Guardians of Slumber: Unraveling The Prediction of Sleep Apnea in Premature Infants

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Received September 22, 2023
Accepted December 27, 2023
Electronic access December 31, 2023

Sleep apnea is prevalent in premature infants due to their respiratory underdevelopment. While research has been conducted to detect and predict sleep apnea in adults, currently, sleep apnea can only be detected in premature infants, but not predicted. This research aims to bridge this gap by predicting the Apnea-Hypopnea Index (AHI) of an apneic premature infant. Due to a lack of available data focusing on apnea in premature infants, the neural network was trained using adult apnea data and then applied to create a model based on synthetically generated data mimicking apneic events in premature infants. The results indicated premature infants tend to have a none to minimal severity score. The results also indicated that as each factor studied (height, age, etc.) increased, the AHI tended to increase as well, with each individual's sex and weight being the only exception.

Introduction: Unlocking the Mysteries of Sleep Apnea

Sleep Apnea

Sleep apnea is a sleep disorder where an individual stops breathing for an extended period of time. Currently, 30 million individuals, or around 12% of the United States population, are affected by sleep apnea1. There are three types of sleep apnea - obstructive sleep apnea (OSA), central sleep apnea, and complex sleep apnea. OSA is the most common of the three and occurs when the path from the nose to the upper airway has narrowed or has an obstruction. One of the most common causes for an OSA episode is when the tissue at the back of the throat becomes soft and collapses, blocking the airway[1]. Central sleep apnea occurs when there is a delay in the neural signal responsible for telling our body to breathe while sleeping. This type of apnea is idiopathic, meaning its cause is unknown. However, neural degenerative diseases such as sclerosis have been linked to sleep apnea. The final type of sleep apnea, complex sleep apnea, is a combination of OSA and central sleep apnea. This is a newer, unknown type of sleep apnea. While the complex sleep apnea episode may first appear similar to an OSA episode, breathing is still irregular after the obstruction is removed or the airway returns to its original state, indicating that collapsed throat muscles are not the only cause of the apnea. Currently, researchers are trying to gather more information about complex sleep apnea to determine its cause and defining traits[1].

Some common symptoms of sleep apnea include a slow heartbeat (around 60 beats per minute in adults and around 80 beats per minute in premature infants), trouble swallowing, breathing from the mouth, cyanosis, or bluish color of the skin, and respiratory distress, which is common in premature infants[2,3]. Respiratory distress can be indicated by fast, shallow breathing, grunting, flaring of the nostrils, and pulling the muscles of the rib inbound while breathing[3]. There are also many risk factors that may contribute to sleep apnea. The most common factor of sleep apnea is obesity, which can cause the lungs to collapse due to excess weight. There are also some neuromuscular diseases that can cause OSA, such as Down syndrome, which causes muscles to weaken. Additionally, small airways can pose a risk. This can occur due to a cleft palate, which is a birth defect where the lips and mouth are not formed properly. Another cause for sleep apnea is gastroesophageal reflux, where stomach acid flows upwards in the esophagus[4].

There are various methods of measuring the severity of sleep apnea. The apnea index (AI) is the number of apneic episodes that occur per hour while the hypopnea index (HI) is the number of hypopnea episodes that occur per hour. While an apneic episode is characterized by periods of an individual's breathing completely stopping, a hypopnea episode occurs when the breathing rate is reduced with less oxygen intake. To be considered an episode, the apnea or hypopnea must last at least ten seconds[5]. The apnea hypopnea index (AHI) is the number of apnea and hypopnea events per hour and is typically used to describe the severity of OSA. In adults, the following table can determine the severity of sleep apnea[6].

Sleep Apnea in Premature Infants

Premature infants, or preterm infants, are born between 33-35 weeks and are more prone to apnea due to their underdevelopment. Sleep apnea in premature infants, or apnea of prematurity (AOP), presents itself during the first week after birth or later.

