Automated screening of children with obstructive sleep apnea using nocturnal oximetry: An alternative to respiratory polygraphy in unattended settings

Running head (short title/subtitle): At-home automated screening of childhood OSAHS

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Abstract

Study Objectives: Nocturnal oximetry has emerged as a simple, readily available, and potentially useful diagnostic tool of childhood obstructive sleep apnea-hypopnea syndrome (OSAHS). However, at-home respiratory polygraphy (HRP) remains the preferred alternative to polysomnography (PSG) in unattended settings. The aim of this study was two-fold: (1) to design and assess a novel methodology for pediatric OSAHS screening based on automated analysis of at-home oxyhemoglobin saturation (SpO_2), and (2) to compare its diagnostic performance with HRP.

Methods: SpO_2 recordings were parameterized by means of time, frequency, and conventional oximetric measures. Logistic regression (LR) models were optimized using genetic algorithms (GAs) for 3 cutoffs for OSAHS: 1, 3, and 5 events per hour (e/h). The diagnostic performance of LR models, manual obstructive apnea-hypopnea index (OAHI) from HRP, and the conventional oxygen desaturation index ≥3% (ODI3) were assessed.

Results: For a cutoff of 1 e/h, the optimal LR model significantly outperformed both conventional HRP-derived ODI3 and OAHI: 85.5% Accuracy (HRP 74.6%; ODI3 65.9%) and 0.97 AUC (HRP 0.78; ODI3 0.75) were reached. For a cutoff of 3 e/h, the LR model achieved 83.4% Accuracy (HRP 85.0%; ODI3 74.5%) and 0.96 AUC (HRP 0.93; ODI3 0.85) whereas using a cutoff of 5 e/h, oximetry reached 82.8% Accuracy (HRP 85.1%; ODI3 76.7) and 0.97 AUC (HRP 0.95; ODI3 0.84).

Conclusions: Automated analysis of at-home SpO_2 recordings provide accurate detection of children with high pre-test probability of OSAHS. Thus, unsupervised nocturnal oximetry may enable a simple and effective alternative to HRP and PSG in unattended settings.

Keywords: childhood obstructive sleep apnea-hypopnea syndrome; at-home respiratory polygraphy; nocturnal oximetry; blood oxygen saturation; automated pattern recognition; genetic algorithms

Brief Summary box

Current Knowledge/Study Rationale. Increasing accessibility to the diagnosis of childhood obstructive sleep apnea-hypopnea syndrome (OSAHS) by means of simplified as well as effective techniques is a challenging task. Unattended nocturnal oximetry has emerged as a potentially useful tool even if well-validated algorithms are still sorely needed.

Study impact. We show that automated analysis of at-home blood oxygen saturation (SpO_2) from nocturnal oximetry is a reliable and accurate alternative to home-based respiratory polygraphy in the identification of OSAHS in children with high pre-test probability. Therefore, unattended oximetry could be an essential approach in order to develop abbreviated diagnostic tools for childhood OSAHS.

Introduction

In the last decades, pediatric obstructive sleep apnea-hypopnea syndrome (OSAHS) has emerged as a highly prevalent sleep-related disorder that may lead to major long-term adverse consequences in neurocognitive and behavioral development and in cardiovascular and metabolic function, reducing overall health and quality of life,[1,2] while increasing healthcare use and associated costs.[3] In-lab nocturnal polysomnography (PSG) is the current recommended test to reach a definitive diagnosis of OSAHS.[2,4] However, in most countries the availability of pediatric sleep laboratories is too limited to enable generalized implementation of PSG to match clinical needs.[4,5] Moreover, several factors decrease PSG effectiveness and utility as the gold standard for young children and infants, particularly due to the inconvenience it imposes for both parents and children who need to spend the whole night in a sleep laboratory, and the high aversion manifested by a proportion of children when multiple attached sensors are placed.[4,6]

Accordingly, the major question is whether simplified techniques may be explored to increase the accessibility to OSAHS diagnosis while still preserving overall effectiveness. In this context, there is ever growing research efforts on development and validation of cost-effective diagnostic methodologies, which include history and physical examination, sleep quality questionnaires, nocturnal oximetry, respiratory polygraphy (RP), daytime (nap) PSG, and ambulatory PSG.[2,4,7-11] The American Academy of Pediatrics reported in 2012 that these methods are helpful when patients test positive, but have a poor predictive value if results are negative.[2] Nevertheless, more recently published guidelines[11] for the diagnosis and management of childhood OSAHS still point out the importance of conducting an objective diagnostic test in every symptomatic child, *de facto* highlighting that further research is still needed to effectively simplify pediatric OSAHS diagnosis.

Despite robust published evidence showing that the apnea-hypopnea index is inherently underestimated,[12] RP is rapidly becoming a widely implemented alternative to PSG in clinical settings.[8,9,11] Furthermore, ambulatory RP at home (HRP) has been suggested as a valid approach in low resource settings when in-lab PSG is not available.[11] In this context, a recent study demonstrated the feasibility of HRP to evaluate children with OSAHS at home.[13] Similarly, nocturnal oximetry has long been proposed as a screening tool for pediatric OSAHS in high-risk patients due to its reliability, simplicity, and suitability for children.[14-16] In this regard, recent systematic reviews have reported that oximetry can provide essential information about OSAHS when PSG is not accessible.[11,17] Nevertheless, most of available studies have in fact analyzed the blood oxygen saturation (SpO_2) profiles that were recorded during attended in-lab PSG.[14,18-21] Therefore, there is still little if any evidence supporting the reliability of unattended oximetry. Moreover, further research is needed to compare the diagnostic performance of the 2 principal simplified diagnostic approaches, namely oximetry and HRP. In the present study, we hypothesized that single-channel SpO_2 from nocturnal oximetry will provide a non-inferior alternative to HRP in the diagnosis of childhood OSAHS when recorded at home without supervision of trained personnel.

