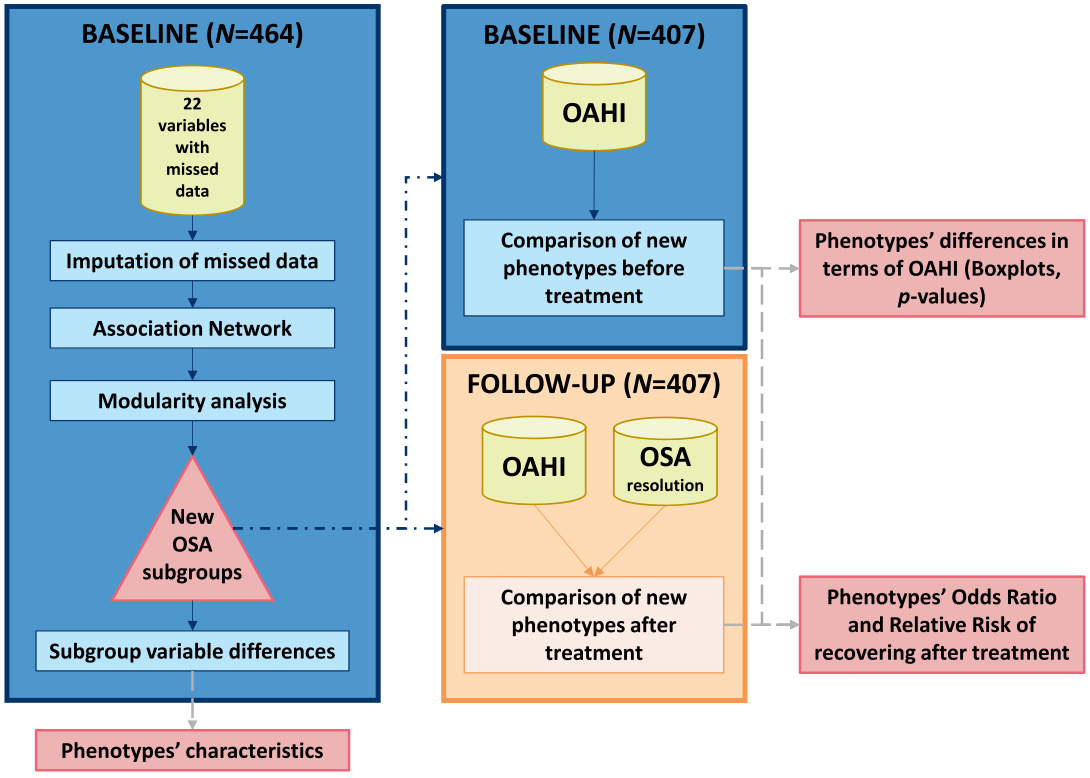

Fig. 1. Schematic of the study design. Yellow cylinders represent data. Light blue and orange boxes represent analyses. Red figures represent important results of the study. After defining the phenotypes, only 407 subjects with complete datasets at both baseline and follow-up were used in our analyses.

available 22 variables. The selection of the 22 variables was adapted from those used in prior adult studies and based on standard measures in children [12,13]. Continuous variables were categorized according to previously defined clinically relevant thresholds in the literature. For the sake of simplicity, a mode-based imputation strategy was followed for the missed categories [34]. Previous studies involving clinical and sociodemographic categorical data have shown that this method reaches consistently high imputation accuracy for up to 50 % of missing data, equaling the performance of more complex methods [35]. Table 1 specifies the 22 variables, their categories, rules for continuous variables categorization, the studies proposing these rules, and the percentage of imputed data. Each child under study was then defined by a pattern (or vector) of 22 values. Association networks conducted a modularity analysis on these patterns to search for pediatric OSA phenotypic clusters. OAHI values from the 407 children included in both baseline and follow-up groups were evaluated for possible differences in the treatment effects on each phenotype. This was conducted by comparing pre- and post-treatment OAHI values and calculating odds ratios for pediatric OSA resolution (OAHI<1 events/hour total sleep time) by phenotype.

3.2. Subject-based association networks and modularity analysis

Association networks are graphs where nodes typically represent variables and links measure their pairwise relationships [46]. In our adaptation, nodes represent children characterized by 22 variables, with links measuring the similarity between subjects' information, aiding children's subgroup definition. Correlation typically evaluates associations between continuous data [20,46]. However, since we have categorical and continuous information, we categorized the 22 variables, enabling the use of the χ-square test to measure associations between nodes. The algorithm visualizing the association networks was ForceAtlas2 [47], which emulates physical attraction and repulsion forces as reflections of association strength [47]. According to the distance of connected nodes (subjects), and the sum of all the χ-square values reaching each node (node degree), ForeceAtlas2 transforms structural proximities into visual ones. Thus, subjects with stronger associations tend to be positioned closer together.

Once the association network is built, a modularity (cluster) analysis is conducted to define subgroups of nodes with higher association. We used an unsupervised learning algorithm for data clustering, which does not require prior information about the number of clusters or assumptions about relationships within the data. Specifically, we used Blondel's modularity (also known as the Louvain method), which has shown robust performance regarding computation time [25], being important in large networks. The algorithm relies on the modularity parameter Q, which measures the density of the (weighted) links within a given module (cluster) compared to the (weighted) links between all different given modules [25]. It can be computed as follows [25,48]:

$$Q = \frac{1}{2m}\sum_{i,j}\left[\chi_{i,j} - \frac{k_i k_j}{2m}\right]\delta(c_i, c_j), \tag{1}$$

with

$$k_i = \sum_j \chi_{i,j} \tag{2}$$

where $\chi_{i,j}$ represents the χ-square value (weight of the link) between i and j nodes, c_i is the community to which node i is assigned, with:

$$\delta = \begin{cases} 1 \text{ if } c_i = c_j \\ 0 \text{ otherwise} \end{cases} \tag{3}$$

and

$$m = \frac{1}{2}\sum_{i,j}\chi_{i,j} \tag{4}$$

Using Q modularity, the algorithm follows two iterative stages [25]. First, each node is assigned to a unique community (or module), resulting in as many communities as nodes. Then, for each node i, the modularity gain (ΔQ) of removing i from its community and placing it in the communities of all its j neighbors is evaluated. If ΔQ is positive, node i joins the community with the highest gain. Otherwise, i remains in its current community. This process continues until no gain is observed in any node, completing the first stage. The second stage involves creating a new network where the discovered communities act as nodes, with weighted links between these new nodes being the sum of the weighted links between the old nodes included within each pair of communities. After this second stage, the first iterative stage can be applied again to maximize Q in the new network. The two stages combined are iterated until no more changes in Q are observed, reaching maximum modularity and assigning a module to each original node [25].

3.3. Statistical analysis: connectivity matrix, statistical differences, odds ratios

The χ-square test of independence measured the relationship between nodes to build association networks. However, χ-square values were not directly used but derived from a bootstrap procedure of 1000 runs for the sake of results robustness [20]. Accordingly, a random selection of 22 variables with replacement was conducted 1000 times, allowing for repeated variables. Then, χ-square for each pair of nodes (subjects from baseline CHAT) was computed to form the full connectivity matrix of each bootstrap run. After the 1000 runs, the connectivity matrix of χ-square mean values was used to feed the ForceAtlas2 algorithm, build the final association network, and conduct the modularity analysis.