Table 1 AHI Severity Scale for Adults

AHI Severity Scale for Adults	
Severity	**AHI Score**
None or Minimal	$0 \leq AHI < 5$
Mild	$5 \leq AHI < 15$
Moderate	$15 \leq AHI < 30$
Severe	$AHI \geq 30$

While sleep apnea is rare in full term infants, around 50% of preterm infants develop sleep apnea3. Luckily, many premature infants outgrow their apnea by the time they become 36 weeks old[7]. AOP can cause a slower heart rate as well as lowered oxygen levels in a premature infant's blood. In the long term, AOP can create weakened or damaged lungs, which can increase the risk of respiratory distress[8].

Premature infants also tend to struggle with periodic breathing, during which an individual stops breathing for a moment, and then follows with short, shallow breaths. Compared to apnea, periodic breathing does not exhibit respiratory impact within the three seconds following the cessation of breathing[9]. AOP, on the other hand, not only affects the respiratory system, but is also associated with bradycardia and desaturation[9]. A study conducted by Fenner et al. in 1973 found that periodic breathing inversely varied with the weight of an infant[10]. Specifically, only 36.1% of infants who weighed more than 2.5 kg at birth struggled with periodic breathing. On the other hand, infants who weighed less, which is common in premature infants, had a periodic breathing rate of 94%[10].

Similar to the AHI severity scale for adults, children also have their own severity scale. However, since children have a faster breathing rate than adults to support their lungs, apneic or hypopneic episodes are more severe and potentially fatal for children[11].

Table 2 AHI Severity Scale for Children

AHI Severity Scale for Children	
Severity	**AHI Score**
None or Minimal	$0 \leq AHI < 1$
Mild	$1 \leq AHI < 5$
Moderate	$5 \leq AHI < 10$
Severe	$AHI \geq 10$

Sleep Apnea Research

Most of the artificial intelligence-based work previously completed in sleep apnea involves the detection of an apneic episode. For example, in 2019, an algorithm was created, using electromyography (EMG), electrocardiogram (ECG), and electroencephalogram (EEG) signals to reliably detect sleep apnea using Physionets Apnea-ECG Database[12]. Using a multilayer perceptron classifier, the algorithm developed could accurately detect 98.09% of sleep apnea episodes[12]. Another study created the Obstructive Sleep Apnea Stroke Unit Dataset (OSASUD), which was produced to create a detection algorithm for sleep apnea in patients who had strokes (which are a risk factor for sleep apnea)[13]. However, these studies only detected apneic episodes and did not predict when an apneic episode may occur. Kim et al. created an algorithm that used respiratory sounds to predict an apneic episode[14]. When employing a binary classifier, the algorithm faced challenges in accurately assessing the severity of OSA, resulting in an accuracy rate of approximately 80%. Additionally, the study did not consider other factors such as the EMG, ECG, EEG, and blood pressure[14]. Furthermore, these studies were only conducted in adults in determining or predicting sleep apnea.

There is very little data regarding sleep apnea when it comes to full-term or premature infants, with only two major studies conducted concerning sleep apnea in infants. In recent years, researchers created an algorithm to detect sleep apnea in infants by using techniques that did not involve touching the infant, such as monitoring the breathing of the infant with video processing[15]. They were able to create a program with a 90% accuracy rate to detect apneic episodes[15]. Another study conducted by Goffinski et al. assessed sleep apnea in infants less than six months old with Down syndrome[16]. While the focus was on Down syndrome, other risk factors such as congenital heart diseases, gastrointestinal malformations, and prematurity were considered. However, Goffinski et al. have not released any data that could help create an algorithm for predicting an apnea episode[16].

Research Proposal

The aim of this research is to predict the apnea index and hypopnea index (which can be summed to predict the AHI) of a premature infant who struggles with sleep apnea. Currently, there is research to both detect and predict sleep apnea in adults. However, the only research about sleep apnea in premature infants focuses more on the detection of sleep apnea, not the prediction. The goal of this research is to utilize the very small amount of available adult apnea data to create a method to predict a sleep apnea episode in premature infants.