Well-validated algorithms for the interpretation of oximetric recordings are essential to achieve both high positive and negative predictive values, especially for low cutoffs such as the ones traditionally employed in the PSG-based diagnosis of pediatric OSAHS.[17] Signal processing techniques provide useful tools to gain not only insights into the pathological mechanisms influencing biological recordings, but also to improve the diagnostic ability of single-channel recordings when searching for simplified approaches. In this study, we propose to apply genetic algorithms (GAs) in order to compose an

optimum model derived from oximetry data in childhood OSAHS diagnosis. GAs are optimization procedures from the field of evolutionary computation that are able to construct optimum models composed of the most relevant features characterizing the problem under study.[22] Previous studies have assessed their usefulness and applicability in the context of OSAHS diagnosis in adults.[23,24]

The aims of this study were two-fold. Firstly, to exhaustively characterize at-home SpO_2 recordings and to compose models aimed at classifying children showing high-risk for OSAHS. Secondly, to further assess our methodology by comparing our results with manual scoring from HRP and conventional ODI3. To achieve these goals, automated pattern recognition techniques were applied in order to improve diagnostic ability of SpO_2 as single screening tool for OSAHS in children.

Methods

Patients

A total of 50 children (27 boys and 23 girls) ranging 3–13 years old referred to the Respiratory Sleep Disorders Unit of the University Hospital of Burgos in Spain for clinical suspicion of OSAHS composed the population under study. The sample was representative of the clinical population commonly referred to our sleep unit. Patients were recruited regardless of the severity of their symptoms. Additionally, in order to avoid potential bias linked with the inclusion process only those children who arrived to the sleep unit on the days of the week selected using a random sequence participated in the study. Table 1 summarizes the demographic and clinical data of the cohort. All patients underwent in-laboratory PSG due to habitual snoring and/or witnessed breathing pauses during sleep reported by their parents or caretakers. Exclusion criteria were the following: children suffering from serious chronic medical and/or psychiatric additional conditions, those showing symptoms indicative of sleep disorders other than OSAHS, and those children who required urgent interventions. Children did not receive intranasal steroids, oral montelukast, or other pharmacological treatment for symptoms before they were recruited into the study. The Ethical Review Committee of the hospital approved the protocol (#CEIC 936) and informed consent to participate in the study was obtained prior to the enrollment.

Sleep studies

Sleep studies consisted of unattended HRP at children's home and a subsequent (18.2 ± 20.0 days after) in-laboratory PSG. HRP was carried out using a polygraph eXim Apnea Polygraph (Bitmed ®, Sibel S.A., Barcelona, Spain). The following channels were recorded: oronasal flow (thermistor) and pressure (nasal cannula), chest and abdominal effort (impedance plethysmography), body position, snoring, and heart rate and SpO_2 by means of pulse oximetry.

In-hospital supervised PSG was carried out from 22:00 to 08:00 using a digital polysomnograph Deltamed Coherence® 3NT version 3.0 (Diagniscan, S.A.U., Group Werfen, Paris, France). The following signals were recorded: EEG, right and left EOG, tibia and submental EMG, ECG, airflow (thermistor and nasal cannula), chest and abdominal movements (effort bands), oximetry, continuous transcutaneous carbon dioxide (PtcCO2), snoring, and body position.

HRP and PSG were scored manually by the same independent investigators, who were blinded to the goals of the study. The American Academy of Sleep Medicine criteria were

used to perform sleep staging and quantify cardiorespiratory events.[25] Apneas were defined as the absence of oronasal airflow lasting at least 2 respiratory cycles, whereas hypopneas were defined as decreases greater than or equal to 50% in the amplitude of the nasal pressure or alternative signal for more than 2 respiratory cycles, accompanied by a desaturation ≥3% or an arousal. The obstructive apnea-hypopnea index (OAHI) was defined as the number of obstructive apneas and hypopneas per hour of sleep in the PSG ($OAHI_{PSG}$) and per recorded hour in the HRP ($OAHI_{HRP}$), respectively. The $OAHI_{PSG}$ was used as gold standard for OSAHS diagnosis. In this study, the following common OAHI cutoff points were assessed[2,4]: 1, 3 and 5 events/hour (e/h). Table 1 shows OSAHS prevalence in the cohort according to these cutoffs, as well as the averaged respiratory indices from PSG, HRP and oximetry of the population under study.

SpO_2 recordings from HRP were originally recorded at a sampling rate of 100 Hz. Each recording was then saved to a separate file and subsequently processed offline by means of the proposed automated algorithms.

Oximetry Signal Processing

Unattended SpO_2 recordings from HRP were used to perform automated binary classification of children showing symptoms of sleep apnea as OSAHS negative or OSAHS positive according to PSG. The following signal processing stages were implemented: (i) feature extraction, using conventional oximetric indexes and measures from time and frequency domain analyses; (ii) feature selection, by means of GAs; and (iii) feature classification, by means of binary logistic regression (LR).

Feature extraction

This stage is aimed at obtaining as much information as possible from the SpO_2 signal. To achieve this, three complementary analyses were conducted to exhaustively characterize the influence of recurrent apneic events on the overnight SpO_2 profile: (i) statistical moments and nonlinear measures in time domain, (ii) statistical moments and spectral measures in frequency domain, and (iii) conventional oximetric indices. Finally, up to 18 features composed our initial feature set. Recent studies have shown the usefulness of these automated methods in the context of childhood OSAHS diagnosis from supervised in-lab pulse oximetry and airflow signals.[21,26] In the present study, a comprehensive analysis of input parameters and frequency bands was carried out to properly characterize the influence of OSAHS in SpO_2 unattended recordings at home.

