# Abstract

Gracia, Fernando, Role of Arousal Threshold in Sleep Health Disparities and Outcomes Among Pediatric Patients with Obstructive Sleep Apnea. Master of Science (Medical Sciences Research Track), April, 2022, 63 pp. 5 tables, 5 figures, bibliography.

Black/African American (Black) children are at increased risk of experiencing continued obstructive sleep apnea (OSA) disease following adenotonsillectomy (A&T), which is the first-line treatment for OSA in children. The nadir epiglottic pressure preceding arousal, known as the arousal threshold (ArTH), and allostatic load (AL), a measure of the impact of environmental stress on the body, are both associated with the severity and incidence of the disease. However, the contribution of these factors to the sleep health disparities among Black pediatric patients is unknown. Therefore, our overall objective of this study was to determine the role of arousal threshold and allostatic load in sleep health disparities amongst treatment outcomes in pediatric patients with OSA. The current study leveraged archival data from the Childhood Adenotonsillectomy Trial (CHAT). 464 children aged 5 to 9 years with obstructive sleep apnea were randomized to receive either early adenotonsillectomy or watchful waiting. Polysomnographic, cognitive, behavioral, and health outcomes were examined at baseline and after seven months. Our sample included 183 participants who had the required allostatic load baseline data for the analysis and a sub-sample of 98 participants who underwent adenotonsillectomy surgery and had follow-up data. We examined AL index among Black and White children to identify differences and create a model that could explain the noted sleep disparities in response to adenotonsillectomy surgery. To achieve the overall objective and test the first hypothesis that Black children will have increased arousal threshold and allostatic load

compared to their White counterparts, univariate ANCOVAs were conducted to determine potential differences between Black and White children for ArTH and AL adjusted for demographic and socioeconomic factors. To test the second hypothesis that increased arousal threshold and allostatic load will predict higher adenotonsillectomy failure rates. Quadratic discriminant function analysis was used to determine if ArTH and AL load predicts adenotonsillectomy failure. A&T failure is defined as a participant having an obstructive apnea index (OAI) $\geq 1$ and an apnea-hypopnea index (AHI) $\geq 2$ at follow-up 7 months after A&T.

Key findings were an increased allostatic load in Black children (P=0.09) and an interaction effect between race and premature birth. Black Children born premature had a higher allostatic load than White children born premature (P=0.09). Additionally, among the subsample of participants who underwent adenotonsillectomy surgery, a difference between Black and White race was found for ArTH ($p < 0.05$). For predicting the success and failure of adenotonsillectomy surgery, the test model showed a 54.8% success rate in predicting group membership. The findings from our study can be used to guide the development and testing of future sleep health interventions and further elucidate the etiology of sleep health disparities

# Role of Arousal Threshold in Sleep Health Disparities and Outcomes Among Pediatric Patients with Obstructive Sleep Apnea

Fernando Gracia, B.S.

_____

Caroline A. Rickards, PhD., Major Professor,

_____

Harlan Jones, PhD., Committee Member

_____

Riyaz Basha, PhD., Committee Member

_____

Thomas Cunningham, Ph.D., Committee Member

_____

Johnathan Tune, Ph.D., Department Chair

_____

Caroline A. Rickards, Ph.D., Program Director

_____

Michael Mathis, Ph.D., Dean

Graduate School of Biomedical Sciences

# ROLE OF AROUSAL THRESHOLD IN SLEEP HEALTH DISPARITIES AND OUTCOMES AMONG PEDIATRIC PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

PRACTICUM REPORT

Presented to the Education Council of the

School of Biomedical Sciences

University of North Texas

Health Science Center at Fort Worth

In Partial Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE

By

Fernando Gracia

Fort Worth, Texas

April 26, 2022

# ACKNOWLEDGEMENTS

During my time at the University of North Texas Health and Science Center, I had the chance to meet some amazing people, all of whom had a part in helping me complete this journey. I would first like to thank Dr. Roane for her guidance and mentorship. I am forever grateful for her encouraging me to pursue research that I am genuinely passionate about. This moment would not be possible without my amazing and gracious committee members, Dr. Jones, Dr. Basha, and Dr. Cunningham. When I first started the medical science program, I remember hearing Dr. Jones speak during a health disparities conference. His presentation and speech were inspiring and influenced my interest in health disparities research. I would also like to especially thank Dr. Rickards, who, as director of the medical science research track, gave me the opportunity to be a part of this wonderful program. While serving as my major professor, Dr. Rickards's leadership and advice were invaluable. She is truly an inspiration and role model for me all her students. I also wanted to say thank you to Dr. Ahmad, who was one of my undergraduate professors at the University of Texas Rio Grande Valley. His encouragement and unwavering support are huge reasons I was able to continue my education.

Finally, I would like to thank my friends, family, and fiancée Jennifer. Without their love and support, this moment would not be possible. I also need to make a shout out to my dog Ellie and cat Popo for making those stressful moments a lot less stressful.

## TABLE OF CONTENTS

**Page**

## LIST OF FIGURES



## LIST OF TABLES

# CHAPTER I. BACKGROUND AND LITERATURE REVIEW

## Significance

The rationale for this analysis is that a better understanding of how arousal threshold and allostatic load impact disparities in treatment outcomes among pediatric patients with obstructive sleep apnea (OSA) would help promote changes in the "standard of care" to insure health equity. Knowledge of whether arousal threshold and allostatic load can predict failure of adeno-tonsillectomy to resolve OSA may improve the identification of children who are more likely to have neuromuscular control deficiencies, and other treatment options could be pursued. Although most children who still have OSA after A&T improve in their condition, indicated by a decrease in AHI from baseline. Untreated OSA patients face a variety of poor outcomes, ranging from excessive daytime drowsiness and impaired cardiovascular health to behavioral difficulties, cognitive impairment, and academic performance impairment (Chervin et al., 2006; Gottlieb et al., 2004). Therefore, it is of the utmost importance to identify how arousal threshold and allostatic load both independently and synergistically impact adenotonsillectomy outcomes and contribute to surgical failure rates.

## Background

**Objective: Determine the role arousal threshold and allostatic load play in sleep health disparities among pediatric patients with OSA**

Health inequities are systematic, socially produced, and unjust differences in health that are avoidable (Hardeman, Murphy, Karbeah, & Kozhimannil, 2018). A growing body of literature supports substantial sleep health disparities in the prevalence, risk factors, presentation,

diagnosis, and treatment of obstructive sleep apnea (OSA) (Dudley & Patel, 2016; Marcus et al., 2012; Ruiter, DeCoster, Jacobs, & Lichstein, 2010). The most substantial evidence for a racial disparity in OSA exists among Black/African American children (Dudley & Patel, 2016). Even when adjusting for preterm birth and body mass index (BMI), Black American race was shown to be a risk factor for OSA (Rosen et al., 2003). OSA is fundamentally a breathing disorder that only occurs at night. Sleep apnea is classified as either central or obstructive, depending on the etiology. OSA in children is caused by upper airway dysfunction, which causes total or partial airway blockage during sleep and increased respiratory effort, resulting in reduced oxygen saturation and arousals from sleep (Marcus et al., 2012). Whereas central sleep apnea develops when the central nervous system does not provide adequate signals to the muscles that govern breathing, thus increasing respiratory effort is not a feature of central apneas (Dempsey, Veasey, Morgan, & O'Donnell, 2010).

Polysomnography (PSG) in a laboratory setting is the gold standard for diagnosing OSA in combination with the evaluation of patient symptoms. PSG involves recording EEG, pulse oximetry, oronasal airflow, abdomen and chest wall movements, and partial pressure of carbon dioxide over the course of an overnight period (Carole L. Marcus et al., 2012). Using data from PSG, apnea-hypopnea Index and obstructive apnea index can be calculated. The Apnea-Hypopnea Index (AHI) is defined as the number of apneas which is quantified as a drop in ventilatory flow by ≥ 90% and hypopneas (drop in ventilation by ≥ 30 %) divided by the number of hours slept (Richard B. Berry et al., 2012). The obstructive apnea index (OAI) is defined as the number of obstructive apneas divided by the number of hours slept. Obstructive apneas are drops in ventilation by 90% like apneas, but for at least the duration of two breaths and are associated with the presence of respiratory effort for the entire event (Ruehland et al., 2009).

When a patient undergoes PSG, and if they have an AHI of $\geq 2$ or an OAI of $\geq 1$, then this indicates that the pediatric patient has OSA (Marcus et al., 2012). The similarity between the negative-feedback processes that regulate breathing and engineering control systems has enabled researchers to better understand the causes underlying ventilatory instability in individuals with OSA. Recent research has made it possible to phenotype ventilatory stability and arousal threshold. Using only standard polysomnography (PSG) data. This has allowed for the exploration of factors that were not previously known for their role in OSA (Finnsson et al., 2021; Terrill et al., 2015).

The respiratory arousal threshold is a concept that defines an individual's proclivity to awaken from sleep (D. J. Eckert & M. K. Younes, 2014). Numerous respiratory stimuli can contribute to arousal during a respiratory event, such as hypoxia or hypercapnia (Chamberlin, 2013; E. S. Katz & White, 2004). However, studies have shown that the final common pathway to trigger arousal is negative intrathoracic pressure, quantified as the nadir esophageal or epiglottic pressure before arousal (Eckert & Malhotra, 2008; Edwards et al., 2014; Gleeson, Zwillich, & White, 1990; Terrill et al., 2015). It should be noted that the respiratory arousal threshold is not used to diagnose OSA on its own, but arousal threshold can give insight into the pathophysiology of the disease. Thus, a patient can be diagnosed with OSA having either a higher or lower arousal threshold than an individual who has fewer or more apneas in sleep. Although the amount of negative intrathoracic pressure created varies considerably across individuals and sleep phases, the amount of negative pressure necessary for arousal is relatively consistent within a particular individual (Eckert, White, Jordan, Malhotra, & Wellman, 2013; Eliot S. Katz, Lutz, Black, & Marcus, 2003), and is independent of the source of the respiratory disturbance, such as hypoxia, hypercapnia, or respiratory loading (R. B. Berry & Gleeson, 1997).

Upper airway collapse defines OSA during sleep, which results in increased $CO_2$, ventilatory drive, and negative pharyngeal pressure (Osman, Carter, Carberry, & Eckert, 2018). The collapse of the upper airway primarily occurs due to two contributing forces; negative intraluminal pressure generated by the diaphragm during inhalation, extraluminal tissue pressure, and bone structures surrounding the airway. Factors that can increase the extraluminal tissue pressure are enlarged tonsils and adenoids, obesity, a large tongue, and a small lower jaw (Azagra-Calero, Espinar-Escalona, Barrera-Mora, Llamas-Carreras, & Solano-Reina, 2012). Opposing compensatory responses include the activity of pharyngeal dilator muscles, but airway traction resulting from lung expansion is also a contributor (White, 2005).

Children with OSA exhibit appropriate ventilatory responses to hypoxemia and hypercapnia while awake (Busch et al., 2016). However, compared to control participants, children with OSA have a blunted arousal response to respiratory loading and hypercapnia during sleep (Marcus, Lutz, Carroll, & Bamford, 1998; Marcus, Moreira, Bamford, & Lutz, 1999). Previous research on children with OSA indicates that they experience intermittent obstructive cycling linked with arousals. Because of this, children with OSA will depend on arousal-linked respiratory mechanisms to maintain minute ventilation (Marcus et al., 1999). In contrast, children without OSA are able to increase pharyngeal dilator activity during sleep without the need for arousal (E. S. Katz & D'Ambrosio, 2008).

Studies in adults have shown that after patients received treatments aiming to correct OSA, such as upper airway surgery (A&T, nasal surgery) and continuous positive airway pressure (CPAP), the arousal threshold decreased from baseline (Joosten et al., 2017). Because of this phenomenon, researchers have suggested that the increase in arousal threshold seen in OSA is an adaptive response that occurs due to chronic sleep fragmentation and

hypoxemia/hypercapnia (Edwards et al., 2014). One previous study found that the arousal threshold in pediatric patients without sleep apnea ranges from −5.9 $cmH_2O$ to −11.9 $cmH_2O$ in comparison to the ranges of arousal threshold in pediatric patients with OSA, which was shown to be from −8 $cmH_2O$ to −65 $cmH_2O$ (Eliot S. Katz et al., 2003). The findings from this pediatric study also echo similar results in adults, where a higher arousal threshold was associated with the severity of OSA (Suzuki et al., 2005). A higher arousal threshold may aid in stabilizing breathing by enabling time for pharyngeal dilator muscles to be activated by mechanoreceptors or chemoreceptors. This allows for the negative pressure forces to be counteracted without arousal (E. S. Katz & D'Ambrosio, 2008). However, a lower arousal threshold may contribute to the disease in some patients with OSA. This is because frequent arousals may leave insufficient time for respiratory impulses to engage the pharyngeal muscles and reopen the airway before arousal is triggered by negative pressure (Danny J. Eckert & Magdy K. Younes, 2014). A low arousal threshold may also elicit a destabilizing ventilatory response, contributing to the persistence of respiratory episodes or fragmented sleep, preventing the patient from establishing stable slow-wave sleep (Joosten et al., 2017).