Once subgroups (potential phenotypic clusters) were obtained, the χ-square goodness of fit test with p-values (<0.05 with Bonferroni's correction) was used to evaluate differences between variables from each subgroup at baseline, allowing phenotype description based on differential characteristics. Boxplots and Wilcoxon signed rank test (p-value <0.05 after Bonferroni's correction) evaluated differences in OAHI within the new subgroups, before (baseline) and after (follow-up) OSA treatment in the 407 subjects with follow-up data. Mann-Whitney U test assessed differences between phenotypes at baseline and follow-up. These analyses considered subjects who underwent eAT or WWSC separately, as well as in aggregate. Odds ratios (OR) alongside 95 % confidence intervals evaluated the relative chance of each newly defined phenotype recovering after OSA treatment, also differentiated by treatment arm and in aggregate. Finally, two machine learning models (GentleBoost [49]) were trained to predict OSA resolution based on the main variables defining phenotypes.

3.4. Explainable Gentleboost

GentleBoost, or gentle adaptive boosting (gentle AdaBoost), is an ensemble-learning algorithm known for its robustness against outliers [49]. It aims to train and combine the classification performance of multiple base learners of the same type to create more generalizable models [49,50]. An iterative process trains each new base learner, giving more importance to observations misclassified in previous iterations [50]. The final prediction is conducted by combining the predictions of each base classifier, which are weighted by their individual performance. In this study, GentleBoost was used with decision trees as base learners to predict recovery from OSA after two interventions (eAT or WWSC). Specifically, the purpose was to predict at baseline whether children would normalize their OAHI after intervention, i.e., at follow-up. The predictors included for training the GentleBoost models were those variables that showed statistical differences between at least two phenotypes derived from the modularity analysis. Moreover, we assessed whether adding a variable with the Phenotype category would improve performance. For GentleBoost, the number of base learners is a

hyperparameter that we optimized after a leave-one-out cross-validation procedure. Another validation method (bootstrap with 100 runs) was used to estimate GentleBoost's performance. The *relative importance* measure served as a global explainable method for assessing each variable's contribution to the obtained GentleBoost models [51]

4. Results

4.1. Baseline: pediatric OSA phenotypes definition

Fig. 2 displays the association network after applying the ForceAtlast2 algorithm to the 22 variables and the subsequent modularity analysis. Each node represents a pediatric subject, while the three colors (red, purple, blue) indicate the three OSA clusters as automatically obtained. Table 2 summarizes the 8 out of the 22 categorical variables that reached statistical significance differences between 2 of the subgroups at least, along with the χ-square value (with p-value after Bonferroni's correction). The imputed data percentage for each subgroup and variable is also shown.

The three subgroups, or phenotypes (PH_{OSA1}- PH_{OSA3}), have similar sizes. Only the variable Sex is significantly different among the three phenotypes and is also the only significantly different between PH_{OSA1} and PH_{OSA3}. Five variables (Sex, Age, BMI, Waist circumference, and Neck circumference) show significant differences in PH_{OSA2} compared to both PH_{OSA1} and PH_{OSA3}. Additionally, PH_{OSA2} is significantly different from PH_{OSA1} in Mallampati score, and from PH_{OSA3} in Asthma presence and nighttime Gasps and Chokes. No significant differences were found in the remaining 14 variables (supplementary Table S1), including hypertension, total cholesterol level, daytime sleepiness (either ESS or PSQ), and race. Based on this, the expected features of a child in each phenotype are:

- PH_{OSA1}: male (94.2 %); pediatric subjects 5 or 6 years old (83.9 %); non-obese (79.4 %); normal neck circumference (98.7 %); no class I Mallampati score (94.2 %).
- PH_{OSA2}: pediatric subjects between 7 and 10 years old (89.9 %); overweight or obese (81.6 %); enlarged waist circumference (92.3 %).
- PH_{OSA3}: female (97.87 %) pediatric subjects 5 or 6 years old (80.1 %); non-obese (89.4 %); no asthma (80.85 %); and normal neck circumference (100.0 %).

4.2. Follow-up: differences in treatment effectiveness

Fig. 3 presents boxplots of the differences in OAHI among the three phenotypes before and after treatment. The differences within treatment arms (eAT and WWSC) are also included. OAHI values were significantly lower (Wilcoxon signed rank test p-value < 0.05 after Bonferroni's correction) at follow-up regardless of the treatment arm or phenotype, except for WWSC of PH_{OSA3}. Conversely, there were no OAHI statistical differences at baseline among phenotypes, nor between PH_{OSA1} and PH_{OSA3} at follow-up

(Mann-Whitney U test p-value > 0.05 after Bonferroni's correction). PH_{OSA2} did show significantly higher OAHI after treatment compared to PH_{OSA1} and PH_{OSA3}, when assessing the whole groups, and significantly higher OAHI compared to PH_{OSA3} when only assessing eAT subjects. Table 3 details the number of pediatric subjects per phenotype whose OSA resolved (OAHI < 1 e/h) or not (OAHI ≥ 1 e/h). The ORs of OSA resolution after treatment are shown in Table 4. No statistically significant differences were found in the OR of OSA resolution between PH_{OSA1} and PH_{OSA3}. However, the odds of OSA resolution after treatment for PH_{OSA1} or PH_{OSA3} were 1.64 and 1.65 times the odds for PH_{OSA2}. The largest difference was in the eAT arm between PH_{OSA2} and PH_{OSA3}, where PH_{OSA3} had 2.6 times greater odds of normalizing their OAHI with eAT treatment.

4.3. OSA resolution prediction using phenotypic cluster information

As mentioned above, 8 out of the 22 variables (Sex, Age, BMI, Asthma presence, Enlarged Neck circumference, Gasp and Choke presence, Mallampati score, and Enlarged Waist circumference) reached

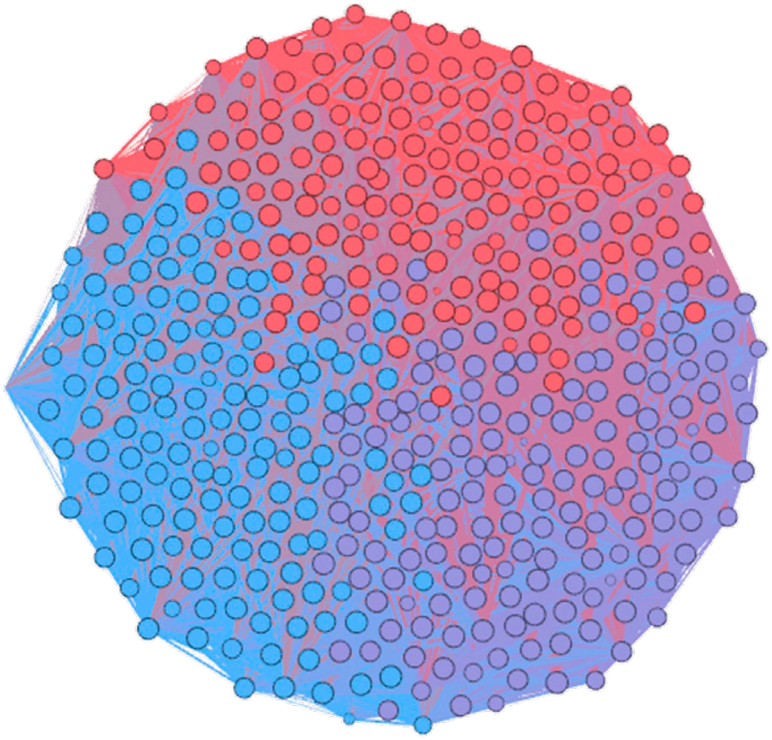

Fig. 2. Association network of the three clusters in pediatric OSA (red, purple, and blue) automatically defined after the modularity analysis.