One Artificial Intelligence (AI) and Machine Learning (ML) model that can assist with predictions is a neural network, a nonlinear regression model. These predictions can assist doctors create a personalized treatment plan which can increase the patient's survival rate against apnea. In this research, neural networks will be used to predict the severity of sleep apnea in premature infants.

Methods: Synchronizing Vital to Predict Apnea

MIT-BIH Polysomnographic Database 1.0.0

The MIT-BIH Polysomnographic Database contains numerous recordings of physiologic signals. There are 80+ hours of polysomnographic recordings of 16 male subjects. Their ages range from 32 to 56 years while their weights range from 89 to 152kg, and they were monitored in Boston Beth Israel Hospital Sleep Laboratory to assess OSA[17]. The database does not have any ethical or privacy concerns with collecting, maintaining, and sharing the data.

Each of the recordings contains an ECG signal, EEG signal, respiration signal which is usually measured via nasal thermistor, and a blood pressure signal which was obtained using a catheter in the radial artery. Many of the recordings had signals including EOG signals, EMG signals, respiratory effort signals which were measured via inductance plethysmography, cardiac stroke volume signals, and earlobe oximeter signals. Additionally, the database contains a table including the following parameters for each record - sleep length (minutes), non-apnea length (minutes), apnea length (minutes), hours with apnea, age, sex, height, weight, AI, HI, and AHI[17].

Artificial Intelligence & Machine Learning Model

Neural networks have three components - the input layer, the hidden layers, and the output layer. The input layer passes the data values to the next layers, known as the hidden layers. These hidden layers are crucial to neural networks, as neural networks use mathematical functions to manipulate the data to improve the prediction. The hidden layers output the predictions in the output layer. Each layer is composed of nodes, which take input values. These nodes are connected to a set of weights, which adjust the value in the node. Finally, an activation function is applied to each neuron in the layer. This process is repeated until the output layer outputs the prediction. Once a neural network is trained, it is a very powerful prediction model.

The neural network utilized in this paper was trained on 85% of the data and tested on the remaining 15% of the data to avoid overtraining. An 80:20 split has been justified by the Pareto principle[18]. However, since the dataset used in this study has a limited amount of data, increasing the training ratio would improve the learning of the neural network since there would be more data points to train from.

The proposed neural network began with an eight-node input layer, followed by three hidden layers with node counts of five, three, and five, respectively. The network also featured a scalar layer with two nodes to optimize the final output layer's accuracy. Figure 1 represents the architecture of the neural network used in this study. The sigmoid activation was used and is shown in Equation 1 and an alpha level, which is the learning rate, of 5 was utilized.

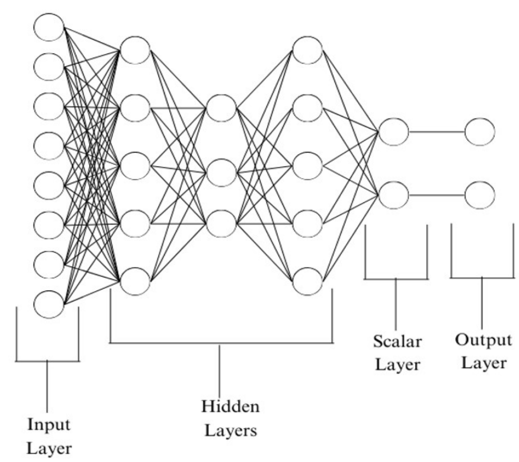

Fig. 1 Neural Network Structure.

The sigmoid function is defined as:

$$\text{sigmod: } f(x) = \frac{1}{1+e^{-x}} \tag{1}$$

The neural network utilized in this paper is meant to predict the apnea index and the hypopnea index of a patient. To accomplish this, the neural network uses the following features as input: sleep length (minutes), non-apnea length (minutes), apnea length (minutes), hours with apnea, age (years), sex, height (centimeters), and weight (kilograms), to output the AHI prediction.