Enlarged tonsils & adenoids are not the only anatomical trait present in children with OSA that may impact airway patency. OSA can persist after adenotonsillectomy (A&T), and in some children, OSA resolved after A&T but recurred during adolescence (Guilleminault, 1987; Guilleminault, Huang, Quo, Monteyrol, & Lin, 2013). Some researchers have suggested that childhood OSA can be caused by a combination of anatomical anomalies and dynamic neuromuscular variables influencing the upper airway (Marcus et al., 2005). Pharyngeal dilator muscle activation is one of the primary processes triggered by arousal. Upper airway muscles are known to have robust responsiveness to respiratory stimuli, including $CO_2$ (via chemoreceptor

stimulation) and intrapharyngeal negative pressure (via mechanoreceptor stimulation) during wakefulness (Oliven et al., 2018). Negative pressure in the airway reflexively stimulates laryngeal mechanoreceptors, resulting in increased superior laryngeal nerve afferent activity and greater hypoglossal output to the genioglossal muscle (Horner, Innes, Holden, & Guz, 1991; Li et al., 2019; van Lunteren, 1993). Therefore, any event that compromises airway patency will increase negative airway pressure and eventual genioglossal activation to restore the airway (Malhotra et al., 2000; Malhotra et al., 2002; Taranto-Montemurro et al., 2016). The genioglossus muscle has been the subject of most of the research into pharyngeal muscle regulation. This is likely due to the difficulty of recording other airway dilator muscles and the fact that the genioglossus is regarded to be especially crucial in the etiology of OSA (Dempsey et al., 2010; E. S. Katz & White, 2004). This is due to the genioglossus's increased activity in OSA, respiratory-related activity, and responsiveness to $CO_2$ and negative airway pressure, among other respiratory stimuli (Jordan & White, 2008).

The medulla's respiratory pattern-generating neurons also affect genioglossal activation, and this is demonstrated by the activation of the genioglossus muscle 50-100 ms before inspiratory airflow (E. S. Katz & White, 2003; van Lunteren, 1993). Genioglossal activation helps prepare the airway for negative pressure generated by the diaphragm. Thus, respiratory neurons and the negative-pressure reflex affect muscle activity during inspiration.

The nucleus tractus solitarius (NTS) is the medulla's primary sensory nucleus and is responsible for receiving signals from the cardiovascular system (via the baroreceptors), respiration (via chemoreceptors and mechanoreceptors), and integrating the cardiopulmonary reflexes (Loeliger, Tolcos, Leditschke, Campbell, & Rees, 2000). The glossopharyngeal and vagus nerves carry afferent fibers from chemo- and baro-receptors, and increased afferent

laryngeal nerve activity sends sensory information to specific regions of the NTS (Kubin, 2016) (Baker & Lui, 2022). The hypoglossal nucleus (HGN) is located in the dorsal region of the medulla oblongata and innervates the tongue's intrinsic and extrinsic muscles (Sakamoto, 2019). The role of the HGN is not only crucial for coordinating swallowing, chewing, and vocalization, but it also has a peak activity while breathing (Roda, Gestreau, & Bianchi, 2002). Furthermore, the HGN is vital for maintaining upper airway patency during sleep, and has been shown to have a role in the modulation of respiration (Loeliger et al., 2000). Neurons that regulate arousal, such as serotonergic or noradrenergic neurons, have an excitatory tonic effect on upper airway motor neurons such as hypoglossal motoneurons (Robert B. Fogel et al., 2003; Jelev, Sood, Liu, Nolan, & Horner, 2001). This excitatory effect is referred to as the "wakefulness stimulus," resulting in increased muscular activity, which leads to an increase in airflow (Orem, 1990; Orem & Trotter, 1992).

Compared to children without OSA, children with OSA show higher genioglossus electromyography (EMG) activity during wakefulness and decreased activity during sleep (E. S. Katz & White, 2003). This indicates that children with OSA need increased reflex-driven responses during wakefulness in order to stabilize breathing due to an anatomically compromised airway. However, during sleep, children with OSA have decreased hypoglossal EMG activity compared to children without OSA and need to generate larger negative inspiratory intrathoracic pressures sufficient to stimulate the airway musculature (E. S. Katz & White, 2003). A concise framework for how pharyngeal muscle activation is coupled to breathing, local airway circumstances (negative pressure), and arousal state is illustrated in figure 1.

The majority of individuals with OSA have a pharyngeal airway that is anatomically narrow, most likely owing to increased soft tissue around the airway, such as the adenoids or

tonsils, or a small bony compartment in which the airway is contained (Weinstock et al., 2014). When sleep begins, the regulation of these upper airway muscles is altered because of the decreased "wakeful" input to these muscles (Eckert & Malhotra, 2008; E. S. Katz & D'Ambrosio, 2008). Although the upper airway muscles may still react to negative pressure, they do so less efficiently and rapidly than when a person is awake (Oliven et al., 2018). During times of wakefulness, pharyngeal patency is maintained predominantly by reflex-induced pharyngeal dilator muscle activity, which results in normal breathing (Robert B Fogel et al., 2001; E. S. Katz & White, 2004). However, reflex muscle activation is reduced at sleep onset by modulating the excitatory arousal output to the upper airway muscles apneas (Dempsey, Veasey, Morgan, & O'Donnell, 2010). If the airway structure is severely compromised because of factors such as adenotonsillar hypotrophy or obesity, this will lead to hypopnea or apnea and eventual hypoxia and hypercapnia. Ventilatory drive will be stimulated until the right conditions are met for an arousal response, thus restoring airway patency and allowing for the recovery of ventilation. (Edwards et al., 2014; White, 2005.).

The role of neuromuscular compensatory reflexes is considered to be a contributing factor in pediatric OSA due to the weak association between adenotonsillar size and apnea severity, and the significant overlap between airway size in children with and without OSA (Arens et al., 2001; E. S. Katz & White, 2003; Monahan, Larkin, Rosen, Graham, & Redline, 2002). The extent to which arousal threshold explains the sleep health disparities within treatment outcomes in pediatric patients who under ago adenotonsillectomy has not been elucidated. Interestingly, a measure of ventilatory instability known as loop gain, which measures the magnitude of response to a ventilatory disturbance, is a strong predictor of upper airway surgery success for OSA, as defined by a 50% reduction in AHI post-surgery (Joosten et

al., 2017). While A&T reduces the AHI in responders (defined as 50% reduction in apnea-hypopnea index (AHI) and AHI <10 events/hour post-surgery) and in non-responders, non-responders showed a lower AHI reduction. In the same study, patients who were responders to surgery decreased their arousal threshold post-surgery (Joosten et al., 2017). However, the AHI used to diagnose children with OSA is more specific compared to adults (Redline et al., 2011). The reduction in arousal threshold and AHI that is seen in upper airway surgery responders who are adults may still leave a pediatric patient within the criteria for OSA diagnosis. This is because an AHI $\geq 2$ or more is required for children to be diagnosed with OSA; for adults, an AHI $\geq 5$ is required (Ruehland et al., 2009). If a lower arousal threshold results from adenotonsillectomy and OSA is still present, this could indicate that a combination of neuromuscular and anatomical pathology is contributing to the condition. The neuromuscular contribution to pediatric OSA has not been studied extensively, and most pediatric treatments are centered on addressing anatomical abnormalities. Since OSA, in some cases, can reappear in adolescence or adulthood and persist after successful adenotonsillectomy, the neuromuscular contribution to the disease in pediatric patients deserves further investigation (Guilleminault, 1987; Guilleminault et al., 2013).

In 2021, the Centers for Disease Control and Prevention (CDC) identified racism as a fundamental driver of racial and ethnic health disparities (CDC 2021). Although race is a rough proxy for socioeconomic status, culture, and genes, it most accurately depicts people's social classification in a race-conscious country such as the United States (Jones, 2000). Substantial research demonstrates the significance of race as a social-political category with biological consequences resulting from the impact of social inequality on people's health (Chae et al., 2019; Geronimus, Hicken, Keene, & Bound, 2006; Roberts, 2011; D.R. Williams, Priest, & Anderson, 2016). Social constructs such as race and economic factors are associated with OSA prevalence and access to healthcare. Among patients evaluated in a sleep clinic, Black children exhibited an

average AHI 20% higher than that of other non-Black children, as well as greater oxygen desaturation (Weinstock et al., 2014). Other studies have found that socioeconomic factors, and not race alone, are the primary predictors of OSA. For instance, after controlling for neighborhood socioeconomic characteristics, such as poverty rate and percentage of single–female-headed families, a cross-sectional study found no association between race and OSA prevalence and severity in children (R. Wang et al., 2017). Additional studies, however, suggest that race and socioeconomic factors have a synergistic effect. For example, when examining the combined effect of race and neighborhood disadvantage on OSA, 50% of the race effect could be explained by neighborhood-level variables (Spilsbury et al., 2006; Weinstock et al., 2014).

Socioeconomic factors can be contextualized as stressors, and as such, their physiological effect, or "wear and tear on the body," "can be captured by allostatic load. Allostatic load can be measured by using biomarkers that indicate the effects of prolonged stress exposure (Shelley, Robert-Paul, Kristen, & Julie, 2021). Using quartiles to determine a high-risk group for each marker has been the standard for calculating an allostatic load score. However, some studies use clinical guidelines to determine cut-off values (McLoughlin, Kenny, & McCrory, 2020). The highest quartile is designated as the high-risk group for most markers, except for where the lowest quartile is designated as the high-risk category, such as for the biomarker high-density lipoprotein cholesterol. Markers with values in the high-risk group are given one point, and an overall allostatic load summary score is generated. Calculating allostatic using this technique implies that each marker contributes equally to allostatic burden, which has not been tested (Mauss, Li, Schmidt, Angerer, & Jarczok, 2015). Prior literature has shown that an elevated allostatic load index is positively associated with OSA diagnosis (Chen, Redline, Shields, Williams, & Williams, 2014). This finding is not surprising given that OSA is a condition

associated with oxidative stress, increased expression of redox-sensitive genes, and the inflammatory cascade (Entzian, Linnemann, Schlaak, & Zabel, 1996; Ryan, Taylor, & McNicholas, 2005, 2006). Rapid re-oxygenation following apneas/hypopneas results in the formation of free radicals, causing oxidative stress and NF-kB upregulation (Israel, Benharoch, Gopas, & Goldbart, 2013). Because of the potential of NF-kB to elicit cell and tissue inflammatory responses via multiple signaling pathways, NF-kB upregulation due to cyclic apneas may help promote systemic inflammation and interact with the processes relating to allostasis (T. Wang, Zhang, & Li, 2002) (Liu, Zhang, Joo, & Sun, 2017). An active NF-kB molecule is a homodimer/heterodimer made up of Rel family proteins such as p65 and p50 (Yu, Wan, & Huang, 2009). The most common type of NF-kB that is rapidly produced after stimulation is the p65/p50 complex and is overexpressed in the adenoids and tonsils of children with OSA (Israel et al., 2013). These well-described pathways support the hypothesis that the inflammatory stress response associated with OSA could lead to airway inflammation. In addition, inflammation can blunt chemoreception, and elevated C-reactive protein (CRP) is a known inflammatory biomarker that can predict the presence of OSA after A&T (Bhattacharjee, Kheirandish-Gozal, Kaditis, Verhulst, & Gozal, 2016).