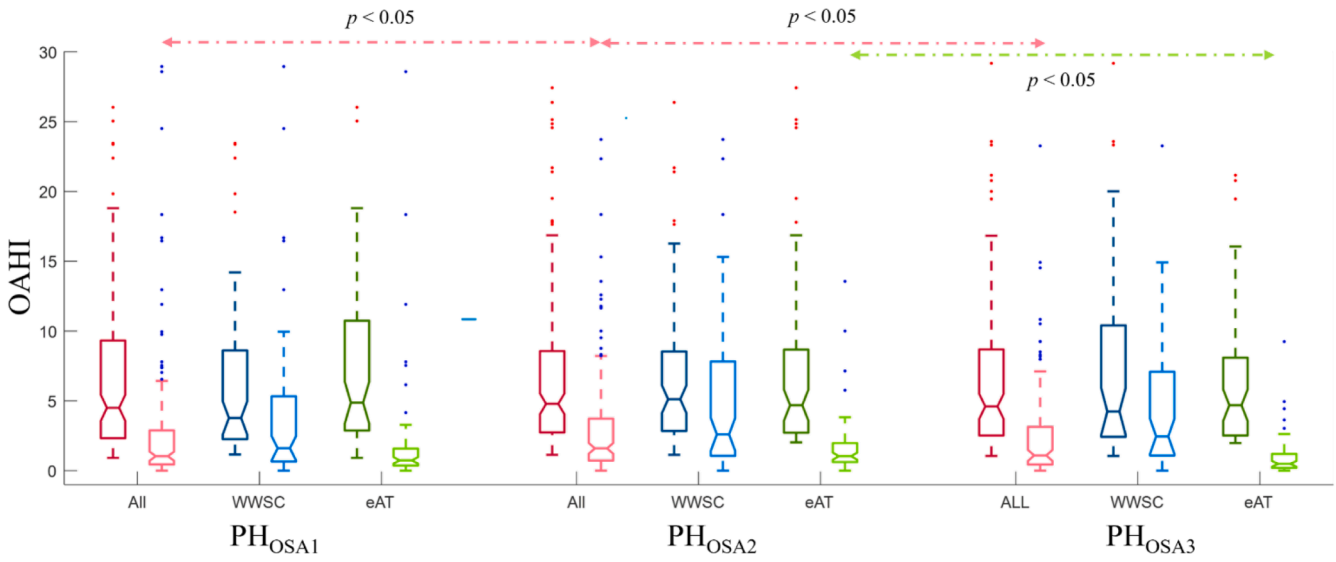

Fig. 3. Boxplots comparing OAHI at baseline (dark colors) and follow-up (light colors) by the new phenotypes and treatment arm (WWSC and eAT). Dashed lines connect the three significant comparisons **between phenotypes** after Bonferroni's correction, which only appeared at follow-up. As noted, all comparisons **within phenotypes** (between baseline and follow-up) were significant, except for WWSC of PH_{OSA3}.

Table 3
Number of subjects at follow-up and for each phenotype who showed OSA resolution or lack thereof. Overall numbers are presented as well as split into treatment arms.

Phenotype (# at follow-up)	Resolved (OAHI < 1 e/h)			Non-resolved (OAHI ≥ 1 e/h)		
	All	eAT	WWSC	All	eAT	WWSC
PH_{OSA1} ($N = 139$)	67	42	25	72	26	46
PH_{OSA2} ($N = 152$)	55	35	20	97	36	61
PH_{OSA3} ($N = 116$)	56	43	13	60	17	43

eAT: early Adenotonsillectomy; *OAHI:* Obstructive Apnea-Hypopnea Index; *WWSC*: Watchful Waiting with Supportive Care.

Table 4
Odds ratio and 95 % confidence interval of normalizing their OAHI at follow-up according to phenotypic clusters. Overall results are presented as well as split into treatment arms.

Treatment arm	PH_{OSA1} relative to PH_{OSA2} OR (95 % CI)	PH_{OSA3} relative to PH_{OSA2} OR (95 % CI)	PH_{OSA1} relative to PH_{OSA3} OR (95 % CI)
All	**1.64 (1.03–2.62)**	**1.65 (1.00–2.69)**	1.00 (0.61–1.64)
eAT	1.66 (0.85–3.26)	**2.60(1.25–5.39)**	0.64 (0.30–1.34)
WWSC	1.65 (0.82–3.34)	0.92 (0.41–2.05)	1.80 (0.82–3.96)

Bold values represent statistical significance at 5 % level according to the 95 % CI. *eAT*: early Adenotonsillectomy; *CI*: Confidence interval; *OAHI:* Obstructive Apnea-Hypopnea Index; *OR*: Odds ratio; *WWSC*: Watchful Waiting with Supportive Care.

statistically significant differences between at least two phenotypes, thereby being included as predictors in the training and validation of the GentleBoost models. Besides, Fig. 4 shows the procedure to optimize the number of base learners and evaluate the convenience of the Phenotype variable as a ninth predictor. A total of 50 base learners for WWSC and 15 for eAT were obtained as optimum after a leave-one-out cross-validation procedure used alongside the two-class Cohen's kappa value. Phenotype variable was shown to reach improved performance for the models of both treatments, so it was also included as a predictor in the final models.

Table 5 presents the performance of the GentleBoost algorithm for the two cases: eAT ($N = 199$) and WWSC ($N = 208$). Both models were trained using 9 characteristics: the 8 with statistically significant differences in any of the 3 defined phenotypes (sex, age,

BMI, asthma presence, enlarged neck circumference, gasp and chokes presence, Mallampati score, and enlarged waist circumference) and a ninth categorical variable codifying the phenotype (1, 2 or 3). Each statistic is shown as median and 95 % confidence interval, obtained via bootstrap validation with 100 repetitions. Both models showed moderate predictive ability, with the eAT model presenting higher Se, PPV, and LR-, and WWSC higher Sp, NPV, and LR+. However, only Se and PPV showed statistically significant differences, as indicated by no overlap in the corresponding 95 % CI. Thus, the eAT model demonstrated improved overall performance.