To validate the accuracy of the neural network model, the mean squared error (MSE) is used. The following equation describes how the MSE is obtained:

$$\text{MSE} = \frac{1}{n}\sum_{i=1}^{n}(Y_i - \hat{Y}_i)^2 \tag{2}$$

where n is the number of data points, Y_i is the observed value, and $\hat{Y}_i$ is the predicted value.

The MSE was chosen as the evaluation metric since the output of the neural network was numerical rather than categorical. The neural network was tested with 15% of the data, which had been set aside previously.

Synthetic Data Generation

To test the neural network on premature infant data, a simulated dataset was created to model the conditions of the premature infants. A uniformly distributed dataset was created using the random.uniform() function in Python. Although some inputs for the neural network such as the length, number of apnea minutes, number of non-apnea minutes, and number of hours with apnea were generated using numbers similar to those recorded in the original dataset, inputs such as the age, height, and weight were generated using data collected about premature infants. Figure 2 illustrates how the synthetically generated data will be used in the study while Table 3 displays the range of values used to generate the data.

Table 3 Range of Premature Infant Characteristics

Range of Premature Infant Characteristics	
Characteristic	**Range**
Age	7 - 42 (days)
Height	30 - 46.5 (cm)
Weight	0.6 - 2.6 (kg)

Results: Revealing the Night's Whisper

Neural Network Performance

Once the neural network was trained using back propagation, the performance was assessed using the mean squared error. The lowest error was an error of 0.0489, resulting in an accuracy of 95.10%. This shows that on average, the neural network could predict the AHI with a 95% confidence interval for adults with sleep apnea.

When predicting the severity of premature infants using the trained neural network and the simulated data, the AHI, tended to be closer to 0. Although there were a few data points that had an AHI around 15 or 50, a majority of the data points either had a severity of none/minimal. In a sample run with 200 synthetically generated premature baby apneic data, the following table summarizes the results of the data.

Table 4 Frequency of AHI Scores in Premature Babies

Frequency of AHI Scores in Premature Babies	
AHI	**Frequency**
0	105
1 - 5	32
6 - 9	4
10 - 45	30
46 - 79	18
80 - 100	11

Around 50% of the AHI in premature babies had a severity of none/minimal. On the other hand, around 30% of the AHIs were categorized as severe. Finally, around 15% of the premature, apneic baby data points had a mild severity while the remaining 5% had a severity of moderate.

Characteristic Weightings

To determine which of the inputs for the neural network has the most impact on the outcome, a SHAP (SHapley Additive exPlanations) assessment was run. SHAP uses game theory to explain machine learning model outputs. The SHAP analysis graphs depict the influence of the inputs on the prediction of the neural network. Figure 3 illustrates the result of the SHAP analysis.

The graph illustrates that a patient's gender has a minimal impact on AHI, as it remains close to zero. On the other hand, factors such as the number of hours with apnea increased the prediction (AHI) value. Furthermore, each factor exhibits a positive relationship with the SHAP value, indicating their role in augmenting the neural network output.

Discussion: Understanding Sleep Apnea Breath by Breath

Analysis

The results of this research show that there are numerous factors that can impact the severity of sleep apnea in premature infants. While the neural network was successfully trained on data focusing on adults with sleep apnea, the neural network was also able to create predictions using simulated data for premature infants.

The SHAP results were rather interesting. Although weight can be a huge factor in sleep apnea for adults, the SHAP graphs indicated that weight did not have much effect on the overall output of the neural network in premature infants. This correlation could have occurred because premature infants are severely underweight, so their lungs would not struggle to stay intact. However, this does not suggest that weight does not impact the severity of an apnea episode for premature infants. While weight does impact an apnea episode's severity, especially in adults, it is not the primary factor in the severity for premature babies.