Systemic inflammation stimulates brainstem and spinal inflammatory responses, affecting chemoreflexes and respiratory adaptability, according to exogenously produced inflammation models (Huxtable et al., 2011). Due to the effects between mechanoreceptors and chemoreceptors in determining the arousal threshold, allostatic load can theoretically influence the arousal threshold of a patient due to the effects of prolonged stress and inflammation on ventilatory processes (Beyeler, Hodges, & Huxtable, 2020). While allostatic load has been extensively studied in adult populations, a paucity of research has examined the role allostatic

load may play in sleep health disparities among pediatric populations. Individually, both arousal threshold and allostatic load have been shown to relate to and explain the pathophysiology of OSA. What is not known is whether these two factors contribute to the sleep health disparities found among Black pediatric patients with OSA.

## Problem/Hypothesis

Black/African American (Black) children are five times more likely to experience obstructive sleep apnea (OSA) and were shown to have lower rates of polysomnography normalization after adenotonsillectomy (A&T) (Marcus et al., 2013; Rosen et al., 2003). While elevated arousal threshold and allostatic load are implicated in the pathophysiology of OSA (Eckert et al., 2013; Edwards et al., 2014; Wellman et al., 2004; Younes, Ostrowski, Thompson, Leslie, & Shewchuk, 2001), their contribution to sleep health disparities is unknown among pediatric populations. To address this gap in knowledge, the overall objective of this project is to determine the role arousal threshold and allostatic load may play in sleep health disparities amongst pediatric patients with OSA. We **hypothesized** that Black children will have increased arousal threshold and allostatic load compared to their White counterparts. We further **hypothesized** that increased arousal threshold and allostatic load will predict increased failure rates for adenotonsillectomy to resolve OSA (OSA not resolved: OAI $\geq$1, AHI $\geq$ 2 at follow up).

# CHAPTER II. RESEARCH PROJECT

## Research Design and Methods

### Population

Our study used archival data from the Childhood Adenotonsillectomy Trial (CHAT) (Weinstock et al., 2014; Zhang et al., 2018), in which 464 children were randomly allocated to one of two treatment groups (early A&T, watchful waiting) in six clinical locations across the United States (Philadelphia, PA Cincinnati, OH Cleveland, OH Boston, MA St. Louis, MO; Bronx, NY). The study population included children aged 5.0-9.9 years with mild to moderate obstructive sleep apnea (OSA). OSA was identified by parental reports of habitual snoring and results of laboratory-based polysomnography. Data from polysomnography was used to calculate the obstructive apnea index (OAI) and apnea-hypopnea index (AHI). OSA diagnosis was defined as OAI ≥ 1 or AHI ≥ 2 (Redline et al., 2007). Children with severe OSAS were excluded from randomization if they had an OAI > 20, an AHI > 30, or spent > 2% of total sleep duration with an oxyhemoglobin saturation of <90%. Additionally, participants needed a tonsillar diameter of ≥1 on a standardized scale of 0-4 and were evaluated for adenotonsillar hypertrophy by an otolaryngologist. Comorbidities, medication use for attention deficit hyperactivity disorder, and a z-score of >3 for body mass index were all deemed exclusion criteria (Redline et al., 2011). Participants were recruited from pediatric sleep centers/laboratories, pediatric ENT clinics, general pediatric clinics, and the general population at seven clinical locations (Redline et al., 2011). Each facility obtained ethical approval and obtained consent from children older than 7 (unless assent is waived by IRB) and written informed consent from parents.

## Research Design

The study design of CHAT has been previously described (Redline et al., 2007). To summarize, the principal objective of CHAT was to determine if children with mild to moderate OSA who were randomly assigned to early adenotonsillectomy eAT had higher neurocognitive functioning than children assigned to watchful waiting following a seven-month observation period (Redline et al., 2007). The study examined whether children assigned to eAT had improved behavioral, neurocognitive, and physical development, as well as blood pressure, metabolic profile, and overall quality of life. Additionally, CHAT examined whether direct measures of OSA, such as the number of breathing disturbances recorded on overnight polysomnography and arterial oxygenation during sleep, improved more in the eAT arm than in the watchful waiting arm, and whether improvements in sleep and breathing measures were related to improvements in neuropsychological and health measures (Redline et al., 2011)

## Measures

For this study, the following measurements were obtained from the CHAT database:

**Biological sex**: Biological sex (female, male) as identified by the parent when enrolling their child in the study.

**Race:** Race (Black, White) as identified by the parent when enrolling their child in the study.

**Socioeconomic index**: Median family income, education level of the mother and father, and employment of the mother and father were defined based on a family history questionnaire (Marcus et al., 2013).

**Arousal Threshold:** Based on previous research, PSG values were input into the following equation in order to calculate the arousal threshold (Edwards et al., 2014):

Arousal threshold = −65.39 + (0.06 × age) + (3.69 × Gender [male = 1, female = 0]) − (0.03 × body mass index) − (0.11 × AHI) + (0.53 × nadir $SpO_2$) + (0.09 × % of the overall respiratory events that were hypopneas).

**Allostatic load**: The specific measurement of allostatic load varies widely between research studies. However, it has generally included concentrations of hormones, inflammatory biomarkers, and physiological/metabolic measures (blood pressure, BMI, glucose) that reflect the effects of stress on the body (Rodriquez, Kim, Sumner, Nápoles, & Pérez-Stable, 2019). Some studies use behavioral or psychosocial factors to measure allostatic load (Deuster, Su Jong, Remaley, & Poth, 2011). Broad consensus indicates that allostatic load should incorporate a variety of biological indicators. However, there is widespread debate on the number of biological systems that should be analyzed (e.g., immunological, metabolic, cardiovascular, etc.) or on the specific biological marker that should indicate such systems (Whelan, O'Shea, Hunt, & Dockray, 2021). Previous evaluations reported significant differences in the number of biomarkers used to calculate AL, ranging from six to seventeen (Mauss et al., 2015). The original allostatic load index is based on ten physiological measurements, including four primary mediators: dehydroepiandrosterone-sulfate (DHEA-S), epinephrine, norepinephrine, and cortisol, as well as six secondary outcomes: systolic blood pressure, diastolic blood pressure, cholesterol, high-density lipoprotein (HDL), glycosylated hemoglobin (HbA1c), and waist-hip ratio (WHR). The index's ten biomarkers are then converted to summary scores, with higher values suggesting greater physiological strain in response to stressors and lower values indicating more effective adaptation (Rodriquez et al., 2019).

More recent studies, however, have shown using the 10 original biomarkers can be a challenge in particular when leveraging large datasets such as the NHANES or CHAT because biomarkers of physiological function, specifically neuroendocrine and immune, are not always accessible (Shelley et al., 2021). Fortunately, these studies have also shown that allostatic load can be captured without neuroendocrine measures (Shelley et al., 2021). This is important to note because this study used publicly available data, the CHAT dataset (Marcus et al., 2013). The CHAT, much like the NHANES study, measured a variety of biological markers that can be used to assess allostatic load. However, CHAT does not include neuroendocrine markers proposed in the original allostatic load index (see Table 1). Using the validated methods of allostatic load without neuroendocrine markers allows us to approach the theoretical framework of allostatic load in relation to the proposed research and the availability of biomarkers (Whelan et al., 2021).

Allostatic load index was a cumulative total score calculated from the binary coding of the identified variables available in the CHAT study (see Table 1). Binary coding was based on prior research that informs the determination of cut-off scores for each factor using quartiles to determine a high-risk group for each marker (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). Recommended biological sex cut-offs informed the binary coding when available, as outlined previously (McLoughlin et al., 2020).

**Adenotonsillectomy failure.** Participants failed to meet the criteria for OSA symptoms being resolved as OAI $\geq 1$ or AHI $\geq 2$ at follow-up.

**Additional covariates: Asthma diagnosis** and **preterm birth** were defined by a medical history questionnaire as "ever had the condition" and "Was your child born early (prematurely, or 4 or more weeks early)?" respectively. Yes, no, or not sure were used as identifiers in the parent guardian medical history baseline (Marcus et al., 2013).

**Data analysis**

To achieve the overall objective and test the first hypothesis, univariate ANCOVAs were conducted to determine differences between Black and White children for arousal threshold and allostatic load adjusted for demographic and socioeconomic factors. To test the second hypothesis, discriminant function analysis was used to determine if arousal threshold and allostatic load predicts adenotonsillectomy failure.

# Results

## Participant Demographics

Of the original 464 participants in the CHAT dataset, 183 of the participants had baseline data, and a subsample of 98 of these participants underwent adenotonsillectomy surgery and had follow-up data. Participants were excluded if they did not have the allostatic load variables required at follow-up (Table 1). 263 participants were excluded based on not having c-reactive protein within detectable limits. 18 participants were excluded for being a race other than Black or White. Tables 3 and 4 outline participant characteristics for the total sample and subsample. In the larger sample, 59.5% were Black, and 55.7% were female. Similar rates occurred in the subsample, with 57.1% Black and 58.1% female. For socioeconomic status variables in the larger sample, a larger percent of Black children lived in households with an annual income of less than $20,000 and reported maternal and paternal education being less than high school in contrast to their White counterparts. Asthma rates were higher among Black children; however, premature birth rates and average BMI were similar. Total Apnea-Hypopnea Index (AHI) scores, Allostatic Load (AL) Index, and Arousal Threshold (ArTH) were higher among Black children. Similar patterns were shown for the subsample.

## Race and Arousal Threshold

Assumption testing for the ANCOVA analysis examining race differences for arousal threshold identified two exceptions: homogeneity of variance, which was accounted for in the analysis, and homogeneity of regression assumption testing indicated all covariates except sex and maternal education should be kept as covariates in the model. ANCOVA analysis revealed no differences between groups (Table 5).

For the subsample that received surgery, assumption testing for the ANCOVA analysis examining race differences for arousal threshold identified two exceptions: homogeneity of variance, which was accounted for in the analysis, and homogeneity of regression assumption testing indicated all covariates except sex should be kept as covariates in the model. ANCOVA analysis revealed a difference between the races for arousal threshold (Table 6). Specifically, Black children who underwent adenotonsillectomy surgery on average had a higher baseline arousal threshold than their white counterparts (Figure 2).

**Race and Allostatic Load**

Assumption testing for the ANCOVA analysis examining race differences for arousal threshold identified two exceptions: homogeneity of variance, which was accounted for in the analysis, and homogeneity of regression assumption testing indicated all covariates except asthma should be kept as covariates in the model. ANCOVA analysis revealed no differences between groups, but P values were (0.09) for both the main effect for race and the interaction effect for race and premature birth on allostatic load (Table 5). As shown in Figure 3, Black children exhibited a higher allostatic load compared to white children. Black children born premature also had a higher allostatic load than their white counterparts born premature (Figure 4).

For the subsample who received surgery, assumption testing for the ANCOVA analysis examining race differences for arousal threshold identified two exceptions: homogeneity of variance, which was accounted for in the analysis, and homogeneity of regression assumption testing indicated all covariates except asthma should be kept as covariates in the model.

ANCOVA analysis revealed no group differences for allostatic load index among children who underwent adenotonsillectomy surgery (Table 6).

**Predicting Response to Adenotonsillectomy Surgery**

For participants who underwent surgery, quadratic discriminant analysis was run to predict a failure in response in adenotonsillectomy surgery, defined as OAI $\geq 1$ or AHI $\geq 2$. The predictive model included race, arousal threshold, allostatic load, sex, asthma, premature birth, annual income, maternal education level, and paternal education level. Data was partitioned into a training (n=67) and testing (n=31) dataset in order to develop a predictive model and test its accuracy. The training model showed an accuracy of 82.1%, correctly predicting the success and failure of surgery. The subsequent testing model showed an accuracy of 54.8% in successfully predicting group membership. Figure 5 (A/B) shows the results for the training and testing model's accuracy.

# Discussion

## Discussion of Findings

The current analysis examined differences in ArTH and AL Index among Black and White children with OSA, and a model was created in an attempt to explain noted sleep disparities in response to adenotonsillectomy surgery. Key findings were that among the subsample who underwent adenotonsillectomy surgery, a difference between race was found for ArTH; Black children had a higher arousal threshold as compared to White children ($p < 0.05$). In the total sample that included the control group, there was an effect of race and an interaction effect of race and premature birth for differences in AL Index ($P<0.09$) for both findings). Black children had an increased allostatic load compared to white children, and Black premature born children also had a higher allostatic load compared to white premature born children. When predicting the success and failure of adenotonsillectomy surgery, the test model showed a 54.8% success rate in predicting group membership.