Fig. 5 shows the relative importance of the predictor variables for each model [51]. These values were obtained as the median from the bootstrap validation procedure and scaled to represent percentages. Similarities in the relative importance of the variables in both models are observed, with the main differences being the Mallampati score and Gasp and Cokes presence. The Mallampati score shows the highest relative importance (18.3 % for WWSC and 20.4 % for eAT), while other variables in eAT do not exceed 13.8 % (BMI). Additionally, Gasp and Cokes presence reaches 11.5 % in eAT and 7.8 % in WWSC. In both models, Mallampati score, Age, and BMI account for about 50 % of the relative importance: 51.0 % for WWSC and 46.8 % for eAT. The Phenotype Cluster has similar relative importance in both models (9.6 % and 10.1 %, respectively).

5. Discussion

We have developed and evaluated a robust subject-based association network that has automatically identified 3 pediatric OSA phenotypes based on 22 sociodemographic, anthropometric, and clinical variables. The phenotypic clusters show varying odds of OSA recovery after treatment. Notably, a phenotype linked to increased BMI (PH_{OSA2}) exhibited significantly higher OAHI and lower odds of recovering from OSA than the two other phenotypes (PH_{OSA1} and PH_{OSA3}), which were associated with normal BMI, neck, and waist circumferences. This finding was observed at follow-up when the OSA treatment arm was not considered, as well as when comparing eAT subjects from PH_{OSA2} and PH_{OSA3}.

Unveiling a phenotype (PH_{OSA2}) with a marked obesity profile is consistent with both the specific characteristics of this subgroup within

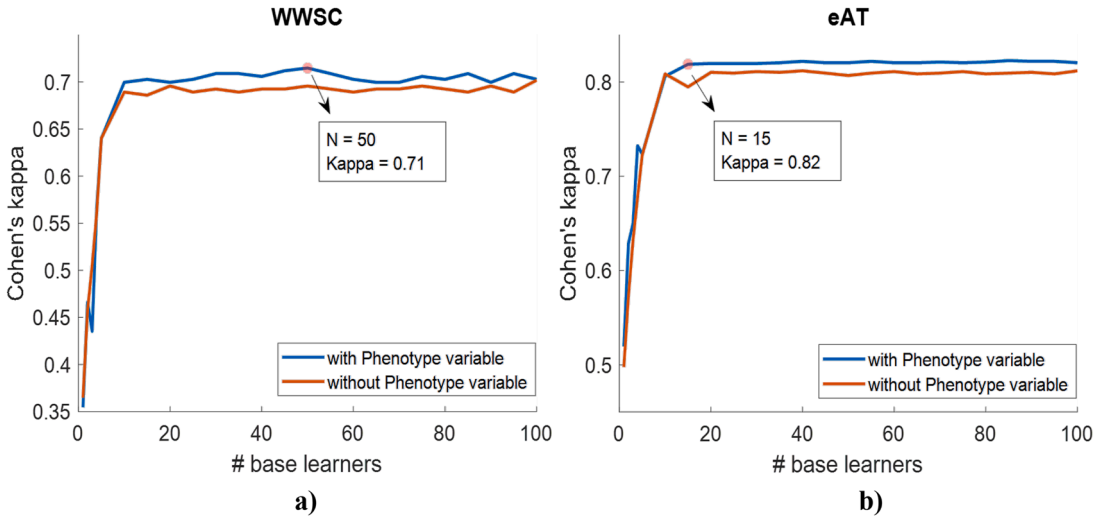

Fig. 4. Base learner hyperparameter optimization and Phenotype variable evaluation for a) the WWSC model and b) the eAT model.

Table 5
Performance of the GentleBoost models on pediatric OSA resolution prediction after the bootstrap validation procedure (median and 95 % CI).

Treatment arm	Se	Sp	PPV	NPV	LR+	LR-
eAT	**79.4 (69.9–88.0)**	65.0 (51.7–77.3)	**77.8 (70.3–86.0)**	66.5 (57.7–76.2)	5.6 (3.4–27.0)	0.4 (0.3–0.7)
WWSC	49.5 (34.0–63.1)	82.7 (74.0–90.0)	51.4 (41.2–63.4)	81.5 (75.7–86.6)	7.0 (4.0–20.9)	0.7 (0.5–0.8)

Bold values represent statistical significance at 5 % level according to the 95 % CI. *eAT*: early Adenotonsillectomy; *CI*: Confidence interval; *LR+/LR-*: positive and negative likelihood ratios; *NPV*: negative predictive value; *PPV*: positive predictive value; *Se:* sensibility; *Sp*: specificity; *WWSC*: Watchful Waiting with Supportive Care.

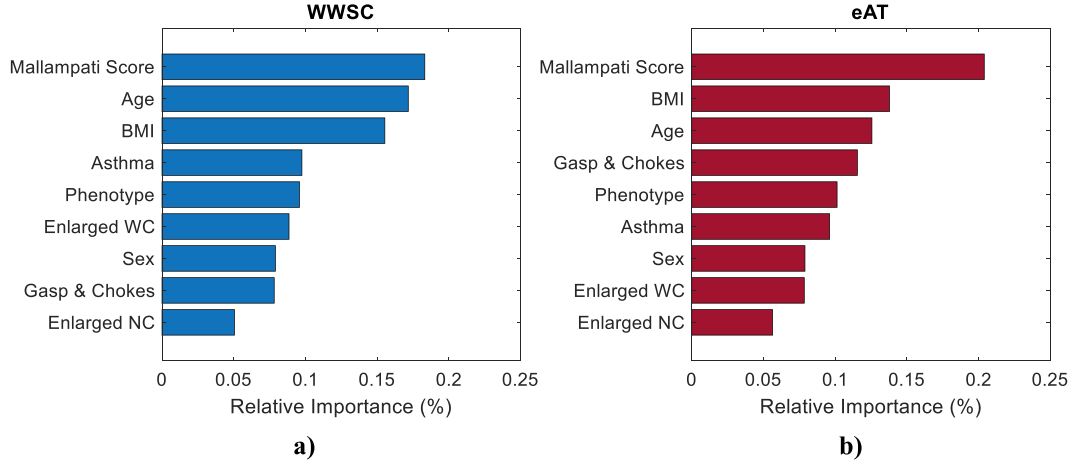

Fig. 5. Relative importance (%) of the 9 variables used as predictors for a) the WWSC model and b) the eAT model.

pediatric OSA patients and their difficulty in resolving OSA [52,53]. This finding, accordingly, supports the suitability of our subject-based association network for identifying clinically relevant subgroups or phenotypes. Moreover, adding to the connections between metabolic syndrome and pediatric OSA [54], it reinforces the clinical importance of considering obesity as a distinct condition that requires a differential protocol within the sleep apnea context, which, according to our current results, could include specific (possibly personalized) therapeutic interventions and preventive strategies like closer monitoring or adjunctive therapies beyond eAT. Another interesting finding relates to a female-sex-related phenotype. Prepubertal children, as those involved in this study, show no or minimal differences in male *vs.* female prevalence [55,56]. However, combined with normal-weight characteristics, being 5–6 years old, and the absence of asthma, our results suggest another distinctive profile (PH_{OSA3}) that could benefit the most from eAT intervention.