Another observation that SHAP results highlighted was how gender does not impact the AHI in premature infants. However, in adults, OSA is more frequent and severe in males compared to females, which can be attributed to the fact that testosterone has been shown to increase the AHI score[19]. A study found that while gender can impact apnea episodes in children undergoing puberty, there is a similarity in apnea episodes regardless of gender in prepubertal children[19].

Limitations & Future Studies

One limitation with this study was a lack of data - not only for premature infants but also for adults. Although the premature infant data was modeled with synthetically generated data, a

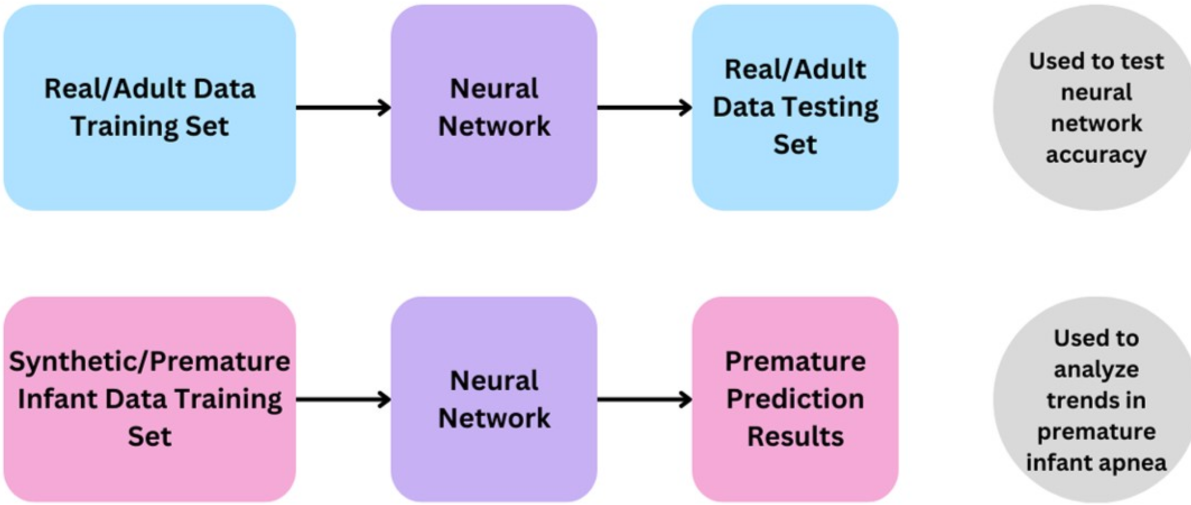

Fig. 2 Usage of Synthetically Generated Data

stronger neural network prediction could be made by testing on collected premature infant data. Ideally, the neural network should also be trained on premature infant data, but this requires hundreds of data points which are currently not available. Currently, the synthetically generated data does not account for any underlying correlation between the AHI and the inputs. For example, there is a positive correlation between height and weight[20]. However, the synthetic data does not consider this correlation, which is a potential source of error.

Potential future studies include monitoring the EEG and pulse oximetry data and looking at abnormalities in the data to detect or predict an apnea episode in premature infants. EEG signals are used to track human brain activity, which can be used to analyze sleep patterns and detect apnea episodes[21]. Pulse oximetry data can be used to noninvasively measure the oxygen saturation levels in a patient's blood. A lower oxygen saturation level indicates a higher heart rate, which suggests sleep apnea[22]. This proposed study could help predict when an apnea episode would occur, alerting caretakers and giving them more time to prepare for the apnea episode.

Research Contributions & Implications

This paper shows that the severity of sleep apnea in premature infants can be predicted using their vital signs. This current model is only the baseline and with more data and ML models, the accuracy will only keep improving, helping more premature infants who struggle with sleep apnea.

One of the major implications of this study is how it can change clinical practice. Healthcare workers could feed a premature infant's vitals into the neural network to predict the severity of apnea episodes. This would allow healthcare workers to prioritize premature infants who have a more extreme AHI.