The data showed noted sleep health disparities in OSA presence and severity with higher rates among Black children. Additionally, identified socioeconomic status variables (annual household income, maternal and paternal education level) evidenced group differences with higher rates of Black children living in lower-income households and reporting maternal and paternal education levels of less than high school compared to their White counterparts. Similarly, among the larger sample, Black children also evidenced higher AL Indexes and ArTH as expected. However, our alpha for this difference was only ($P<0.09$). These results may have been due to several factors. For instance, these findings may have been due to the restricted age range of 5 – 9.9 years. Since the sample consisted of only children with OSA, the presence of OSA could have mitigated notable race differences previously found for allostatic load (Chen et

al., 2014; Deuster et al., 2011; Duru, Harawa, Kermah, & Norris, 2012; Rodriquez et al., 2019). This is because older individuals will have a more pronounced weathering effect from allostasis. Thus, allostatic load can better show differences between a group's social experience and environment due to prolonged stress response (Rodriquez et al., 2019).

The variables that are available from the CHAT data set to create an AL index did not include primary hypothalamic-pituitary-adrenal (HPA) axis mediators, or markers that are related to sympathetic nervous system activity, such as epinephrine and norepinephrine. The HPA axis plays a key role in allostatic load theory, and biomarkers of HPA axis activity, primarily cortisol, have been proposed as a measure to include in any index of allostatic load (Badanes, Watamura, & Hankin, 2011). The HPA axis is a potential key mechanism contributing to negative health outcomes experienced in adolescence, and sufficient sleep is required for optimal functioning of the hypothalamic-pituitary-adrenal (HPA) axis (Minkel et al., 2012) (Whelan et al., 2021). Additionally, salivary cortisol may be a useful biomarker for pediatric OSA (Park et al., 2013). The apnea-hypopnea score in pediatric patients has been shown to be significantly linked with noradrenaline and adrenaline urine levels (Kaditis et al., 2009; Snow, Gozal, Valdes, & Jortani, 2010). AL markers that are related to sympathetic nervous system activity, such as epinephrine and norepinephrine, are shown to be elevated in individuals with severe sleep apnea and have a role in the arousal response (White, 2005). Considering the importance of including primary neuroendocrine mediators (Cortisol, NE, EP) in Allostatic Load indexes, using these biomarkers could have increased the predictive power of our model.

AL Index and ArTH may contribute to the pathophysiology of OSA but not to the noted sleep health disparities in this population (Billings et al., 2019; Marcus et al., 1998). This age

range is notable for being relatively well protected against many of the adverse outcomes of sleep disturbances compared to other age ranges (Capdevila, Kheirandish-Gozal, Dayyat, & Gozal, 2008; E. S. Katz & D'Ambrosio, 2008). In addition, the diagnostic criteria for OSA in children does not require a decrease in blood oxygen saturation to accompany an apnea or hypopnea event (Ruehland et al., 2009). Alternatively, one or both may contribute to sleep health disparities, but the impact may take longer to manifest than by age 9.9 years using our model. Thus, further research is needed to better understand the true impact AL Index and ArTH have in this age group. ArTH may also not be the most sensitive measure alone to capture potential structural and obstructive contributors to OSA.

**Strengths**

The current analysis has several strengths, including the examination of potential contributors to sleep health disparities among pediatric patients with OSA. The examination of AL Index and ArTH combined with socioeconomic factors as contributors to sleep health disparities in OSA was novel and a starting point for much-needed research to better understand these disparities in this population. These findings also provide a solid foundation for further exploration into contributing factors that may be more sensitive to the pathophysiology of OSA, and how these play into the response to surgery as adenotonsillectomy is the most common treatment for pediatric OSA. The predictive power of the current model was not as strong as anticipated; however, a success rate of nearly 60% incorrectly identifying treatment response group membership is a promising start for developing models that may allow for improved clinical treatment planning and outcomes. An additional strength was using data collected from a large multi-center clinical trial, providing confidence in the integrity of the original dataset.

**Limitations**

The current analysis utilized an archival data set and not a new data set designed specifically for the purposes of this study. The data set used was, however, initially intended to ascertain treatment outcomes following adenotonsillectomy among pediatric patients with OSA and is, therefore, an acceptable source of data for this study. The only means to calculate ArTH from the data within this established dataset was using measurements from PSG. This method for calculating ArTH is not the gold standard measurement, which uses esophageal catheters or manipulation of continuous positive airway pressure (CPAP); however, the method used in the current analyses has been used and verified by a multitude of studies (Gray, McKenzie, & Eckert, 2017; Joosten et al., 2017; Lee et al., 2017). Additionally, this equation has not been rigorously tested on children within our age group (Edwards et al., 2014). Therefore, additional validation of the accuracy within this population needs to be done because the multiple regression equation used to calculate arousal threshold was originally designed to predict the arousal threshold in adults. It may be that there are different factors for children that would give a more accurate estimation of arousal threshold due to the differences in diagnostic criteria for children compared to adults (Richard B. Berry et al., 2012).

Race is a social-political category with biological consequences resulting from the impact of social inequality on people's health (David R. Williams, Mohammed, Leavell, & Collins, 2010; D.R. Williams et al., 2016). Using race as a variable in our predictive model reinforces the idea that the observed health inequities within underserved populations are due to racial differences and not social inequality. Variables such as allostatic load, socioeconomic status, and neighborhood disadvantage can describe how racial health disparities are due to differences in

environmental and daily experiences between racial groups, due to factors such as systemic and structural racism (Deuster et al., 2011; Duru et al., 2012; R. Wang et al., 2017). Therefore, using race as part of our predictive model equation is a limitation.

As previously described, the dataset did not include neuroendocrine biomarkers for the measure of AL Index, although calculations leveraged alternative validated biomarkers of AL (Shelley et al., 2021). Additionally, the data were from a limited pediatric sample (children ages 5-9.9 years), which limits the generalizability of these findings to the larger pediatric population. However, the purpose of the current analysis was to examine an area that has not previously been well explored. As such, this study can inform future studies by raising awareness about this current gap of knowledge regarding sleep health disparities.

**Future Directions**

Given the prior literature and the current findings, further research is needed to investigate the true impact AL Index and ArTH have in this age group. Identifying when these factors may shift from being non-significant to significant predictors of adverse health outcomes and health disparities would better inform the standard of care for these patients. Additionally, exploring more sensitive measures that may better explain differences in response to treatment is needed for this population as this would allow for a better understanding of treatment options for patients. One such possibility is exploring the role loop gain has in the pathophysiology of OSA among pediatric patients and their response to treatment.

Loop gain (a measure of ventilatory instability) has been shown to predict adenotonsillectomy failure in children (Armoni Domany et al., 2019). However, the extent to which loop gain can help explain the racial health disparities within adenotonsillectomy

outcomes has not been elucidated. However, performing loop gain analysis requires high-quality PSG data, and many acquisition systems do not sample at high enough frequency, or data are over-filtered.

When using AL as a measure of environmental stress exposure, pediatric populations are much more sensitive to the severity of stress exposure rather than to the accumulation of stress (Whelan et al., 2021). However, in adults, allostatic load can induce more pronounced "weathering" effects due to an accumulation of years of stress exposure. Most studies using allostatic load focus on adults for this reason (McLoughlin et al., 2020; Shelley et al., 2021). However, the effect allostatic load can have on children deserves further investigation due to the observed health disparities within pediatric populations.

One of our goals was to help patients receive a timely, effective treatment and avoid a surgery that has a high likelihood of not treating the condition. However, in very severe cases of pediatric OSA with a high grade of adenotonsillar hypertrophy, delaying treatment for a serious health condition by requesting a PSG may not be the best course of action (Friedman, 2007; Redline et al., 2011). However, OSA persisting post A&T regardless of OSA severity is a possibility, and post-operative PSG should be a standard practice ensuring OSA is no longer present. Further research into developing pre-treatment screening tools based on PSG data could help clinicians ensure proper treatment is given to pediatric patients with mild to moderate OSA. The findings from our study could be used to guide the development and testing of future sleep health interventions.

# References


Arens, R., McDONOUGH, J. M., Costarino, A. T., Mahboubi, S., Tayag-Kier, C. E., Maislin, G., . . . Pack, A. I. (2001). Magnetic resonance imaging of the upper airway structure of children with obstructive sleep apnea syndrome. *American Journal of Respiratory and Critical Care Medicine, 164*(4), 698-703.

Armoni Domany, K., He, Z., Nava-Guerra, L., Khoo, M. C. K., Xu, Y., Hossain, M. M., . . . Amin, R. S. (2019). The effect of adenotonsillectomy on ventilatory control in children with obstructive sleep apnea. *Sleep, 42*(5). doi:10.1093/sleep/zsz045

Azagra-Calero, E., Espinar-Escalona, E., Barrera-Mora, J. M., Llamas-Carreras, J. M., & Solano-Reina, E. (2012). Obstructive sleep apnea syndrome (OSAS). Review of the literature. *Med Oral Patol Oral Cir Bucal, 17*(6), e925-929. doi:10.4317/medoral.17706

Badanes, L. S., Watamura, S. E., & Hankin, B. L. (2011). Hypocortisolism as a potential marker of allostatic load in children: Associations with family risk and internalizing disorders. *Development and psychopathology, 23*(3), 881-896.

Baker, E., & Lui, F. (2022). Neuroanatomy, Vagal Nerve Nuclei. In *StatPearls*. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.

Berry, R. B., Budhiraja, R., Gottlieb, D. J., Gozal, D., Iber, C., Kapur, V. K., . . . Tangredi, M. M. (2012). Rules for Scoring Respiratory Events in Sleep: Update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. *Journal of Clinical Sleep Medicine, 08*(05), 597-619. doi:doi:10.5664/jcsm.2172

Berry, R. B., & Gleeson, K. (1997). Respiratory arousal from sleep: mechanisms and significance. *Sleep, 20*(8), 654-675. doi:10.1093/sleep/20.8.654

Beyeler, S. A., Hodges, M. R., & Huxtable, A. G. (2020). Impact of inflammation on developing respiratory control networks: rhythm generation, chemoreception and plasticity. *Respiratory Physiology & Neurobiology, 274*, 103357. doi:https://doi.org/10.1016/j.resp.2019.103357

Bhattacharjee, R., Kheirandish-Gozal, L., Kaditis, A. G., Verhulst, S. L., & Gozal, D. (2016). C-reactive Protein as a Potential Biomarker of Residual Obstructive Sleep Apnea Following Adenotonsillectomy in Children. *Sleep, 39*(2), 283-291. doi:10.5665/sleep.5428

Billings, M. E., Gold, D., Szpiro, A., Aaron, C. P., Jorgensen, N., Gassett, A., . . . Redline, S. R. (2019). The Association of Ambient Air Pollution with Sleep Apnea: The Multi-Ethnic Study of Atherosclerosis. *Ann Am Thorac Soc, 16*(3), 363-370. doi:10.1513/AnnalsATS.201804-248OC

Busch, D. R., Lynch, J. M., Winters, M. E., McCarthy, A. L., Newland, J. J., Ko, T., . . . Tapia, I. E. (2016). Cerebral Blood Flow Response to Hypercapnia in Children with Obstructive Sleep Apnea Syndrome. Sleep, 39(1), 209-216. doi:10.5665/sleep.5350

Capdevila, O. S., Kheirandish-Gozal, L., Dayyat, E., & Gozal, D. (2008). Pediatric obstructive sleep apnea: complications, management, and long-term outcomes. Proc Am Thorac Soc, 5(2), 274-282. doi:10.1513/pats.200708-138MG

CDC. (2021, November 24). Racism and health. Centers for Disease Control and Prevention. Retrieved April 21, 2022, from https://www.cdc.gov/healthequity/racism-disparities/index.html

Chae, D. H., Martz, C. D., Fuller-Rowell, T. E., Spears, E. C., Smith, T. T. G., Hunter, E. A., . . . Lim, S. S. (2019). Racial Discrimination, Disease Activity, and Organ Damage: The

Black Women's Experiences Living With Lupus (BeWELL) Study. *Am J Epidemiol, 188*(8), 1434-1443. doi:10.1093/aje/kwz105

Chamberlin, N. L. (2013). Brain circuitry mediating arousal from obstructive sleep apnea. *Curr Opin Neurobiol, 23*(5), 774-779. doi:10.1016/j.conb.2013.06.001

Chen, X., Redline, S., Shields, A. E., Williams, D. R., & Williams, M. A. (2014). Associations of allostatic load with sleep apnea, insomnia, short sleep duration, and other sleep disturbances: findings from the National Health and Nutrition Examination Survey 2005 to 2008. *Ann Epidemiol, 24*(8), 612-619. doi:10.1016/j.annepidem.2014.05.014