The use of automatic methods for defining OSA phenotypes in adults is well-documented in the literature [11–14]. A recent review summarized findings from various clustering methods, identifying 4 OSA subtypes (A, B, C, and D) distinguished mainly by age, weight, and sex [11]. Similar results were reached in a study involving 23,000 OSA adult patients in Europe, with only 1 out of the 7 identified phenotypes ("Pulmonary disease") not relying on weight, age, or sex [14]. However, similar studies in children are limited. Spruyt et al. identifyed 6 pediatric OSA categories, from non-pathological to more abnormal polysomnographic indices of apneic events, blood oxygen desaturations, and arousals [17]. While their age range aligns with ours (5–9 years old), they aimed to support and objectivize different pediatric OSA severity

degrees, whereas we intentionally left aside sleep indices such as OAHI to search for clinical phenotypes. Liu *et al.* applied *k*-means on OAHI, heart periodicity during N2 and REM sleep, and thoracic-abdominal asynchrony during N3 to cluster pediatric OSA subjects [18]. Like our study, they utilized the CHAT study database but aimed to identify criteria to prevent unnecessary AT in OSA-affected children, thus restricting the cluster subgroups to two: treat or not treat. Lastly, Zaffannello *et al.* used *k*-medoids clustering to identify three clusters among 326 habitually snoring children based on anthropometric variables and respiratory indices from overnight tests [19]. They found weight and age-related differences in some comparisons between the 3 clusters, aligning with our findings. They also reported significant differences in respiratory-related indices that, as explained above, were intentionally excluded from our study. However, no sex differences were noted, and waist or neck circumference was not evaluated alongside other characteristics. Furthermore, the treatment response in these subgroups was not evaluated, focusing instead on objectifying severity categories traditionally used in pediatric OSA [19].

Marked differences in the objectives of these studies make it challenging to compare our results. However, we believe these studies highlight the potential clinical usefulness of clustering approaches in pediatric OSA phenotyping. Beyond this, some methodological aspects deserve mention when comparing our different approaches. First, the *k*-means, *k*-medoids, and *k*-modes methods require a prior setting of the number (*k*) of clusters to be defined [22]. In contrast, our association network approach involves no prior assumptions, enhancing the objectivity of the findings. *K*-means and *k*-modes also are known to be sensitive to outliers when defining the clusters [23]. Additionally, all partition-based clustering methods (*k*-means, *k*-modes, *k*-medoids) assume that detected clusters, if indeed found, are spherically shaped [24]. Finally, *k*-medoids is inefficient with large datasets [23], unlike the Blonde's method used in our modularity analysis [25].

Another way to enhance the usefulness of our phenotype cluster analysis is through the performance of the two machine learning models trained to predict the intervention's success. The eAT model demonstrated higher robustness, achieving 79.4 % Se and 77.8 % PPV. Although insufficient for clinical use, it illustrates the additional potential of pediatric OSA phenotypes information. Moreover, the relative importance of the predictor variables showed similar patterns in eAT and WWSC models, with a higher Mallampati score and presence of Gasp and Choke identifying key differences favoring the eAT model. Relative importance also showed the convenience of the phenotypic information gathered in the Phenotype variable.

Nevertheless, aspects that limit our results must be acknowledged. While our sample size is large, a larger cohort would enhance generalizability, especially regarding the age span of children (5–9 years), as age has emerged as an important feature in defining our phenotypes. Thus, including subjects outside this range is a desirable target for future studies before a potential clinical adoption. This should be done in conjunction with the evaluation of data from other sleep centers for further external validation. Although CHAT is a multi-center dataset, this future approach could strengthen our conclusions. Related to the design of CHAT study, future approaches should consider evaluating OSA resolution in different periods after AT, as the 7 months established is also a limitation of our results and conclusions. Similarly, children showing extreme OSA-related findings [9] -presumably needing immediate intervention-, severe obesity (z-score BMI ≥ 3), recurrent tonsilitis, or taking medication for attention deficit-hyperactivity syndrome, were not included or were excluded from the CHAT study. This strategy might have affected our definition of OSA-related phenotypes. However, in agreement with our results and the established lack of OSA resolution linked to obesity and OSA severity [52,53], we speculate that excluding these cohorts did not compromise our findings on the differential odds of OSA resolution, nor did it overestimate the effectiveness of our methods for identifying phenotypes (modularity analysis) and predicting OSA resolution (machine learning models). The 22 variables used in our study also limit our results and conclusions. We adapted the design of previous studies to the specific case of the available data in CHAT dataset. However, other clinical variables, like tonsil size, were not included in our study. Although tonsil size has been questioned regarding its OSA-related predictive ability [57,58], particularly in the case of children with abnormal weight [58], it has been commonly evaluated in the pediatric OSA context, so its inclusion may have led to different phenotype definitions. Another clear limitation is missing data; while relatively minor (see Table 1), the total cholesterol level had 20 % missing values. We used a mode-based data imputation technique to minimize this issue. Despite its simplicity and proven efficiency [35], it has limitations that might lead to the underestimation of the variance of the imputed variable [35]. Accordingly, more complex methods, such as multiple imputation or model-based approaches, or eventual data availability, could have led to different outcomes for this variable. Similar limitations apply to the percentage of imputed data assigned to each phenotype. However, our results (see Table 2) indicate that significant differences among phenotypes are likely preserved, with only the Gasp and Choke variable having realistic chances of being impacted. Similarly, imputed data is unlikely to affect the trend of variables that did not show significant differences between phenotypes (supplementary Table S1). Additionally, a future goal is to associate our phenotypes with co-morbidities, including evaluating relationships between clusters and specific end-organ dysfunction. The applicability of the GentleBoost models is another limitation. This study aimed to show whether the baseline data used to define the phenotypes contained useful information about OSA resolution after intervention. Our results support this idea but also show that further research is needed to reach a reliable, fully automated prediction on OSA resolution. Future evaluation of other machine-learning methods could be an interesting approach to overcome this limitation. Finally, using information from overnight signals from PSG to define pediatric OSA phenotypes constitutes another future working avenue.

6. Conclusions

Our new subject-based association network methodology has revealed pediatric OSA phenotypes with significantly different odds of recovery after treatment. Unlike previous research, our modularity approach was conducted without assuming any prior conditions on the number of phenotypes or their related data shape. Moreover, it is particularly useful when databases are large. Therefore, an important conclusion is that our method is an objective solution that could be extendable to other health problems, being those complex ones with multifactorial and large datasets, which might benefit the most. Moreover, we can draw two key conclusions specific to pediatric OSA. First, regardless of sex and therapeutic intervention, affected children aged 7 to 9 years, overweight or obese, with enlarged waist circumference (PH_{OSA2}) have reduced odds of normalizing their OAHI. Second, younger, non-obese females (5–6 years) with no enlarged neck (PH_{OSA3}) have higher odds of benefiting from adenotonsillectomy. Thus, our study has contributed to both refining modularity analysis and defining clinically useful pediatric OSA phenotypes, paving the way for more precise clinical management decisions.