Conclusions

Medical science is largely focused on detecting and treating sleep apnea after the apnea event has already occurred. There has been very limited focus so far on proactively predicting and eliminating the occurrence of sleep apnea. This research shows that the severity of sleep apnea in premature infants can be predicted using their vital signs. The emerging AI techniques will play a big role in improving the accuracy of the predictions.

When the neural network was trained and tested with adult apnea data, there is 95% accuracy. The neural network structure was also trained and tested with simulated apneic premature infant data to predict the severity of sleep apnea. These predictions suggested that the AHI for premature infants tend to be less severe, with a none to minimal severity level and AHI around 0. Finally, the results indicate that the weight and gender of a premature infant does not affect the overall severity by a significant factor.

Acknowledgements

This paper would not have been possible without the help of my mentor, Katie McCullar, and her guidance, encouragement, and explanations. I would also like to thank Rohan Gorantla, who guided me through the computational aspect of this paper. This

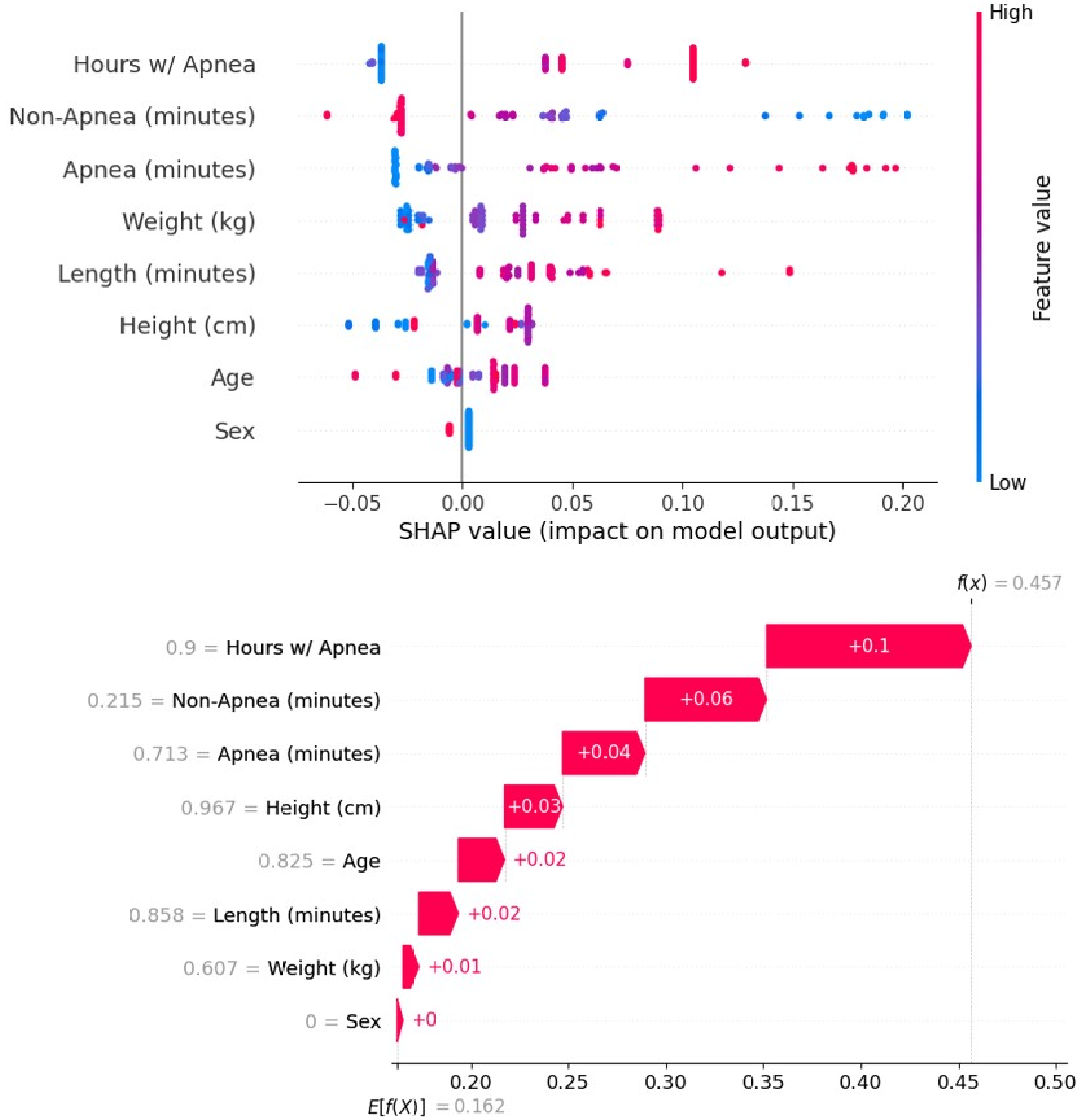

Fig. 3 SHAP Analysis Graphs

paper was created as a part of the Lumiere Education Research Program. I would like to thank everyone of the Lumiere team, especially my project manager Aakriti Arora for helping me with each step of the program.

References

1 K. Lee and J. Warner, *EverydayHealth.com*.

2 *Apnea and bradycardia*, https://med.emory.edu/departments/pediatrics/divisions/neonatology/apnea.html, accessed Nov. 24,.

3 J. Summer and N. Vyas, *Sleep Foundation*.