Chervin, R. D., Ruzicka, D. L., Giordani, B. J., Weatherly, R. A., Dillon, J. E., Hodges, E. K., . . . Guire, K. E. (2006). Sleep-disordered breathing, behavior, and cognition in children before and after adenotonsillectomy. *Pediatrics, 117*(4), e769-778. doi:10.1542/peds.2005-1837

Dempsey, J. A., Veasey, S. C., Morgan, B. J., & O'Donnell, C. P. (2010). Pathophysiology of sleep apnea. *Physiol Rev, 90*(1), 47-112. doi:10.1152/physrev.00043.2008

Deuster, P. A., Su Jong, K.-D., Remaley, A. T., & Poth, M. (2011). Allostatic Load and Health Status of African Americans and Whites. *American Journal of Health Behavior, 35*(6), 641-653. doi:10.5993/AJHB.35.6.1

Dudley, K. A., & Patel, S. R. (2016). Disparities and genetic risk factors in obstructive sleep apnea. *Sleep Med, 18*, 96-102. doi:10.1016/j.sleep.2015.01.015

Duru, O. K., Harawa, N. T., Kermah, D., & Norris, K. C. (2012). Allostatic load burden and racial disparities in mortality. *J Natl Med Assoc, 104*(1-2), 89-95. doi:10.1016/s0027-9684(15)30120-6

Eckert, D. J., & Malhotra, A. (2008). Pathophysiology of adult obstructive sleep apnea. *Proc Am Thorac Soc, 5*(2), 144-153. doi:10.1513/pats.200707-114MG

Eckert, D. J., White, D. P., Jordan, A. S., Malhotra, A., & Wellman, A. (2013). Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. *Am J Respir Crit Care Med, 188*(8), 996-1004. doi:10.1164/rccm.201303-0448OC

Eckert, D. J., & Younes, M. K. (2014). Arousal from sleep: implications for obstructive sleep apnea pathogenesis and treatment. *J Appl Physiol (1985), 116*(3), 302-313. doi:10.1152/japplphysiol.00649.2013

Eckert, D. J., & Younes, M. K. (2014). Arousal from sleep: implications for obstructive sleep apnea pathogenesis and treatment. *Journal of Applied Physiology, 116*(3), 302-313. doi:10.1152/japplphysiol.00649.2013

Edwards, B. A., Eckert, D. J., McSharry, D. G., Sands, S. A., Desai, A., Kehlmann, G., . . . Malhotra, A. (2014). Clinical predictors of the respiratory arousal threshold in patients with obstructive sleep apnea. *Am J Respir Crit Care Med, 190*(11), 1293-1300. doi:10.1164/rccm.201404-0718OC

Entzian, P., Linnemann, K., Schlaak, M., & Zabel, P. (1996). Obstructive sleep apnea syndrome and circadian rhythms of hormones and cytokines. *Am J Respir Crit Care Med, 153*(3), 1080-1086. doi:10.1164/ajrccm.153.3.8630548

Finnsson, E., Ólafsdóttir, G. H., Loftsdóttir, D. L., Jónsson, S., Helgadóttir, H., Ágústsson, J. S., . . . Wellman, A. (2021). A scalable method of determining physiological endotypes of sleep apnea from a polysomnographic sleep study. *Sleep, 44*(1). doi:10.1093/sleep/zsaa168

Fogel, R. B., Malhotra, A., Pillar, G., Edwards, J. K., Beauregard, J., Shea, S. A., & White, D. P. (2001). Genioglossal activation in patients with obstructive sleep apnea versus control subjects: mechanisms of muscle control. *American Journal of Respiratory and Critical Care Medicine, 164*(11), 2025-2030.

Fogel, R. B., Trinder, J., Malhotra, A., Stanchina, M., Edwards, J. K., Schory, K. E., & White, D. P. (2003). Within-Breath Control of Genioglossal Muscle Activation in Humans: Effect of Sleep-Wake State. *The Journal of Physiology, 550*(3), 899-910. doi:https://doi.org/10.1113/jphysiol.2003.038810

Friedman, N. R. (2007). Polysomnography should not be required both before and after adenotonsillectomy for childhood sleep disordered breathing. *J Clin Sleep Med, 3*(7), 678-680.

Geronimus, A. T., Hicken, M., Keene, D., & Bound, J. (2006). "Weathering" and age patterns of allostatic load scores among blacks and whites in the United States. *Am J Public Health, 96*(5), 826-833. doi:10.2105/ajph.2004.060749

Gleeson, K., Zwillich, C. W., & White, D. P. (1990). The influence of increasing ventilatory effort on arousal from sleep. *Am Rev Respir Dis, 142*(2), 295-300. doi:10.1164/ajrccm/142.2.295

Gottlieb, D. J., Chase, C., Vezina, R. M., Heeren, T. C., Corwin, M. J., Auerbach, S. H., . . . Lesko, S. M. (2004). Sleep-disordered breathing symptoms are associated with poorer cognitive function in 5-year-old children. *J Pediatr, 145*(4), 458-464. doi:10.1016/j.jpeds.2004.05.039

Gray, E. L., McKenzie, D. K., & Eckert, D. J. (2017). Obstructive Sleep Apnea without Obesity Is Common and Difficult to Treat: Evidence for a Distinct Pathophysiological Phenotype. *J Clin Sleep Med, 13*(1), 81-88. doi:10.5664/jcsm.6394

Guilleminault, C. (1987). Obstructive sleep apnea syndrome and its treatment in children: areas of agreement and controversy. *Pediatr Pulmonol, 3*(6), 429-436. doi:10.1002/ppul.1950030610

Guilleminault, C., Huang, Y. S., Quo, S., Monteyrol, P. J., & Lin, C. H. (2013). Teenage sleep-disordered breathing: recurrence of syndrome. *Sleep Med, 14*(1), 37-44. doi:10.1016/j.sleep.2012.08.010

Hardeman, R. R., Murphy, K. A., Karbeah, J., & Kozhimannil, K. B. (2018). Naming Institutionalized Racism in the Public Health Literature: A Systematic Literature Review. *Public Health Rep, 133*(3), 240-249. doi:10.1177/0033354918760574

Horner, R. L., Innes, J. A., Holden, H. B., & Guz, A. (1991). Afferent pathway(s) for pharyngeal dilator reflex to negative pressure in man: a study using upper airway anaesthesia. *The Journal of Physiology, 436*(1), 31-44. doi:https://doi.org/10.1113/jphysiol.1991.sp018537

Huxtable, A. G., Vinit, S., Windelborn, J. A., Crader, S. M., Guenther, C. H., Watters, J. J., & Mitchell, G. S. (2011). Systemic inflammation impairs respiratory chemoreflexes and plasticity. *Respir Physiol Neurobiol, 178*(3), 482-489. doi:10.1016/j.resp.2011.06.017

Israel, L. P., Benharoch, D., Gopas, J., & Goldbart, A. D. (2013). A pro-inflammatory role for nuclear factor kappa B in childhood obstructive sleep apnea syndrome. *Sleep, 36*(12), 1947-1955. doi:10.5665/sleep.3236

Jelev, A., Sood, S., Liu, H., Nolan, P., & Horner, R. L. (2001). Microdialysis perfusion of 5-HT into hypoglossal motor nucleus differentially modulates genioglossus activity across

natural sleep-wake states in rats. *The Journal of Physiology, 532*(2), 467-481. doi:https://doi.org/10.1111/j.1469-7793.2001.0467f.x

Jones, C. P. (2000). Levels of racism: a theoretic framework and a gardener's tale. *American Journal of Public Health, 90*(8), 1212-1215. doi:10.2105/AJPH.90.8.1212

Joosten, S. A., Leong, P., Landry, S. A., Sands, S. A., Terrill, P. I., Mann, D., . . . Edwards, B. A. (2017). Loop Gain Predicts the Response to Upper Airway Surgery in Patients With Obstructive Sleep Apnea. *Sleep, 40*(7). doi:10.1093/sleep/zsx094

Jordan, A. S., & White, D. P. (2008). Pharyngeal motor control and the pathogenesis of obstructive sleep apnea. *Respir Physiol Neurobiol, 160*(1), 1-7. doi:10.1016/j.resp.2007.07.009

Kaditis, A. G., Alexopoulos, E. I., Damani, E., Hatzi, F., Chaidas, K., Kostopoulou, T., . . . Gourgoulianis, K. (2009). Urine levels of catecholamines in Greek children with obstructive sleep-disordered breathing. *Pediatric Pulmonology, 44*(1), 38-45. doi:https://doi.org/10.1002/ppul.20916

Katz, E. S., & D'Ambrosio, C. M. (2008). Pathophysiology of pediatric obstructive sleep apnea. *Proc Am Thorac Soc, 5*(2), 253-262. doi:10.1513/pats.200707-111MG

Katz, E. S., Lutz, J., Black, C., & Marcus, C. L. (2003). Pulse Transit Time as a Measure of Arousal and Respiratory Effort in Children with Sleep-Disordered Breathing. *Pediatric Research, 53*(4), 580-588. doi:10.1203/01.PDR.0000057206.14698.47

Katz, E. S., & White, D. P. (2003). Genioglossus activity in children with obstructive sleep apnea during wakefulness and sleep onset. *Am J Respir Crit Care Med, 168*(6), 664-670. doi:10.1164/rccm.200301-092OC

Katz, E. S., & White, D. P. (2004). Genioglossus activity during sleep in normal control subjects and children with obstructive sleep apnea. *Am J Respir Crit Care Med, 170*(5), 553-560. doi:10.1164/rccm.200403-262OC

Kubin, L. (2016). Neural Control of the Upper Airway: Respiratory and State-Dependent Mechanisms. *Compr Physiol, 6*(4), 1801-1850. doi:10.1002/cphy.c160002

Lee, R. W. W., Sutherland, K., Sands, S. A., Edwards, B. A., Chan, T. O., S, S. S. N., . . . Cistulli, P. A. (2017). Differences in respiratory arousal threshold in Caucasian and Chinese patients with obstructive sleep apnoea. *Respirology, 22*(5), 1015-1021. doi:10.1111/resp.13022

Li, Y., Orr, J., Jen, R., Sands, S. A., DeYoung, P., Smales, E., . . . Malhotra, A. (2019). Is there a threshold that triggers cortical arousals in obstructive sleep apnea. *Sleep, 42*(6). doi:10.1093/sleep/zsz047

Liu, T., Zhang, L., Joo, D., & Sun, S. C. (2017). NF-κB signaling in inflammation. *Signal Transduct Target Ther, 2*, 17023-. doi:10.1038/sigtrans.2017.23

Loeliger, M., Tolcos, M., Leditschke, J., Campbell, P., & Rees, S. (2000). Tracing Cranial Nerve Pathways (Glossopharyngeal, Vagus, and Hypoglossal) in SIDS and Control Infants: A Dil Study. *Journal of Neuropathology & Experimental Neurology, 59*(9), 822-829. doi:10.1093/jnen/59.9.822

Malhotra, A., Pillar, G., Fogel, R. B., Beauregard, J., Edwards, J. K., Slamowitz, D. I., . . . White, D. P. (2000). Genioglossal but not palatal muscle activity relates closely to pharyngeal pressure. *American Journal of Respiratory and Critical Care Medicine, 162*(3), 1058-1062.

Malhotra, A., Pillar, G., Fogel, R. B., Edwards, J. K., Ayas, N., Akahoshi, T., . . . White, D. P. (2002). Pharyngeal pressure and flow effects on genioglossus activation in normal subjects. *American Journal of Respiratory and Critical Care Medicine, 165*(1), 71-77.