Data availability statement

Raw data from the Children Adenotonsillectomy Trial analyzed during the current study are available in the National Sleep Research Resource repository (https://sleepdata.org/datasets/chat). Data generated during the current study are available from the corresponding author upon reasonable request.

Declaration of ethics

All participants and data were involved and recorded during the

Childhood Adenotonsillectomy Trial (CHAT) (clinical trial NCT00560859). The protocol of the original study followed the Declaration of Helsinki, with written consent obtained from all parents and assent from children over 7.

For this work, the Ethics Committee of the University of Valladolid approved the study (number PI-24–473-H) on the date 09/11/2024, ensuring that all procedures were performed in compliance with the norm established by the European Medicines Agency under EMA/CHMP/ICH/135/1995.

CRediT authorship contribution statement

Gonzalo C. Gutiérrez-Tobal: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Javier Gomez-Pilar:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Daniela Ferreira-Santos:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Pedro Pereira-Rodrigues:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Daniel Álvarez:** Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis. **Félix del Campo:** Writing – review & editing, Writing – original draft, Formal analysis. **David Gozal:** Writing – review & editing, Writing – original draft, Resources, Funding acquisition, Formal analysis. **Roberto Hornero:** Writing – review & editing, Writing – original draft, Supervision, Resources, Funding acquisition.

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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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cmpb.2025.109209.

References

[1] E. Dehlink, H. Tan, Update on paediatric obstructive sleep apnoea, J. Thorac. Dis. (2016).
[2] C.L. Marcus, L.J. Brooks, S.D. Ward, K.A. Draper, D. Gozal, A.C. Halbower, J. Jones, C. Lehmann, M.S. Schechter, S. Sheldon, others, Diagnosis and management of childhood obstructive sleep apnea syndrome, Pediatrics 130 (2012) e714–e755.
[3] E. Katz, C.D.-P. of the A. Thoracic, undefined 2008, Pathophysiology of pediatric obstructive sleep apnea, Atsjournals.Org 5 (2008) 253–262, https://doi.org/10.1513/pats.200707-111MG.
[4] M. Ohn, D. Sommerfield, J. Nguyen, D. Evans, R.N. Khan, N. Hauser, B.S. von Ungern-Sternberg, Predicting obstructive sleep apnoea and perioperative respiratory adverse events in children: role of upper airway collapsibility measurements, Br. J. Anaesth. 131 (6) (2023) 1043–1052, https://doi.org/10.1016/j.bja.2023.09.021.
[5] D. Gozal, M.B.-A. journal of respiratory and critical, undefined 2004, Increased upper airway collapsibility in children with obstructive sleep apnea during wakefulness, Atsjournals.OrgD Gozal, MM Burnside, Am. J. Respir. Crit. Care Med. 169 (2004) 163–167, https://doi.org/10.1164/rccm.200304-590OC, 2004, atsjournals.Org.
[6] D. Gozal, Sleep-disordered breathing and school performance in children, Pediatrics 102 (1998) 616–620, https://doi.org/10.1542/peds.102.3.616.
[7] R. Bhattacharjee, L. Kheirandish-Gozal, K. Spruyt, R.B. Mitchell, J. Promchiarak, N. Simakajornboon, D. Gozal, Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study, Am. j. respir. crit. care med. 182 (5) (2010) 676–683, https://doi.org/10.1164/rccm.200912-1930OC.
[8] D. Costa, Adenotonsillectomy for obstructive sleep apnea in obese children: a meta-analysis, J.Sagepub.Com 140 (2009) 455–460, https://doi.org/10.1016/j.otohns.2008.12.038.
[9] C.L. Marcus, R.H. Moore, C.L. Rosen, B. Giordani, S.L. Garetz, H.G. Taylor, R. B. Mitchell, R. Amin, E.S. Katz, R. Arens, S. Paruthi, H. Muzumdar, D. Gozal, N. H. Thomas, J. Ware, D. Beebe, K. Snyder, L. Elden, R.C. Sprecher, P. Willging, D. Jones, J.P. Bent, T. Hoban, R.D. Chervin, S.S. Ellenberg, S. Redline, A randomized trial of adenotonsillectomy for childhood sleep apnea, N. Engl. J. Med. (2013), https://doi.org/10.1056/nejmoa1215881.
[10] H.-L. Tan, A.G. Kaditis, Phenotypic variance in pediatric obstructive sleep apnea, Pediatr. Pulmonol. (2021).
[11] A. Zinchuk, H.K. Yaggi, Phenotypic subtypes of OSA: a challenge and opportunity for precision medicine, Chest 157 (2) (2020) 403–420, https://doi.org/10.1016/j.chest.2019.09.002.
[12] D. Ferreira-Santos, P.P. Rodrigues, Obstructive sleep apnea: a categorical cluster analysis and visualization, Pulmonology (2021), https://doi.org/10.1016/J.PULMOE.2021.10.003.
[13] D. Ferreira-Santos, P.P. Rodrigues, Enhancing obstructive sleep apnea diagnosis with screening through disease phenotypes: algorithm development and validation, JMIR Med Inf. 9 (6) (2021) E25124, https://doi.org/10.2196/25124. https://Medinform.Jmir.Org/2021/6/E25124, 9 (2021) e25124.
[14] S. Bailly, L. Grote, J. Hedner, S. Schiza, W.T. McNicholas, O.K. Basoglu, C. Lombardi, Z. Dogas, G. Roisman, A. Pataka, M.R. Bonsignore, J.L. Pepin, P. Steiropoulos, J. Verbraecken, T. Georgia, T. Penzel, L. Ondrej, I. Bouloukaki, S. Ryan, R.L. Riha, J.A. Kvamme, R. Tamisier, H. Hein, M.S. Tasbakan, P. Joppa, R. Staats, G. Parati, D. Marta, O. Marrone, M. Petitjean, T. Galic, T. Saaresranta, P. Sliwinski, G. Haralampos, M. Stefan, F. Francesco, R. Winfried, T. Dries, J. Buskova, Clusters of sleep apnoea phenotypes: a large pan-European study from the European Sleep Apnoea Database (ESADA), Respirology 26 (2021) 378–387, https://doi.org/10.1111/RESP.13969.
[15] B. Nguyen, A. Torres, C.W. Espinola, W. Sim, D. Kenny, D.M. Campbell, W. Lou, B. Kapralos, L. Beavers, E. Peter, A. Dubrowski, S. Krishnan, V. Bhat, Development of a data-driven digital phenotype profile of distress experience of healthcare workers during COVID-19 pandemic, Comput. Methods Programs Biomed. 240 (2023) 107645, https://doi.org/10.1016/J.CMPB.2023.107645.
[16] A. Procopio, G. Cesarelli, L. Donisi, A. Merola, F. Amato, C. Cosentino, Combined mechanistic modeling and machine-learning approaches in systems biology - A systematic literature review, Comput. Methods Programs Biomed. 240 (2023) 107681, https://doi.org/10.1016/J.CMPB.2023.107681.
[17] K. Spruyt, G. Verleye, D.G.- Sleep, undefined 2010, Unbiased categorical classification of pediatric sleep disordered breathing, Acad.Oup.Com (n.d.). https://academic.oup.com/sleep/article-abstract/33/10/1341/2454532 (accessed March 29, 2023).
[18] X. Liu, Y. Pamula, S. Immanuel, D. Kennedy, J. Martin, M. Baumert, Utilisation of machine learning to predict surgical candidates for the treatment of childhood upper airway obstruction, Sleep Breath. 26 (2022) 649–661, https://doi.org/10.1007/S11325-021-02425-W.
[19] M. Zaffanello, A. Pietrobelli, D. Gozal, L. Nosetti, S. La Grutta, G. Cilluffo, G. Ferrante, M. Piazza, G. Piacentini, Cluster analysis of home polygraphic recordings in symptomatic habitually-snoring children: a precision medicine perspective, Mdpi.Com (2022), https://doi.org/10.3390/jcm11195960.
[20] G.C. Gutiérrez-Tobal, J. Gomez-Pilar, L. Kheirandish-Gozal, A. Martín-Montero, J. Poza, D. Álvarez, F. del Campo, D. Gozal, R. Hornero, Pediatric sleep apnea: the overnight electroencephalogram as a phenotypic biomarker, Front. Neurosci. 15 (2021), https://doi.org/10.3389/FNINS.2021.644697/PDF.
[21] Z. He, K. Armoni Domany, L. Nava-Guerra, M.C.K. Khoo, M. Difrancesco, Y. Xu, K. McConnell, M.M. Hossain, R. Amin, Phenotype of ventilatory control in children with moderate to severe persistent asthma and obstructive sleep apnea, Sleep 42 (2019), https://doi.org/10.1093/SLEEP/ZSZ130.
[22] B. Lund, J. Ma, A review of cluster analysis techniques and their uses in library and information science research: k-means and k-medoids clustering, Perform. Meas. Metr. 22 (2021) 161–173, https://doi.org/10.1108/PMM-05-2021-0026/FULL/HTML.
[23] H.S. Park, C.H. Jun, A simple and fast algorithm for K-medoids clustering, Expert Syst. Appl. 36 (2009) 3336–3341, https://doi.org/10.1016/J.ESWA.2008.01.039.