4 *Respiratory distress syndrome (RDS*, https://www.nhlbi.nih.gov/health/respiratory-distress-syndrome, accessed Nov. 24,.

5 *Johns Hopkins Medicine*.

6 J. Summer and A. Singh, *Sleep Foundation*.

7 *Boston Children's Hospital*.

8 *Apnea of Prematurity," Stanford Medicine Children's Health - Lucile Packard Children's Hospital Stanford*, https://www.stanfordchildrens.org/en/topic/default?id=apnea-of-prematurity-90-P02922, accessed Nov. 24,.

9 Y. Durani, *KidsHealth*.

10 A. Fenner, U. Schalk, H. Hoenicke, A. Wendenburg and T. Roehling, *Pediatric Research*, **7**, 174–183,.

11 *Sleep Medicine*.

12 M. Moridani, M. Heydar and S. Behnam, 5th Conference on Knowledge Based Engineering and Innovation (KBEI.

13 A. Bernardini, A. Brunello, G. Gigli, A. Montanari and N. Saccomanno, *Scientific Data*, **9**, year.

14 J. Kim, T. Kim, J. Shin, G. Choe, H. Lim, C. Rhee, K. Lee and S. Cho, *Clinical and Experimental Otorhinolaryngology*, **12**, 72–78,.

15 G. Jayatilaka, H. Weligampola, S. Sritharan, P. Pathmanathan, R. Ragel and I. Nawinne, 14th Conference on Industrial and Information Systems (ICIIS.

16 A. Goffinski, M. Stanley, N. Shepherd, N. Duvall, S. Jenkinson, C. Davis, M. Bull and R. Roper, *American Journal of Medical Genetics Part A*, **167**, 324–330,.

17 A. Goldberger, L. Amaral, L. Glass, J. Hausdorff, P. Ivanov, R. Mark and H. Stanley, *PhysioBank, PhysioToolkit, and PhysioNet: Components of a new research resource for complex physiologic signals*.

18 V. Joseph, *Statistical Analysis and Data Mining: The ASA Data Science Journal*, **15**, 531–538,.

19 S.-W. Kim and L. Taranto-Montemurro, *Journal of Thoracic Disease*, **11**, year.

20 G. DePersio, *Investopedia*.

21 T. Sugi, F. Kawana and M. Nakamura, *Oct*.

22 M. Peters, *Verywell Health*.