Marcus, C. L., Brooks, L. J., Draper, K. A., Gozal, D., Halbower, A. C., Jones, J., . . . Spruyt, K. (2012). Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics, 130*(3), e714-755. doi:10.1542/peds.2012-1672

Marcus, C. L., Katz, E. S., Lutz, J., Black, C. A., Galster, P., & Carson, K. A. (2005). Upper Airway Dynamic Responses in Children with the Obstructive Sleep Apnea Syndrome. *Pediatric Research, 57*(1), 99-107. doi:10.1203/01.PDR.0000147565.74947.14

Marcus, C. L., Lutz, J., Carroll, J. L., & Bamford, O. (1998). Arousal and ventilatory responses during sleep in children with obstructive sleep apnea. *J Appl Physiol (1985), 84*(6), 1926-1936. doi:10.1152/jappl.1998.84.6.1926

Marcus, C. L., Moore, R. H., Rosen, C. L., Giordani, B., Garetz, S. L., Taylor, H. G., . . . Redline, S. (2013). A Randomized Trial of Adenotonsillectomy for Childhood Sleep Apnea. *New England Journal of Medicine, 368*(25), 2366-2376. doi:10.1056/NEJMoa1215881

Marcus, C. L., Moreira, G. A., Bamford, O., & Lutz, J. (1999). Response to inspiratory resistive loading during sleep in normal children and children with obstructive apnea. *J Appl Physiol (1985), 87*(4), 1448-1454. doi:10.1152/jappl.1999.87.4.1448

Mauss, D., Li, J., Schmidt, B., Angerer, P., & Jarczok, M. N. (2015). Measuring allostatic load in the workforce: a systematic review. *Ind Health, 53*(1), 5-20. doi:10.2486/indhealth.2014-0122

McLoughlin, S., Kenny, R. A., & McCrory, C. (2020). Does the choice of Allostatic Load scoring algorithm matter for predicting age-related health outcomes? *Psychoneuroendocrinology, 120*, 104789. doi:https://doi.org/10.1016/j.psyneuen.2020.104789

Minkel, J. D., Banks, S., Htaik, O., Moreta, M. C., Jones, C. W., McGlinchey, E. L., . . . Dinges, D. F. (2012). Sleep deprivation and stressors: evidence for elevated negative affect in response to mild stressors when sleep deprived. *Emotion, 12*(5), 1015.

Monahan, K. J., Larkin, E. K., Rosen, C. L., Graham, G., & Redline, S. (2002). Utility of noninvasive pharyngometry in epidemiologic studies of childhood sleep-disordered breathing. *American Journal of Respiratory and Critical Care Medicine, 165*(11), 1499-1503.

Nácher, M., Farré, R., Montserrat, J. M., Torres, M., Navajas, D., Bulbena, O., & Serrano-Mollar, A. (2009). Biological consequences of oxygen desaturation and respiratory effort in an acute animal model of obstructive sleep apnea (OSA). *Sleep Med, 10*(8), 892-897. doi:10.1016/j.sleep.2008.09.014

Oliven, R., Cohen, G., Dotan, Y., Somri, M., Schwartz, A. R., & Oliven, A. (2018). Alteration in upper airway dilator muscle coactivation during sleep: comparison of patients with obstructive sleep apnea and healthy subjects. *Journal of Applied Physiology, 124*(2), 421-429. doi:10.1152/japplphysiol.01067.2016

Orem, J. (1990). The nature of the wakefulness stimulus for breathing. *Prog Clin Biol Res, 345*, 23-30; discussion 31.

Orem, J., & Trotter, R. H. (1992). Postinspiratory neuronal activities during behavioral control, sleep, and wakefulness. *J Appl Physiol (1985), 72*(6), 2369-2377. doi:10.1152/jappl.1992.72.6.2369

Osman, A. M., Carter, S. G., Carberry, J. C., & Eckert, D. J. (2018). Obstructive sleep apnea: current perspectives. *Nat Sci Sleep, 10*, 21-34. doi:10.2147/nss.S124657

Park, C.-S., Guilleminault, C., Hwang, S.-H., Jeong, J.-H., Park, D.-S., & Maeng, J.-H. (2013). Correlation of salivary cortisol level with obstructive sleep apnea syndrome in pediatric subjects. *Sleep Medicine, 14*(10), 978-984. doi:https://doi.org/10.1016/j.sleep.2013.05.012

Redline, S., Amin, R., Beebe, D., Chervin, R. D., Garetz, S. L., Giordani, B., . . . Ellenberg, S. (2011). 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*(11), 1509-1517. doi:10.5665/sleep.1388

Redline, S., Budhiraja, R., Kapur, V., Marcus, C. L., Mateika, J. H., Mehra, R., . . . Quan, S. F. (2007). The scoring of respiratory events in sleep: reliability and validity. *J Clin Sleep Med, 3*(2), 169-200.

Roberts, D. E. (2011). *Fatal invention : how science, politics, and big business re-create race in the twenty-first century*: New York : New Press, [2011] ©2011.

Roda, F., Gestreau, C., & Bianchi, A. L. (2002). Discharge patterns of hypoglossal motoneurons during fictive breathing, coughing, and swallowing. *J Neurophysiol, 87*(4), 1703-1711. doi:10.1152/jn.00347.2001

Rodriquez, E. J., Kim, E. N., Sumner, A. E., Nápoles, A. M., & Pérez-Stable, E. J. (2019). Allostatic Load: Importance, Markers, and Score Determination in Minority and

Disparity Populations. *Journal of Urban Health, 96*(1), 3-11. doi:10.1007/s11524-019-00345-5

Rosen, C. L., Larkin, E. K., Kirchner, H. L., Emancipator, J. L., Bivins, S. F., Surovec, S. A., . . . Redline, S. (2003). Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. *The Journal of Pediatrics, 142*(4), 383-389. doi:https://doi.org/10.1067/mpd.2003.28

Ruehland, W. R., Rochford, P. D., O'Donoghue, F. J., Pierce, R. J., Singh, P., & Thornton, A. T. (2009). The new AASM criteria for scoring hypopneas: impact on the apnea hypopnea index. *Sleep, 32*(2), 150-157. doi:10.1093/sleep/32.2.150

Ruiter, M. E., DeCoster, J., Jacobs, L., & Lichstein, K. L. (2010). Sleep disorders in African Americans and Caucasian Americans: a meta-analysis. *Behav Sleep Med, 8*(4), 246-259. doi:10.1080/15402002.2010.509251

Ryan, S., Taylor, C. T., & McNicholas, W. T. (2005). Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. *Circulation, 112*(17), 2660-2667. doi:10.1161/circulationaha.105.556746

Ryan, S., Taylor, C. T., & McNicholas, W. T. (2006). Predictors of elevated nuclear factor-kappaB-dependent genes in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med, 174*(7), 824-830. doi:10.1164/rccm.200601-066OC

Saboisky, J., Eckert, D., & Malhotra, A. (2010). Stable breathing through deeper sleeping. *Thorax, 65*(2), 95. doi:10.1136/thx.2009.127860

Sakamoto, Y. (2019). Morphological Features of the Branching Pattern of the Hypoglossal Nerve. *The Anatomical record, 302*(4), 558-567. doi:https://doi.org/10.1002/ar.23819

Seeman, T. E., Singer, B. H., Rowe, J. W., Horwitz, R. I., & McEwen, B. S. (1997). Price of Adaptation—Allostatic Load and Its Health Consequences: MacArthur Studies of Successful Aging. *Archives of Internal Medicine, 157*(19), 2259-2268. doi:10.1001/archinte.1997.00440400111013

Shelley, H. L., Robert-Paul, J., Kristen, D.-O. C., & Julie, S. (2021). Allostatic load scoring using item response theory. *Comprehensive Psychoneuroendocrinology, 5*, 100025. doi:https://doi.org/10.1016/j.cpnec.2020.100025

Snow, A., Gozal, D., Valdes, R., Jr., & Jortani, S. A. (2010). Urinary proteins for the diagnosis of obstructive sleep apnea syndrome. *Methods Mol Biol, 641*, 223-241. doi:10.1007/978-1-60761-711-2_13

Spilsbury, J. C., Storfer-Isser, A., Kirchner, H. L., Nelson, L., Rosen, C. L., Drotar, D., & Redline, S. (2006). Neighborhood disadvantage as a risk factor for pediatric obstructive sleep apnea. *J Pediatr, 149*(3), 342-347. doi:10.1016/j.jpeds.2006.04.061

Suzuki, M., Ogawa, H., Okabe, S., Horiuchi, A., Okubo, M., Ikeda, K., . . . Kobayashi, T. (2005). Digital recording and analysis of esophageal pressure for patients with obstructive sleep apnea-hypopnea syndrome. *Sleep Breath, 9*(2), 64-72. doi:10.1007/s11325-005-0015-0

Taranto-Montemurro, L., Edwards, B. A., Sands, S. A., Marques, M., Eckert, D. J., White, D. P., & Wellman, A. (2016). Desipramine Increases Genioglossus Activity and Reduces Upper Airway Collapsibility during Non-REM Sleep in Healthy Subjects. *Am J Respir Crit Care Med, 194*(7), 878-885. doi:10.1164/rccm.201511-2172OC

Terrill, P. I., Edwards, B. A., Nemati, S., Butler, J. P., Owens, R. L., Eckert, D. J., . . . Sands, S. A. (2015). Quantifying the ventilatory control contribution to sleep apnoea using

polysomnography. *European Respiratory Journal, 45*(2), 408-418. doi:10.1183/09031936.00062914

van Lunteren, E. (1993). Muscles of the pharynx: structural and contractile properties. *Ear, nose & throat journal, 72*(1), 27-33.

Wang, R., Dong, Y., Weng, J., Kontos, E. Z., Chervin, R. D., Rosen, C. L., . . . Redline, S. (2017). Associations among Neighborhood, Race, and Sleep Apnea Severity in Children. A Six-City Analysis. *Annals of the American Thoracic Society, 14*(1), 76-84. doi:10.1513/AnnalsATS.201609-662OC

Wang, T., Zhang, X., & Li, J. J. (2002). The role of NF-kappaB in the regulation of cell stress responses. *Int Immunopharmacol, 2*(11), 1509-1520. doi:10.1016/s1567-5769(02)00058-9

Weinstock, T. G., Rosen, C. L., Marcus, C. L., Garetz, S., Mitchell, R. B., Amin, R., . . . Redline, S. (2014). Predictors of obstructive sleep apnea severity in adenotonsillectomy candidates. *Sleep, 37*(2), 261-269. doi:10.5665/sleep.3394

Wellman, A., Jordan, A. S., Malhotra, A., Fogel, R. B., Katz, E. S., Schory, K., . . . White, D. P. (2004). Ventilatory control and airway anatomy in obstructive sleep apnea. *Am J Respir Crit Care Med, 170*(11), 1225-1232. doi:10.1164/rccm.200404-510OC

Whelan, E., O'Shea, J., Hunt, E., & Dockray, S. (2021). Evaluating measures of allostatic load in adolescents: A systematic review. *Psychoneuroendocrinology, 131*, 105324. doi:https://doi.org/10.1016/j.psyneuen.2021.105324

White, D. P. (2005). Pathogenesis of obstructive and central sleep apnea. *Am J Respir Crit Care Med, 172*(11), 1363-1370. doi:10.1164/rccm.200412-1631SO

Williams, D. R., Mohammed, S. A., Leavell, J., & Collins, C. (2010). Race, socioeconomic status, and health: Complexities, ongoing challenges, and research opportunities. *Annals of the New York Academy of Sciences, 1186*(1), 69-101. doi:https://doi.org/10.1111/j.1749-6632.2009.05339.x