First-to-fourth order statistical moments (*M1–M4*) were applied to characterize the data histogram in the time domain. SpO_2 data from non-OSAHS children is expected to be concentrated in a non-pathological limited region, whereas recurrent desaturations, typical of OSAHS, would change data distribution towards lower values. Mean (*M1t*), variance (*M2t*), skewness (*M3t*) and kurtosis (*M4t*) were applied to quantify central tendency, dispersion, asymmetry, and peakedness of the data histogram, respectively.[27] On the other hand, nonlinear methods are able to derive additional and complementary information from biomedical recordings. Hence, sample entropy (*SampEn*) and central tendency measure (*CTM*) were used in this study to quantify irregularity and variability of SpO_2 recordings, respectively.[28-31]

Features from the frequency domain provide information about the duration and the repetitive nature of apneic events. The power spectral density (PSD) was computed using the well-known Welch method, which is suitable for nonstationary signals.[26,31]

Then, a comprehensive analysis was conducted to properly derive a frequency region in the power spectrum related to the recurrence of desaturations in children. In order to obtain such a frequency band of interest, we searched for statistical significant differences in the PSD amplitude between OSAHS positive and OSAHS negative children for every single frequency component.[26] Mean (*M1fb*), variance (*M2fb*), skewness (*M3fb*) and kurtosis (*M4fb*) were applied to quantify central tendency, dispersion, asymmetry, and peakedness of the power spectrum in the band of interest, respectively. In addition, other conventional spectral measures were also derived from this frequency band: maximum (*PAb*) and minimum (*MAb*) amplitudes and the signal relative power (*RPb*).[26]

Finally, conventional oximetric indices commonly used in clinical practice were also included in the study. The oxygen desaturation index ≥3% (ODI3), the minimum (minSat) and average (AvgSat) saturation, and the cumulative time spent below 90% (CT90) and 95% (CT95) saturation were computed.

Feature selection and classification

A GA is an optimization procedure derived from evolutionary computation with ability to inspect efficiently the search space of variables or parameters that govern a model.[22,32] GAs encode a potential solution as a chromosome-like data structure and apply genetic operations (crossover and mutation) to make the population evolve iteratively in order to reach the optimal solution.[33] At each iteration, a particular group of chromosomes (parents) are selected from the whole population to generate the offspring, which will replace chromosomes in the new population.[22] The iterative optimization process is carried out in cycles called generations.

In this study, GAs were applied for feature selection to obtain the optimum input feature subset to a binary classifier in terms of classification performance.[23,24] Therefore, an individual or chromosome from the population is just a combination of features, i.e. a feature subset, from the initial oximetric feature space composed of 18 features. A 2-symbol binary codification was used to encode each feature subset or individual in the population, where the *k*-th bit denotes the absence (0) or the presence (1) of the *k*-th feature. Each individual has *p* bits, where *p* is the number of features in the original set.[34] The classification accuracy of a binary LR model was the performance metric used to drive parent selection. A bootstrapping approach was applied to compute the accuracy of each individual across the whole iteration process in order to deal with overfitting.[35] In the present study, probability of crossover (P_c) values ranging from 0.5 to 0.9 and probability of mutation (P_m) values ranging from 0.01 to 0.09 were used to introduce variations into the offspring along 100 generations.[23,24,33,34] The elite or percentage of the best individuals in the old population preserved after each generation were also varied between 0 and 25%.[23,24] For each cutoff point for childhood OSAHS (1, 3, and 5 e/h), the optimum feature subset from the last generation was selected in terms of diagnostic performance.

LR was used for binary classification, where input patterns are classified into one of two mutually exclusive classes (OSAHS negative *vs.* OSAHS positive). LR classifiers assign an input vector to the class with the maximum a posteriori probability according to a probability density for the response variable modeled by a Bernoulli distribution.[36] The maximum likelihood criterion is used to optimize coefficients of the independent input features in the logistic model.[36]

Statistical analyses

IBM SPSS Statistics version 20 (Chicago, IL) was used to perform statistical analyses. Normality and homoscedasticity analyses revealed that oximetric features derived from the population under study were not normally distributed and variances were unequal. Therefore, descriptive analysis of features was presented in terms of their median and interquartile range. In addition, the non-parametric Mann-Whitney *U* test was applied to search for statistical significant differences between OSAHS negative and OSAHS positive groups. A *p*-value < 0.05 was considered significant.

Matlab R2015a was used to implement feature extraction, selection, and classification stages. Diagnostic performance was assessed by means of sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-), accuracy (Acc), and area under the receiver operating characteristics (ROC) curve (AUC). A bootstrapping approach was carried out in order to ensure the statistical validity of our results since it is particularly useful to estimate statistics in small-sized datasets. The number of bootstrap samples was set to 1000 because it ensures a proper estimation of the 95% confidence interval (CI95%).[26]

Results

Optimization of the frequency band of interest and nonlinear measures

Figs. 1 (a), (c), and (e) show the averaged power spectrum of OSAHS negative and OSAHS positive groups for each cutoff point under study. OSAHS positive children showed greater spectral power than OSAHS negative ones in a very low frequency band (<0.1 Hz) linked with the recurrence and duration of OSAHS typical desaturations, which agrees with previous studies.[21] Furthermore, Figs. 1 (b), (d), and (f) show the *p*-value *vs.* frequency plots to define quantitatively the band of interest. In order to retain a single frequency band regardless of the threshold for positive OSAHS, the broader region showing significant statistical differences between OSAHS groups common to all the cutoffs were selected: 0.02136 – 0.03357 Hz.

Input parameter optimization of nonlinear methods was also carried out in terms of significant statistical differences between OSAHS negative and OSAHS positive groups. Regarding *SampEn* optimization, the recommended *m* = 1 and 2 and *r* = 0.1, 0.15, 0.2, and 0.25 times the standard deviation (SD) of the time series were assessed [Richmann00]. No significant differences were reached for OAHI = 1 e/h (all *p*-values > 0.1) while the greatest differences (*p*-values < 0.05) for OAHI = 3 and 5 e/h were obtained using *m* = 1 and *r* = 0.1 SD. Thus, *SampEn* was computed using *m* = 1 and *r* = 0.1 SD for all the cutoffs. Regarding *CTM*, the greatest significant differences were achieved using rho = 1.1 for all cutoffs under study. Therefore, we finally obtained a single initial feature set independent of the diagnostic threshold for OSAHS, which demonstrates the consistency of the proposed methodology.