[24] T.S. Madhulatha, Comparison between K-means and K-medoids clustering algorithms, Commun. Comput. Inf. Sci. 198 CCIS (2011) 472–481, https://doi.org/10.1007/978-3-642-22555-0_48.
[25] L. Van Nguyen, J.-P. Laval, P. Chainais, A. Iop, V.D. Blondel, J.-L. Guillaume, R. Lambiotte, E. Lefebvre, Fast unfolding of communities in large networks, J. Stat. Mech.: Theory Exp. 2008 (2008) P10008, https://doi.org/10.1088/1742-5468/2008/10/P10008.
[26] N. Jimeno, J. Gomez-Pilar, J. Poza, R. Hornero, K. Vogeley, E. Meisenzahl, T. Haidl, M. Rosen, J. Klosterkötter, F. Schultze-Lutter, Main symptomatic treatment targets in suspected and early psychosis: new insights from network analysis, Schizophr. Bull. 46 (2020) 884–895, https://doi.org/10.1093/SCHBUL/SBZ140.
[27] P.J. Gutiérrez-Díez, J. Gomez-Pilar, R. Hornero, J. Martínez-Rodríguez, M. A. López-Marcos, J. Russo, The role of gene to gene interaction in the breast's genomic signature of pregnancy, Sci. Rep. 11 (2021) 1–17, https://doi.org/10.1038/s41598-021-81704-8, 2021 11:1.
[28] G.H. Kim, J.W. Kim, K.H. Kim, H. Kang, J.Y. Moon, Y.M. Shin, S. Park, FT-GAT: graph neural network for predicting spontaneous breathing trial success in patients with mechanical ventilation, Comput. Methods Programs Biomed. 240 (2023) 107673, https://doi.org/10.1016/J.CMPB.2023.107673.
[29] S. Redline, R. Amin, D. Beebe, R.D. Chervin, S.L. Garetz, B. Giordani, C.L. Marcus, R.H. Moore, C.L. Rosen, R. Arens, D. Gozal, E.S. Katz, R.B. Mitchell, H. Muzumdar, H.G. Taylor, N. Thomas, S. Ellenberg, The Childhood Adenotonsillectomy Trial (CHAT): rationale, design, and challenges of a randomized controlled trial evaluating a standard surgical procedure in a pediatric population, Sleep 34 (2011) 1509–1517, https://doi.org/10.5665/SLEEP.1388.
[30] J. Decuzzi, S. Redline, A. Isaiah, Secondary analyses of the childhood adenotonsillectomy trial: a narrative review, JAMA Otolaryngol.-Head Neck Surg 148 (2022) 779–784, https://doi.org/10.1001/JAMAOTO.2022.1330.
[31] A. Isaiah, K.D. Pereira, G. Das, Polysomnography and treatment-related outcomes of childhood sleep apnea, Pediatrics 144 (2019), https://doi.org/10.1542/PEDS.2019-1097/76963.
[32] G.C. Gutiérrez-Tobal, D. Álvarez, L. Kheirandish-Gozal, F. del Campo, D. Gozal, R. Hornero, Reliability of machine learning to diagnose pediatric obstructive sleep apnea: systematic review and meta-analysis, Pediatr. Pulmonol. 57 (2022) 1931–1943, https://doi.org/10.1002/PPUL.25423.
[33] A. Martín-Montero, G.C. Gutiérrez-Tobal, L. Kheirandish-Gozal, F. Vaquerizo-Villar, D. Álvarez, F. Del Campo, D. Gozal, R. Hornero, Heart rate variability as a potential biomarker of pediatric obstructive sleep apnea resolution, Sleep 45 (2022), https://doi.org/10.1093/SLEEP/ZSAB214.
[34] K.J. Nishanth, V. Ravi, Probabilistic neural network based categorical data imputation, Neurocomputing 218 (2016) 17–25, https://doi.org/10.1016/J.NEUCOM.2016.08.044.
[35] S.M. Memon, R. Wamala, I.H. Kabano, A comparison of imputation methods for categorical data, Inf. Med. Unlocked 42 (2023) 101382, https://doi.org/10.1016/J.IMU.2023.101382.
[36] C.S. Melendres, J.M. Lutz, E.D. Rubin, C.L. Marcus, Daytime sleepiness and hyperactivity in children with suspected sleep-disordered breathing, Pediatrics 114 (3) (2004) 768–775, https://doi.org/10.1542/peds.2004-0730.
[37] R.D. Chervin, R.A. Weatherly, S.L. Garetz, D.L. Ruzicka, B.J. Giordani, E.K. Hodges, K.E. Guire, Pediatric sleep questionnaire: prediction of sleep apnea and outcomes, Arch. otolaryngol. head neck surg. 133 (3) (2007) 216–222, https://doi.org/10.1001/archotol.133.3.216.
[38] J.T. Flynn, D.C. Kaelber, C.M. Baker-Smith, D. Blowey, A.E. Carroll, S.R. Daniels, S. D. De Ferranti, J.M. Dionne, B. Falkner, S.K. Flinn, S.S. Gidding, C. Goodwin, M. G. Leu, M.E. Powers, C. Rea, J. Samuels, M. Simase, V.V. Thaker, E.M. Urbina, M. Simasek, K. Okechukwu, Clinical practice guideline for screening and management of high blood pressure in children and adolescents, Pediatrics 140 (2017), https://doi.org/10.1542/PEDS.2017-1904/38358.
[39] N.F. Krebs, J.H. Himes, D. Jacobson, T.A. Nicklas, P. Guilday, D. Styne, Assessment of child and adolescent overweight and obesity, Pediatrics 120 (2007) S193–S228, https://doi.org/10.1542/PEDS.2007-2329D.
[40] M. Antal, S. Péter, L. Biró, K. Nagy, A. Regöly-Mérei, G. Arató, É. Martos, Prevalence of underweight, overweight and obesity on the basis of body mass index and body fat percentage in Hungarian schoolchildren: representative survey in metropolitan elementary schools, Ann. Nutr. Metab. 54 (3) (2009) 171–176, https://doi.org/10.1159/000217813.