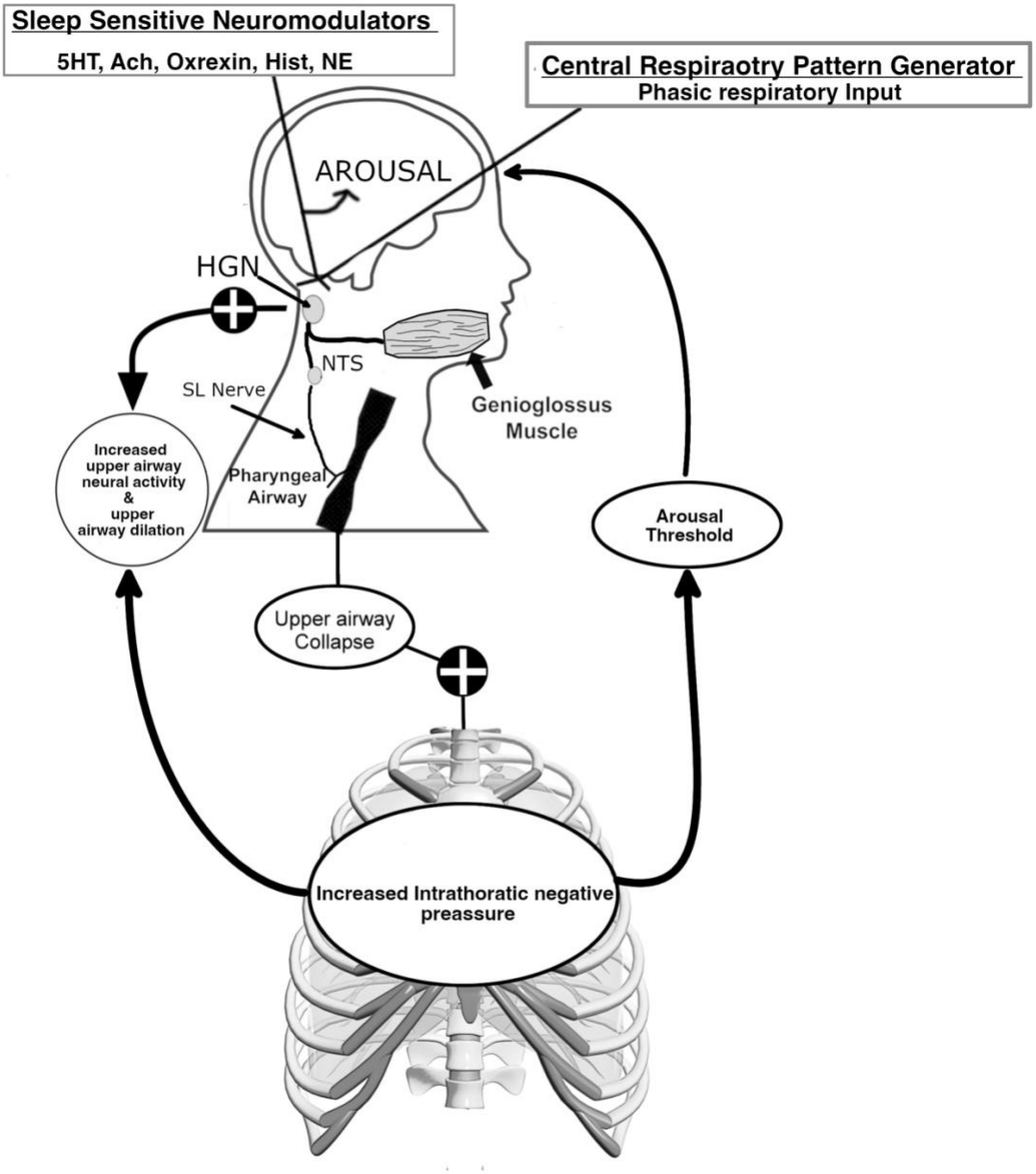
Williams, D. R., Priest, N., & Anderson, N. (2016). Understanding Associations between Race, Socioeconomic Status and Health: Patterns and Prospects. *Health Psychology, 35*(4), 407-411.

Younes, M., Ostrowski, M., Thompson, W., Leslie, C., & Shewchuk, W. (2001). Chemical control stability in patients with obstructive sleep apnea. *Am J Respir Crit Care Med, 163*(5), 1181-1190. doi:10.1164/ajrccm.163.5.2007013

Yu, Y., Wan, Y., & Huang, C. (2009). The biological functions of NF-kappaB1 (p50) and its potential as an anti-cancer target. *Curr Cancer Drug Targets, 9*(4), 566-571. doi:10.2174/156800909788486759

Zhang, G. Q., Cui, L., Mueller, R., Tao, S., Kim, M., Rueschman, M., . . . Redline, S. (2018). The National Sleep Research Resource: towards a sleep data commons. *J Am Med Inform Assoc, 25*(10), 1351-1358. doi:10.1093/jamia/ocy064

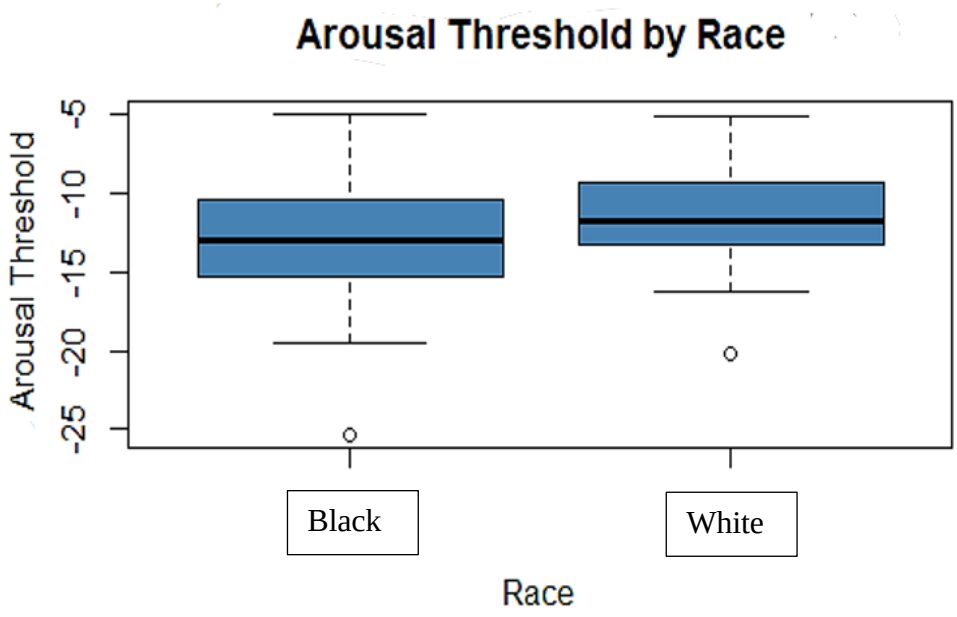
**Figure 1**. Illustration of the arousal response pathways




There are three primary neuronal sources of input to the genioglossus muscle. The precise pathways for the arousal response have not been elucidated. So this figure serves as a estimation.

SL-Superior laryngeal Nerve. HGN-Hypoglossal Nucleus. NTS-Nucleus of Solitary Tract.
Adapted from (Saboisky, Eckert, & Malhotra, 2010) (White, 2005)

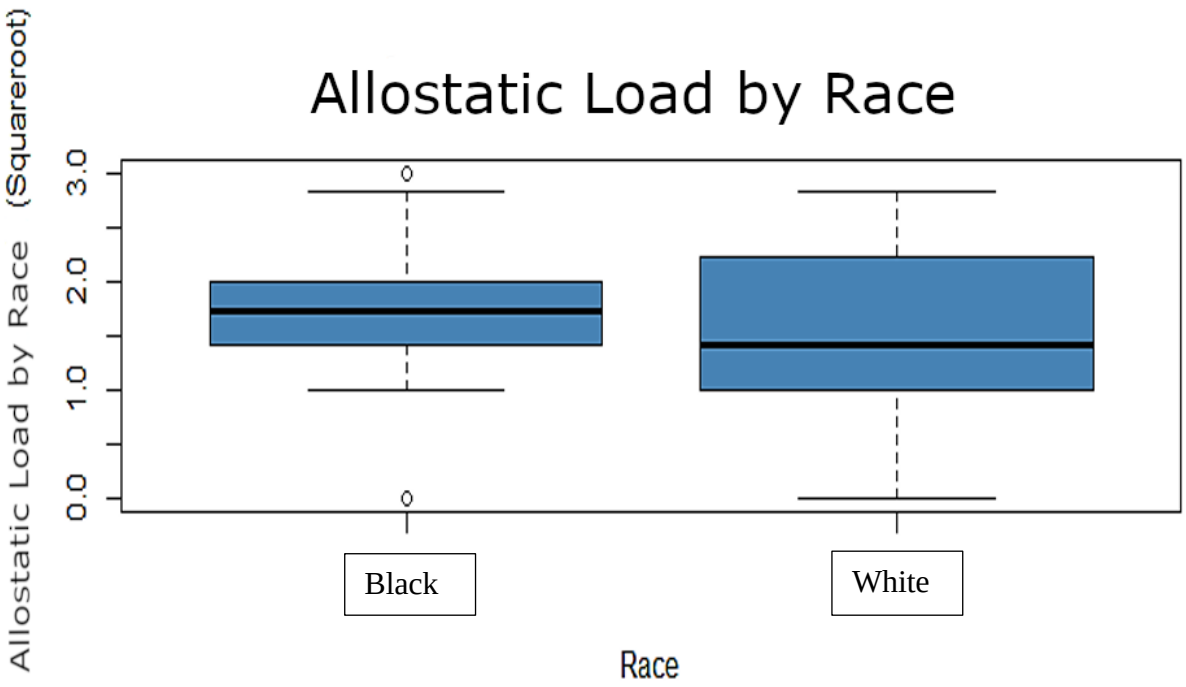
**Figure 2**. Boxplot of race differences for Arousal Threshold (n = 98)




Black children showed an increased negative arousal threshold.

$p < 0.05$

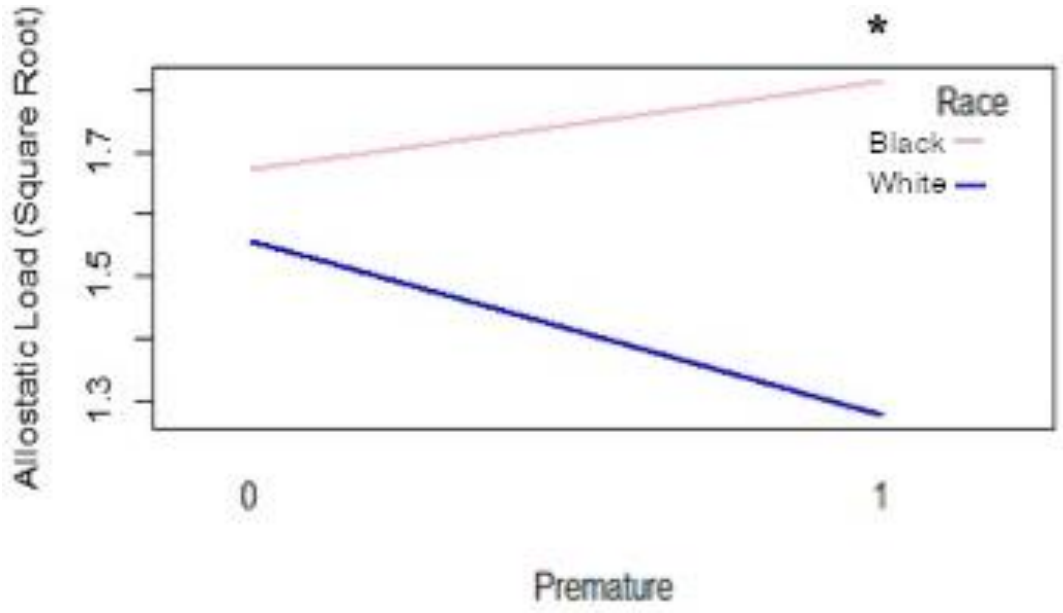
**Figure 3**. Race and Allostatic Load (n = 183)




Black children had a higher allostatic load compared to White children

$p < 0.09$

**Figure 4**. The interaction effect of race and premature birth for Allostatic Load (n=183)




0=Not born Premature (n=150)

1= Born Premature (n=33)

Black children born premature had a higher allostatic load compared to White children born premature.

$p < 0.09$

**Figure 5 (A/B)** Quadratic Discriminant Analysis results predicting A&T Failure (n=98)

A.

| Training | | Predictive model | |
|---|---|---|---|
| | | Success | Failure |
| Actual Outcome | Success | 33 | 2 |
| | Failure | 10 | 22 |

(n=67)

B.

| Testing | | Predictive model | |
|---|---|---|---|
| | | Success | Failure |
| Actual Outcome | Success | 15 | 12 |
| | Failure | 2 | 2 |

(n=31)

The training model showed an accuracy of **82.1%,** in correctly predicting the success and failure of adenotonsillectomy.

The testing model showed an accuracy of **54.6%,** in correctly predicting the success and failure of adenotonsillectomy.

Failure of adenotonsillectomy was defined as a participant having a AHI ≥2 and OAI ≥ 1 (criteria for pediatric OSA diagnosis) at follow up as determined by PSG.