Feature extraction

Table 2 shows the median and interquartile range of every feature involved in the study for each cutoff. Regarding features in the time domain, OSAHS positive children showed overall lower *M1t* (central tendency), higher *M2t* (dispersion), higher (less negative) *M3t* (asymmetry), lower *M4t* (peakedness), higher *SampEn* (irregularity), and lower *CTM* (higher variability) than OSAHS negative children for all the cutoffs. For this clinical threshold for OSAHS, just the *CTM* achieved significant statistical differences in the time

domain. For cutoffs 3 and 5 e/h *M2t*, *M4t*, *SampEn*, and *CTM* reached significant differences. Regarding features in the frequency domain, OSAHS positive children showed significantly higher (p<0.05) *M1f* (mean spectral power), *PAb* (maximum amplitude), *RPb* (relative power), and *MAb* (minimum amplitude) in the frequency band of interest than OSAHS negative children for all cutoffs under study. Finally, conventional oximetric indexes showed an irregular behavior using different clinical thresholds for OSAHS. Only *ODI3* achieved significant statistical differences between OSAHS positive and OSAHS negative children for all cutoffs. Similarly, OSAHS positive children showed significantly higher *CT95* than OSAHS negative when using 3 and 5 e/h as cutoffs for OSAHS.

Feature selection and classification

GAs automatically selected an optimum feature subset for each clinical threshold for positive OSAHS. Table 3 shows the variables included in the proposed optimum feature subsets. A total of 6 variables were automatically selected for cutoffs equal to 1 e/h (*M1t*, *M2t*, *M3t*, *M4t*, *M3fb*, *RPb*) and 3 e/h (*M1t*, *M2t*, *M4fb*, *PAb*, *RPb*, and *ODI3*), whereas 7 features composed the optimum set for a cutoff equal to 5 e/h (*M3t*, *M4fb*, *PAb*, *MAb*, *RPb*, *SampEn*, *ODI3*). It is noteworthy that all the proposed signal processing approaches (time, spectral, and conventional indexes) were represented in these optimum subsets. Table 4 summarizes the diagnostic performance of the LR models composed of these optimal subsets, as well as the performance achieved by the manual OAHI from HRP and the conventional ODI3 alone. Our approach was the most accurate when a cutoff of 1 e/h was used to diagnose childhood OSAHS. The optimum LR model from GAs achieved 85.5% Acc (CI95% 66.4-96.6), which significantly outperformed both the OAHI from HRP (74.6% Acc, CI95% 57.0-88.9) and the conventional ODI3 (65.9% Acc, CI95% 47.5-83.0). When the clinical threshold for positive OSAHS is increased to 3 e/h, our approach reached 83.4% Acc (CI95% 64.2-96.8), which again significantly outperformed the single ODI3 (74.5% Acc, CI95% 58.5-88.7) and almost equaled the manual OAHI from conventional HRP (85.0% Acc, CI95% 71.6-95.5). Finally, the optimum LR model for a cutoff of 5 e/h achieved 82.8% Acc (CI95% 64.5-96.3), which is still higher than that obtained with ODI3 (76.7% Acc, CI95% 59.2-90.9) but slightly lower than the performance reached with HRP (85.1% Acc, CI95% 71.6-95.9). It is important to note that our proposal always reached higher LR+ and AUC than HRP and ODI3 whatever the cutoff.

Discussion

In this study, the diagnostic performance of an automated simplified method based on unattended oximetry was assessed as a single tool for diagnosis of childhood OSAHS. Single-channel SpO_2 recordings from at-home oximetry were automatically analyzed. In-hospital complete PSG was used as the gold standard and three common clinical cutoff points for childhood OSAHS (OAHI of 1, 3, and 5 e/h) were employed to assess the consistency of the proposed methodology. Additionally, two indices from alternative simplified techniques, commonly proposed for OSAHS detection when in-lab PSG is not available, were analyzed for comparison purposes: manual OAHI from HRP and conventional ODI3 from oximetry.

In our aim to maximize the diagnostic ability of oximetry, a wide initial feature set was composed. As expected, spectral and nonlinear features, as well as ODI3, exhibited statistically significant differences between OSAHS positive and OSAHS negative

children, which agrees with previous studies.[21,26] Then, automatic feature selection was accomplished by means of GAs in order to exhaustively analyze the feature space, and obtain the optimum feature subset for each cutoff. We found that a proper selection of variables provided complementary information that improves the diagnostic ability of oximetry. It is noteworthy that these optimum feature subsets showed a consistent composition when considering contiguous cutoffs for childhood OSAHS: optimum subsets using cutoffs equal to 1 and 3 e/h share 50% of features (*M1t*, *M2t*, and *RPb*) whereas subsets from cutoffs equal to 3 and 5 e/h share even more than 50% (*M4fb*, *PAb*, *RPb*, and *ODI3*). In addition, *RPb* was included in all of the optimum feature subsets, which demonstrates the relevancy and consistency of the frequency band of interest identified in this study.

Using the GAs-derived optimum subsets, our LR models from unattended oximetry significantly outperformed the conventional ODI3 in terms of Acc and AUC for all the cutoffs. Furthermore, our proposed models reached similar Acc and higher AUC than HRP for cutoffs equal to 3 e/h (83.4% vs. 85.0% Acc and 0.96 vs. 0.93 AUC) and 5 e/h (82.8% vs. 85.1% Acc and 0.97 vs. 0.95 AUC) and even outperformed manual scoring of HRP using a low cutoff equal to 1 e/h (85.5% vs. 74.6% Acc and 0.97 vs. 0.78 AUC). Noteworthy is the fact that manual rather than automated scoring of HRP is considered the preferred alternative to PSG when the latter is not available. Conversely, our proposed methodological approach is fully automated, which would markedly reduce the workload of specialized technicians, and improve consistency. Finally, it is important to point out that all the optimum models from oximetry reached higher LR+ than HRP and single ODI3 whatever the OAHI cutoff selected, which is an essential characteristic for screening tests. This is particularly relevant in the context of pediatric OSAHS since children are referred to the sleep unit because of existing symptoms of OSAHS.

Overall, we observed that the higher the cutoff, the lower the performance of our automated LR models from unattended oximetry. In contrast, using conventional manual OAHI and ODI3, the performance of these approaches increased when the cutoff moved from 1 to 5 e/h. Notwithstanding, it is important to highlight that conventional ODI3 showed the common imbalance of unattended oximetry, with higher specificity due to underestimation of the severity of the disease, whereas automated LR models showed higher sensitivity than specificity for a clinical threshold of 1 e/h for positive OSAHS and balanced sensitivity and specificity pairs for cutoffs equal to 3 and 5 e/h. Thus, the maximum benefit of our automated methodology in terms of simplicity and screening capability can be achieved when using lower cutoffs for positive OSAHS. Since most sleep laboratories use the cutoff of 1 e/h during interpretation of PSG,[2] the features that emerged in our automated approaches in unattended oximetry further stress the unique superiority afforded by the proposed methodology.