[41] N. Hatipoglu, M.M. Mazicioglu, S. Kurtoglu, M. Kendirci, Neck circumference: an additional tool of screening overweight and obesity in childhood, Eur. J. Pediatr. 169 (2010) 733–739, https://doi.org/10.1007/S00431-009-1104-Z.
[42] N.C.E.P. (US), Expert, Highlights of the Report of the Expert Panel On Blood Cholesterol Levels in Children and Adolescents, 1991. https://books.google.com/books?hl=en&lr=&id=X9OasG1NK90C&oi=fnd&pg=PA1&dq=National+Cholesterol+Education+Program+(NCEP)+Expert+Panel+on+Cholesterol+Levels+in+Children.&ots=1tpXMGURsP&sig=NcO0oTk_HzTHm4j09HzgU2VVOTU (accessed March 20, 2023).
[43] E. Dayyat, L. Kheirandish-Gozal, O.S. Capdevila, M.M.A. Maarafeya, D. Gozal, Obstructive sleep apnea in children: relative contributions of body mass index and adenotonsillar hypertrophy, Chest 136 (2009) 137–144, https://doi.org/10.1378/CHEST.08-2568.
[44] S.R. Mallampati, S.P. Gatt, L.D. Gugino, S.P. Desai, B. Waraksa, D. Freiberger, P. L. Liu, A clinical sign to predict difficult tracheal intubation; a prospective study, Can. Anaesth. Soc. J. 32 (1985) 429–434, https://doi.org/10.1007/BF03011357.
[45] H.D. McCarthy, K.V. Jarrett, H.F. Crawley, The development of waist circumference percentiles in British children aged 5.0–16.9 y, Eur. j. clin. nutr. 55 (10) (2001) 902–907, https://doi.org/10.1038/sj.ejcn.1601240.
[46] D. Borsboom, A.O.J. Cramer, V.D. Schmittmann, S. Epskamp, L.J. Waldorp, The Small World of Psychopathology, PLoS One 6 (2011), https://doi.org/10.1371/journal.pone.0027407.
[47] M. Jacomy, T. Venturini, S. Heymann, M. Bastian, ForceAtlas2, a continuous graph layout algorithm for handy network visualization designed for the Gephi software, PLoS One 9 (2014) e98679, https://doi.org/10.1371/JOURNAL.PONE.0098679.-e98679.
[48] H. Ahmadi, E. Fatemizadeh, A. Motie-Nasrabadi, Deep sparse graph functional connectivity analysis in AD patients using fMRI data, Comput. Methods Programs Biomed. 201 (2021) 105954, https://doi.org/10.1016/J.CMPB.2021.105954.
[49] J. Friedman, T. Hastie, R. Tibshirani, Additive logistic regression: a statistical view of boosting (With discussion and a rejoinder by the authors), Ht tps:/ /Doi. Org/ 10.1214 /Aos/1016218223 28 (2000) 337–407. https://doi.org/10.1214/AOS/1016218223.
[50] I.H. Witten, E. Frank, M.A. Hall, Data Mining: Practical Machine Learning Tools and Techniques, Morgan Kaufmann, USA, 2011.
[51] J.H. Friedman, Greedy function approximation: a gradient boosting machine, Ann. Stat. (2001), https://doi.org/10.2307/2699986.
[52] M. Imanguli, S.O. Ulualp, Risk factors for residual obstructive sleep apnea after adenotonsillectomy in children, Laryngoscope 126 (2016) 2624–2629, https://doi.org/10.1002/LARY.25979.
[53] D.J. Costa, R. Mitchell, Adenotonsillectomy for obstructive sleep apnea in obese children: a meta-analysis, Otolaryngol. - Head Neck Surg. 140 (2009) 455–460, https://doi.org/10.1016/J.OTOHNS.2008.12.038.
[54] P. Armañac-Julián, A. Martín-Montero, J. Lázaro, R. Hornero, P. Laguna, L. Kheirandish-Gozal, D. Gozal, E. Gil, R. Bailón, G. Gutiérrez-Tobal, Persistent sleep-disordered breathing independently contributes to metabolic syndrome in prepubertal children, Pediatr. Pulmonol. 59 (2024) 111–120, https://doi.org/10.1002/PPUL.26720.
[55] S. Romero-Peralta, C. Rubio, M. Castillo-García, P. Resano, M. Alonso, E. Solano-Pérez, L. Silgado, E. Viejo-Ayuso, L. Álvarez-Balado, O. Mediano, Obstructive sleep apnea in pediatrics and adolescent women: a systematic review of sex-based differences between girls and boys, Children 11 (2024) 1376, https://doi.org/10.3390/CHILDREN11111376/S1.
[56] P.E. Brockmann, D. Koren, L. Kheirandish-Gozal, D. Gozal, Gender dimorphism in pediatric OSA: is it for real? Respir. Physiol. Neurobiol. 245 (2017) 83–88, https://doi.org/10.1016/J.RESP.2016.11.010.
[57] M. Zreaqat, R. Hassan, A.R. Samsudin, Y. Stas, A. Hanoun, Tonsil size and mallampati score as clinical predictive factors for obstructive sleep apnea severity in children, J. Contemp. Dent. Pr. 22 (2021) 850–853, https://doi.org/10.5005/JP-JOURNALS-10024-3148.
[58] J. Wang, Y. Zhao, W. Yang, T. Shen, P. Xue, X. Yan, D. Chen, Y. Qiao, M. Chen, R. Ren, J. Ren, Y. Xu, Y. Zheng, J. Zou, X. Tang, Correlations between obstructive sleep apnea and adenotonsillar hypertrophy in children of different weight status, Sci. Rep. 9 (2019) 1–7, https://doi.org/10.1038/S41598-019-47596-5;SUBJMETA.