Several diagnostic alternatives to PSG have been proposed to expand the accessibility of children to diagnosis and treatment in a timely manner. Quite similar to in-lab PSG in terms of percentage of successful recordings, unattended PSG at home has shown similar success rates among school-aged children, but much greater inconsistencies in younger children.[2] Similarly, nap-based PSG studies report high specificity but low sensitivity.[2,13] Although not intrusive and a priori simple, clinical history and sleep quality questionnaires lack the required diagnostic accuracy, precluding their use as a routine diagnostic tool for OSAHS in children.[4,11,13] However, RP-based approaches have become increasingly accepted as an effective diagnostic method when carried out in a clinical setting both in adults and children.[11,37] Furthermore, ambulatory HRP has been considered a feasible means of diagnosing OSAHS when PSG is not available in a

recent report of the European Respiratory Society.[11] In this regard, Alonso-Álvarez *et al.* recently illustrated the effectiveness of HRP for OSAHS diagnosis in an unsupervised setting.[13] Similarly, nocturnal oximetry has emerged as a simple, low-cost, and less intrusive alternative to PSG, RP, or HRP to help in childhood OSAHS diagnosis.[14,17] In the present study, our results suggest that automated analysis of single-channel SpO_2 from unattended oximetry may be as accurate as HRP in the diagnosis of OSAHS.

This is an obvious departure from previous perceptions regarding oximetry. Indeed, oximetry has been characterized as achieving high specificity but low sensitivity.[2] Nevertheless, several studies have shown the usefulness and effectiveness of common oximetric indices based on the number of overnight desaturations in the context of pediatric OSAHS, such as the ODI[19,20,38] and, more recently, the quantification of clusters of desaturations.[18,39] On the other hand, only a few studies have been carried out at home.[38,39] In such unattended settings, both the McGill oximetry score and the ODI ≥4% (ODI4) achieved high night-to-night agreement (mean difference 0.32, limits of agreement -8.00 to 8.64 e/h).[38,39] Regarding the diagnostic performance, ODI4 achieved poor performance (67% Se and 60% Sp) for detecting moderate OSAHS (OAHI≥5 e/h).[38] Our proposal based on unsupervised oximetry clearly outperformed the results reported in this study. Recent approaches analyze the pulse rate (PR) signal from pulse oximetry[40] or combine data derived from the SpO_2 signal with other sources of information to improve diagnostic ability, such as the PR signal from the own pulse oximetry recording[21] or the airflow signal.[26] In the study by Sahadan *et al.*,[40] PR increases of 15 bpm (PRI-15) from ambulatory pulse oximetry were scored automatically. This PR-derived index reached a sensitivity ranging 16%-39% and specificity ranging 79%-97% for a OSAHS cutoff ≥1 e/h. In the study by Garde *et al.*,[21] time, spectral and conventional measures from both SpO_2 and PR recordings obtained by means of a pulse oximeter sensor attached to a smartphone were combined using a linear classifier. These investigators reported 88.4% sensitivity and 83.6% specificity for a AHI cutoff of 5 e/h. Although a portable device was used, all recordings were carried out in the hospital. Finally, in a recent study by our own group, ODI3 from oximetry was combined with spectral measures from the airflow signal using a LR model.[26] All the recordings were obtained during unattended HRP. A sensitivity of 85.9%, a specificity of 87.4%, and an accuracy of 86.3% were reached for a cutoff of 3 e/h.

Some limitations should be taken into account. First of all, the population cohort evaluated herein should be expanded in order to draw more generalizable conclusions. A larger dataset would allow a better optimization of the feature space using GAs since this feature selection method maximizes its usefulness when working with high-dimensional spaces and a large number of instances. Nevertheless, in order to address this issue, a bootstrapping approach was carried out both for feature selection and classification. This procedure is known to provide good estimates from small datasets. Similarly, a wider dataset would let us a better optimization of all input parameters from nonlinear and spectral features, including the frequency band of interest for childhood OSAHS. However, our results revealed quite consistent features and a frequency band linked with recurrent desaturations characteristic of OSAHS. An additional drawback that could affect our results may reside in undesirable differences related to potential temporal changes of the disease. As such, the time interval between in-hospital PSG and at-home RP was set to be lower than 2 months, a timeframe that is clearly shorter than the actual waiting times for a pediatric sleep study in our sleep unit. Nevertheless, even this shorter interval could lead to potential differences between the reference OAHI and oximetry from in-lab PSG and OAHI and oximetry from RP at patient's home due to the widely known night-to-night variability of OSAHS.

The main goal for assessing abbreviated test for pediatric OSAHS just based on oximetry is to use portable oximeters at the patients' home instead of complete PSG or RP equipment. In the present investigation, we analyzed SpO_2 recordings from unattended RP recordings. Therefore, potential differences between oximetric profiles from overnight RP and from a portable standalone device could influence our results. Sampling rates, resolution, and averaging time settings may impose significant influence on the collected data, which could affect time response and reproducibility of SpO_2.[21,41] Notwithstanding, previous studies demonstrated that our approach could be easily optimized for any technical setting in order to achieve a high diagnostic performance.[24,42] In addition, current high-performance oximeters already match technical characteristics of in-hospital equipment overcoming previous limitations of portable devices due to restrictions in memory storage capability and battery life. Finally, the proposed methodology presented herein aims to confirm or discard the presence of OSAHS, i.e. to perform binary classification. Although three commonly used OAHI cutoff points in clinical practice were assessed for positive OSAHS (1, 3, and 5 e/h), it would be very useful to couple the current novel approach to develop and implement a pattern recognition methodology aimed at classifying patients in the 4 common categories of severity (no disease, mild, moderate, and severe) or estimating the actual PSG-derived OAHI of each patient under study.

Conclusions

To the best of our knowledge, this is the first study comparing the diagnostic performance of unattended oximetry and HRP as alternative to standard in-lab PSG in the context of childhood OSAHS. Automated analysis of single-channel at-home SpO_2 recordings emerged as a useful and a reliable alternative to manual scoring of HRP in the detection of children with high clinical suspicion of suffering from OSAHS, particularly when using low OAHI cutoff points for a positive diagnosis of the disease. Furthermore, our optimum LR models significantly outperformed conventional ODI3 for all the cutoffs under study using the same dataset. Therefore, our results suggest that automated processing of the SpO_2 signal could be an essential approach in order to develop abbreviated as well as accurate diagnostic tools for childhood OSAHS in unsupervised settings.

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Tables

Table 1 – Demographic and clinical characteristics and polygraphic indexes of the pediatric population under study.

Measure	**Median [IQR]**
Subjects (n)	50
Age (years)	4 [4, 6]
Males (n)	27 (54.0%)
BMI (kg/m^2)	16.42 [15.00, 17.53]
Recording time (h)	9.05 [8.40, 9.27]
$OAHI_{PSG}$ (e/h)	3.56 [1.21, 17.28]
$OAHI_{HRP}$ (e/h)	5.15 [1.27, 9.79]
$ODI3_{HRP}$ (e/h)	1.89 [0.84, 6.03]
Prevalence	
$OAHI_{PSG} \geq 1$ (e/h)	40 (80%)
$OAHI_{PSG} \geq 3$ (e/h)	26 (52%)
$OAHI_{PSG} \geq 5$ (e/h)	22 (44%)

IQR: interquartile range; BMI: body mass index; e/h: events per hour; $OAHI_{PSG}$: obstructive apnea-hypopnea index from in-lab PSG; $OAHI_{HRP}$: obstructive apnea-hypopnea index from at-home RP; $ODI3_{HRP}$: oxygen desaturation index of 3% from at-home RP

Table 2 – Median and interquartile range for the whole OSAHS negative and OSAHS positive groups according to the different cutoffs under study for every oximetric feature in the original feature space.

	Cutoff $OAHI_{PSG}$ = 1 e/h			**Cutoff $OAHI_{PSG}$ = 3 e/h**			**Cutoff $OAHI_{PSG}$ = 5 e/h**		
	OSAHSn Median [IQR]	**OSAHSp Median [IQR]**	***p***	**OSAHSn Median [IQR]**	**OSAHSp Median [IQR]**	***p***	**OSAHSn Median [IQR]**	**OSAHSp Median [IQR]**	***p***
Time Domain									
M1t	97.3 [96.7, 97.6]	97.5 [96.8, 97.9]	0.536	97.5 [97.1, 98.0]	97.3 [96.6, 97.7]	0.171	97.5 [97.0, 98.0]	97.3 [96.5, 97.7]	0.261
M2t	0.29 [0.18, 0.43]	0.49 [0.27, 0.76]	0.163	0.30 [0.18, 0.48]	0.57 [0.40, 1.20]	<0.05	0.32 [0.18, 0.59]	0.54 [0.40, 1.20]	<0.05
M3t	-2.49 [-3.32, -1.44]	-1.68 [-2.30, -0.97]	0.118	-2.14 [-3.31, -1.18]	-1.57 [-2.11, -0.87]	0.073	-1.99 [-3.19, -1.16]	-1.57 [-2.11, -0.90]	0.194
M4t	91.3 [42.3, 154.9]	41.0 [15.0, 102.9]	0.083	88.1 [34.1, 156.5]	29.8 [8.0, 72.6]	<0.05	70.5 [31.2, 146.3]	29.8 [6.3, 72.6]	<0.05
SampEn ($x10^{-4}$)	8.75 [6.46, 10.5]	11.11 [7.79, 16.50]	0.118	8.88 [6.07, 11.11]	13.61 [9.99, 17.56]	<0.05	9.30 [6.43, 12.88]	12.39 [9.99, 19.25]	<0.05
CTM ($x10^{4}$)	9999.93 [9999.86, 9999.95]	9999.82 [9999.57, 9999.91]	<0.05	9999.94 [999987, 9999.96]	9999.68 [9999.43, 9999.82]	<<0.05	9999.93 [9999.83, 9999.96]	9999.72 [9999.41, 9999.82]	<<0.05
Frequency Domain									
M1fb ($x10^{-2}$)	0.63 [0.56, 0.68]	0.77 [0.67, 0.89]	<0.05	0.67 [0.62, 0.74]	0.78 [0.69, 0.92]	<0.05	0.68 [0.62, 0.77]	0.78 [0.69, 0.92]	<0.05
M2fb ($x10^{-6}$)	1.41 [0.72, 2.13]	2.25 [1.08, 3.48]	0.057	1.71 [1.17, 2.37]	2.42 [1.00, 5.56]	0.218	1.71 [1.02, 2.37]	2.74 [1.12, 5.56]	0.120
M3fb	0.55 [030, 1.22]	0.30 [-0.17, 0.68]	0.136	0.41 [0.27, 0.73]	0.15 [-0.22, 0.78]	0.210	0.38 [0.12, 0.59]	0.21 [-0.25, 0.78]	0.500
M4fb	-0.71 [-0.99, 1.78]	-0.67 [-1.23, -0.11]	0.654	-0.82 [-1.28, -0.12]	-0.57 [-1.22, 0.06]	0.749	-0.85 [-1.35, -0.24]	-0.42 [-1.19, 0.13]	0.333
PAb ($x10^{-2}$)	0.92 [0.67, 0.99]	1.05 [0.93, 1.22]	<0.05	0.95 [0.83, 1.05]	1.07 [0.93, 1.27]	<0.05	0.96 [0.83, 1.05]	1.12 [0.93, 1.27]	<0.05
MAb ($x10^{-2}$)	0.45 [0.39, 0.53]	0.53 [0.47, 0.63]	<0.05	0.49 [0.42, 0.54]	0.56 [0.50, 0.67]	<0.05	0.49 [0.42, 0.56]	0.56 [0.50, 0.67]	<0.05
RPb	0.11 [0.10, 0.12]	0.13 [0.11, 0.15]	<0.05	0.11 [0.11, 0.13]	0.13 [0.12, 0.16]	<0.05	0.12 [0.11, 0.13]	0.13 [0.12, 0.16]	<0.05
Conventional indexes									
ODI3	0.91 [0.34, 1.67]	2.73 [0.93, 6.76]	<0.05	0.87 [0.45, 1.92]	5.90 [1.82, 9.08]	<<0.05	1.04 [0.52, 2.18]	6.1 [1.95, 9.55]	<<0.05
MinSat	91.5 [90.0, 92.0]	90.0 [88.0, 92.0]	0.282	91.0 [90.0, 92.0]	89.0 [87.0, 90.0]	<0.05	91.0 [88.5, 92.0]	89.5 [87.0, 90.0]	0.052
AvgSat	97.0 [96.0, 98.0]	97.0 [96.4, 98.0]	0.804	97.0 [97.0, 98.0]	97.0 [96.0, 97.7]	0.212	97.0 [97.0, 98.0]	97.0 [96.0, 97.7]	0.255
CT90	0 [-, -]	0.0 [0.0, 0.2]	0.260	0 [-, -]	0.05 [0.0, 0.69]	<0.05	0.0 [0.0, 0.07]	0.02 [0.0, 0.69]	0.120
CT95	0.34 [0.11, 0.77]	0.98 [0.23, 3.73]	0.139	0.36 [0.08, 1.17]	1.62 [0.57, 7.18]	<0.05	0.42 [0.08, 1.41]	1.41 [0.57, 7.18]	<0.05

$OAHI_{PSG}$: obstructive apnea-hypopnea index from in-lab PSG; OSAHS: obstructive sleep apnea-hypopnea syndrome; OSAHSn: OSAHS negative group; OSAHSp: OSAHS positive group; IQR: interquartile range; *p*: *p*-value from the Mann-Whitney nonparametric test; M1t – M4t: mean (M1), variance (M2), skewness (M3), and kurtosis (M4) in the time domain; SampEn: sample entropy; CTM: central tendency measure; M1fb – M4fb: mean (M1), variance (M2), skewness (M3), and kurtosis (M4) in frequency band of interest; PAb: peak amplitude in frequency band of interest; MAb: minimum amplitude in frequency band of interest; RPb: relative power in frequency band of interest; ODI3: oxygen desaturation index greater than or equal to 3%; MinSat: minimum saturation; AvgSat: average saturation; CT90 – CT95: cumulative time with a saturation below 90% and 95%, respectively.

Table 3 – Optimum feature subsets from the GAs-based feature selection approach for each cutoff for childhood OSAHS under study.

Cutoff for childhood OSAHS	# variables	Optimum features
$OAHI_{PSG}$ = 1 e/h	6	*M1t*, *M2t*, *M3t*, *M4t*, *M3fb*, *RPb*
$OAHI_{PSG}$ = 3 e/h	6	*M1t*, *M2t*, *M4fb*, *PAb*, *RPb*, *ODI3*
$OAHI_{PSG}$ = 5 e/h	7	*M3t*, *M4fb*, *PAb*, *MAb*, *RPb*, *SampEn*, *ODI3*

OSAHS: obstructive sleep apnea-hypopnea syndrome; $OAHI_{PSG}$: obstructive apnea-hypopnea index from in-lab PSG; M1t – M4t: mean (M1), variance (M2), skewness (M3), and kurtosis (M4) in the time domain; SampEn: sample entropy; M3fb, M4fb: skewness (M3) and kurtosis (M4) in frequency band of interest; PAb: peak amplitude in frequency band of interest; MAb: minimum amplitude in frequency band of interest; RPb: relative power in frequency band of interest; ODI3: oxygen desaturation index greater than or equal to 3%.

Table 4 – Diagnostic performance using a bootstrap approach of each LR model composed of optimum feature subsets from genetic algorithm feature selection.

Cutoff $OAHI_{PSG}$ = 1 e/h

	Se (%)	Sp (%)	PPV (%)	NPV (%)	LR+	LR-	Acc (%)	AUC
$LR_{HOX}(6)$	89.6	71.5	92.5	66.8	4.37	0.18	85.5	0.97
	(63.8, 1)	(28.3, 1)	(78.2, 1)	(16.6, 1)	(1.88, 8.23)	(0, 0.64)	(66.4, 96.6)	(0.89, 1)
$OAHI_{HRP}$	71.3	88.2	96.1	43.4	3.62	0.35	74.6	0.78
	(52.5, 90.4)	(43.8, 1)	(80.2, 1)	(17.5, 72.7)	(1.64, 7.07)	(0.12, 0.78)	(57.0, 88.9)	(0.63, 0.91)
$ODI3_{HRP}$	64.3	73.1	91.6	33.8	2.28	0.52	65.9	0.75
	(39.6, 92.3)	(21.0, 1)	(74.7, 1)	(7.4, 64.0)	(1.02, 5.13)	(0.18, 1.06)	(47.5, 83.0)	(0.58, 0.90)

Cutoff $OAHI_{PSG}$ = 3 e/h

	Se (%)	Sp (%)	PPV (%)	NPV (%)	LR+	LR-	Acc (%)	AUC
$LR_{HOX}(6)$	82.9	84.4	86.2	82.2	7.40	0.22	83.4	0.96
	(56.5, 1)	(51.5, 1)	(61.3, 1)	(57.4, 1)	(2.39, 15.78)	(0, 0.64)	(64.2, 96.8)	(0.88, 1)
$OAHI_{HRP}$	86.1	84.2	86.1	85.6	6.7	0.16	85.0	0.93
	(59.8, 1)	(59.6, 1)	(65.2, 1)	(63.3, 1)	(2.39, 14.96)	(0, 0.42)	(71.6, 95.5)	(0.86, 0.98)
$ODI3_{HRP}$	71.8	77.6	79.7	72.8	3.93	0.36	74.5	0.85
	(43.6, 98.2)	(38.5, 1)	(53.4, 1)	(49.2, 97.4)	(1.47, 11.81)	(0.03, 0.72)	(58.5, 88.7)	(0.73, 0.94)

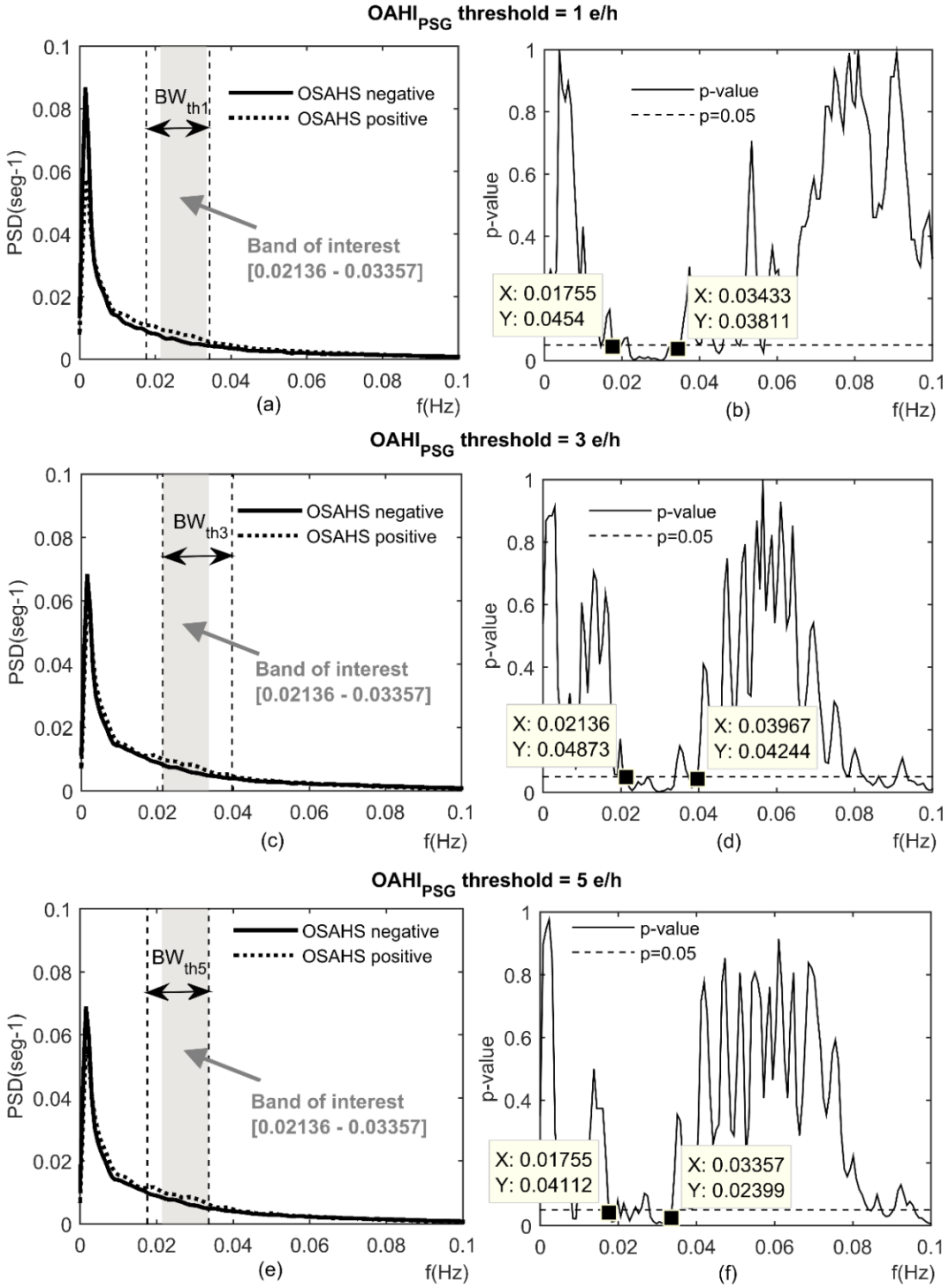
Cutoff $OAHI_{PSG}$ = 5 e/h

	Se (%)	Sp (%)	PPV (%)	NPV (%)	LR+	LR-	Acc (%)	AUC
$LR_{HOX}(7)$	82.2	83.6	80.8	85.9	8.48	0.23	82.8	0.97
	(54.1, 1)	(55.7, 1)	(52.8, 1)	(62.7, 1)	(2.35, 17.48)	(0, 0.64)	(64.5, 96.3)	(0.89, 1)
$OAHI_{HRP}$	83.6	86.4	84.5	87.8	7.04	0.19	85.1	0.95
	(58.8, 1)	(59.2, 1)	(57.2, 1)	(71.5, 1)	(2.31, 17.16)	(0, 0.44)	(71.6, 95.9)	(0.87, 0.99)
$ODI3_{HRP}$	72.7	79.9	76.7	79.4	4.80	0.34	76.7	0.84
	(45.9, 97.3)	(45.9, 1)	(47.4, 1)	(61.4, 97.9)	(1.55, 14.81)	(0.03, 0.68)	(59.2, 90.9)	(0.71, 0.95)

$OAHI_{PSG}$: obstructive apnea-hypopnea index from in-lab PSG; e/h: events per hour; LR_{HOX}: logistic regression model from at-home oximetry; $OAHI_{HRP}$: obstructive apnea-hypopnea index from at-home respiratory polygraphy; $ODI3_{HRP}$: oxygen desaturation index of 3% from at-home respiratory polygraphy; Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR- negative likelihood ratio; Acc: accuracy; AUC: area under the receiver operating characteristic curve.

Figures

Figure 1 – Averaged PSD functions of the OSAHS negative and the OSAHS positive groups from the whole population under study and *p*-value *vs.* frequency plots looking for significant statistical differences between groups (p <0.05) for each cutoff: (a)-(b) $OAHI_{PSG}$≥1 e/h, (c)-(d) $OAHI_{PSG}$≥3 e/h, (e)-(f) $OAHI_{PSG}$≥5 e/h. The region between dashed lines in figures from the left panel represents the frequency region in which significant differences were achieved for each particular cutoff (BW_{thx}), whereas the grey region shows the single frequency band of interest.



$OAHI_{PSG}$: obstructive apnea-hypopnea index from in-lab PSG; e/h: events per hour; PSD: power spectral density; BW_{thx}: spectral band of interest reaching statistical significant differences for the specified particular cutoff; OSAHS: obstructive sleep apnea-hypopnea syndrome; OSAHS negative: OSASH negative group; OSAHS positive: OSASH positive group;