Success of adenotonsillectomy was defined as symptoms being resolved based on PSG (AHI< 2 and OAI < 1),

**Table 1. Variables Used in Prior Literature to Calculate Allostatic Load (AL)**

| Variable | Seeman et al., 1997 | Thorpe et al., 2020 | Shelly, et al., 2021 | CHAT | Reference ID |
|---|---|---|---|---|---|
| **Blood glucose (fasting)** | | | | ^^ | 2,19,21,25 |
| **HbA1c** | * | ** | | NA | |
| **Systolic Blood Pressure (SBP)** | * | | ^ | ^^ | 1-19, 21-25 |
| **Diastolic Blood Pressure (DBP)** | * | | ^ | ^^ | 1-18, 21-25 |
| **Body Mass Index (BMI)** | | | ^ | ^^ | 1-19, 23-25 |
| **C-reactive protein (CRP)** | | ** | ^ | ^^ | 1,2,4,9,19,21,22 |
| **HDL** | * | ** | ^ | ^^ | 1,2,18,19,21,22,25 |
| **LDL** | | | | ^^ | 2,19,21,25 |
| **Total Cholesterol Levels** | * | ** | ^ | ^^ | 1,2,18,22,25 |
| **Cortisol** | * | | | NA | |
| **Cystatine-C** | | ** | | NA | |

| | | | | | |
|---|---|---|---|---|---|
| **DHEA-S** | * | | | NA | |
| **Epinephrine** | * | | | NA | |
| **Norepinephrine** | * | | | NA | |
| **Resting Heart Rate** | | ** | ^ | ^^ | 2,24,25 |
| **Triglycerides** | | | ^ | ^^ | 2,19,21,25 |
| **Waist Circumference** | | ** | | X | |
| **Waist-Hip Ratio (WHR)** | * | | | ^^ | 18,23 |

* Original measure used to calculate AL (Seeman et al., 1997).

** Measure used to calculate AL in Black population (Thorpe et al., 2020)

^ Secondary measures validated by a review of AL measures not using neuroendocrine bio markers (Shelley, Robert-Paul et al., 2021).

^^ Variable in CHAT study

NA Not available in CHAT study

X Not being used due to insufficient support

**Note**. Reference ID refers to ID number for the study as listed in Table 2.

**Table 2. Allostatic Load Studies by Author(s), Title, and Study Design**

| Reference ID | Author(s) | Title | Study Design |
|---|---|---|---|
| Studies included in the adolescent allostatic load systematic review | | | |
| **1** | Augustine et al. (2016) | Exploring the bio-behavioral link between stress, allostatic load & micronutrient status: A cross-sectional study among adolescent boys | Cross-sectional |
| **2** | Berger et al. (2019) | Hair cortisol, allostatic load, and depressive symptoms in Australian Aboriginal and Torres Strait Islander people | Cross-sectional |
| **3** | Brody et al. (2014a) | Neighborhood poverty and allostatic load in African American youth | Longitudinal |
| **4** | Brody et al. (2014b) | Perceived Discrimination Among African American Adolescents and Allostatic Load: A Longitudinal Analysis With Buffering Effects | Longitudinal |
| **5** | Brody et al. (2013a) | Is Resilience Only Skin Deep?: Rural African Americans' Socioeconomic Status–Related Risk and Competence in Preadolescence and Psychological Adjustment and Allostatic Load at Age 19 | Longitudinal |
| **6** | Brody et al. (2013b) | Cumulative socioeconomic status risk, allostatic load, and adjustment: a prospective latent profile analysis with contextual and genetic protective factors | Longitudinal |

| | | | |
|---|---|---|---|
| **7** | Brody et al. (2013c) | Supportive family environments, genes that confer sensitivity, and allostatic load among rural African American emerging adults: a prospective analysis | Longitudinal |
| **8** | Chen et al. (2015) | Neighborhood poverty, college attendance, and diverging profiles of substance use and allostatic load in rural African American youth | Secondary analysis |
| **9** | Chen et al. (2016) | The Great Recession and health risks in African American youth | Secondary analysis |
| **10** | Dich et al. (2015a) | Children's emotionality moderates the association between maternal responsiveness and allostatic load: Investigation into differential susceptibility | Secondary analysis |
| **11** | Dich et al. (2015b) | Children's negative emotionality combined with poor self-regulation affects allostatic load in adolescence | Secondary analysis |
| **12** | Dich et al. (2017) | In risky environments, emotional children have more behavioral problems but lower allostatic load | Longitudinal |
| **13** | Doan et al. (2016) | Stress of stoicism: Low emotionality and high control lead to increases in allostatic load | Longitudinal |
| **14** | Doan and Evans (2011) | Maternal responsiveness moderates the relationship between allostatic load and working memory | Secondary analysis |

| | | | |
|---|---|---|---|
| **15** | Evans and Fuller-Rowell, 2013 | Childhood poverty, chronic stress, and young adult working memory: The protective role of self-regulatory capacity | Longitudinal |
| **16** | Evans and Kim, 2012 | (Evans and Kim, 2012) Childhood poverty and young adult's allostatic load: The mediating role of cumulative risk exposure | Secondary analysis |
| **17** | Fuller-Rowell et al. (2012) | Poverty and health: The mediating role of perceived discrimination | Secondary analysis |
| **18** | Harding et al. (2016) | Longitudinal study of cardiometabolic risk from early adolescence to early adulthood in an ethnically diverse cohort | Longitudinal |

| | | | |
|---|---|---|---|
| **19** | King et al., 2019a, King et al., 2019b | Testing allostatic load factor structures among adolescents: A structural equation modeling approach | Secondary analysis |
| **20** | Skinner et al. (2011) | Allostasis model facilitates understanding race differences in the diurnal cortisol rhythm | Cross-sectional |

| | | | |
|---|---|---|---|
| **21** | Theall et al. (2012) | Cumulative neighborhood risk of psychosocial stress and allostatic load in adolescents | Secondary analysis |
| **22** | Rainisch and Upchurch (2013) | Sociodemographic correlates of allostatic load amongst a national sample of adolescents: findings from the National Health and Nutrition Examination Survey, 1999–2008 | Secondary analysis |
| **23** | Wolpert (2014) | The relation of chronic stress during middle childhood to allostatic load in adolescents | Secondary analysis |
| **24** | Worthman and Panter-Brick (2008) | Homeless street children in Nepal: use of allostatic load to assess the burden of childhood adversity | Cross-sectional |
| **25** | Tian et al. (2020) | Discrimination increases the association between parental and adolescent allostatic load in Chinese rural-to-urban migrants | Cross-sectional |

| | | | |
|---|---|---|---|
| Studies not included in the adolescent allostatic load systematic review | | | |
| **26** | Seeman et al. (1997) | Price of adaptation—Allostatic load and its health consequences: Macarthur studies of successful aging | Secondary analysis |
| **27** | Shelly et al. (2021) | Allostatic load scoring using item response theory | Methodological |
| **28** | Thorpe et al. (2020) | The association between depressive symptoms and accumulation of stress among black men in the health and retirement study | cross-sectional |
| Studies in the Adolescent Allostatic load variable review with the exception numbers 25-28. Reference ID on the left of the author is referencing the numbers in Table 1. Hyperlinks for author(s) links to the original study. | | | |

**Table 3. Participant characteristics at baseline**

| | **Total sample (n = 183)** | | **Surgery sample (n = 98)** | |
|---|---|---|---|---|
| | **Black (n = 109)** | **White (n = 74)** | **Black (n = 56)** | **White (n = 42)** |
| **Age** | 6.72 ± 1.48 | 6.35 ±1.34 | 6.59 ± 1.5 | 6.4 ± 1.38 |
| **Sex (Female)** | 62 (56.9%) | 40 (54.1%) | 32 (57.1%) | 25 (59.5%) |
| **Grade** | | | | |
| Kindergarten | 43 (39.5%) | 35 (47.3%) | 27 (48.2%) | 20 (47.6%) |

| | | | | |
|---|---|---|---|---|
| First | 24 (22%) | 12 (16.2%) | 9 (16.1%) | 7 (16.7%) |
| Second | 14 (12.8%) | 6 (8.1%) | 7 (12.5%) | 4 (9.5%) |
| Third | 15 (13.8%) | 11 (14.9%) | 7 (12.5%) | 6 (14.3%) |
| Fourth | 8 (7.3%) | 0 (0%) | 4 (7.1%) | 0 (0%) |
| Fifth | 0 (0%) | 1 (1.4%) | 0 (0%) | 1 (2.4%) |
| Not attending | 5 (4.6%) | 9 (12.2%) | 2 (3.6%) | 4 (9.5%) |
| **Annual income** | | | | |
| < $20,000 | 57 (52.3%) | 5 (6.8%) | 27 (48.2%) | 2 (4.8%) |
| $20,000 to < $50,000 | 30 (27.5%) | 11 (14.9%) | 4 (7.1%) | 9 (21.4%) |
| >= $50,000 | 22 (20.2%) | 58 (78.4%) | 10 (17.9%) | 33 (78.6%) |
| **Maternal education <high school** | 47 (43.1%) | 10 (13.5%) | 22 (39.3%) | 6 (14.3%) |
| **Paternal education <high school** | 93 (85.3%) | 31 (41.9%) | 52 (92.9%) | 22 (52.4%) |
| **Asthma (current)** | 34 (31.2%) | 8 (10.8%) | 21 (37.5%) | 3 (7.1%) |
| **Premature birth** | 20 (18.4%) | 13 (17.6%) | 9 (16.1%) | 5 (11.9%) |
| **BMI** | 19.5 ± 4.75 | 18 ± 4.47 | 19.3 ± 4.5 | 18.3 ± 4.79 |
| **Total AHI (events/h)** | 8.26 ± 6.13 | 6.15 ± 3.86 | 8.42 ± 6.09 | 5.91 ± 3.58 |
| **HI (events/h)** | 5 ± 4.32 | 3.64 ± 2.91 | 5.28 ± 4.47 | 3.58 ± 2.59 |
| **% hypopneas** | 57.9 ± 21.6 | 56.2 ± 21.9 | 58.9 ± 22.6 | 59 ± 21.9 |
| **$SaO_2$ (average)** | 97.6 ± 0.89 | 97 ± 1.28 | 97.6 ± 0.94 | 97.1 ± 1.04 |
| **Nadir $SaO_2$** | 88.2 ± 5.12 | 89.9 ± 3.89 | 87.3 ± 5.9 | 90 ± 3.99 |
| **OSA Severity** | | | | |

| | | | | |
|---|---|---|---|---|
| Not present | 2 (1.8%) | 1 (1.4%) | 0 (0%) | 0 (0%) |
| Mild | 38 (34.9%) | 37 (50%) | 19 (33.9%) | 21 (50%) |
| Moderate | 39 (35.8%) | 25 (33.8%) | 22 (39.3%) | 16 (38.1%) |
| Severe | 30 (27.5%) | 11 (14.9%) | 15 (26.8%) | 5 (11.9%) |
| **Allostatic Load Index** | 3.26 ± 1.92 | 2.89 ± 2.19 | 3.09 ± 1.79 | 3.05 ± 2.13 |
| **Arousal Threshold** | -12.6 ± 3.76 | -11.5 ± 3.28 | -13 ± 3.78 | -11.4 ± 3.14 |

**Table 4. Participant characteristics at follow-up**

| | Total sample (n = 183) | | Surgery sample (n = 98) | |
|---|---|---|---|---|
| | **Black (n = 109)** | **White (n = 74)** | **Black (n = 56)** | **White (n = 42)** |
| **BMI** | 20.5 ± 4.94 | 18.7 ± 4.60 | 20.4 ± 4.79 | 19 ± 4.78 |
| **Total AHI (events/h)** | 4.83 ± 8.39 | 3.75 ± 8.76 | 2.01 ± 1.82 | 1.98 ± 2.3 |
| **HI (events/h)** | 2.6 ± 4.46 | 1.76 ± 3.32 | 0.93 ± 1.37 | 0.98 ± 2.07 |
| **% hypopneas** | 49.7 ± 26.1 | 42.6 ± 26.7 | 45.5 ± 27.7 | 40.2 ± 25.9 |
| **$SaO_2$ (average)** | 97.8 ± 1.01 | 97.4 ± 1.11 | 97.8 ± 1.21 | 97.5 ± 1 |
| **Nadir $SaO_2$** | 90.2 ± 4.91 | 91.1 ± 4.47 | 91.6 ±3.32 | 91.3 ± 3.51 |
| **OSA Severity** | | | | |
| Not present | 50 (45.9%) | 37 (50%) | 34 (60.7%) | 26 (61.9%) |
| Mild | 30 (27.5%) | 28 (37.8%) | 18 (32.1%) | 14 (33.3%) |
| Moderate | 17 (15.6%) | 4 (5.4%) | 3 (5.4%) | 1 (1.9%) |
| Severe | 12 (11%) | 5 (6.8%) | 1 (1.9%) | 1 (1.9%) |
| **Arousal Threshold** | -8.24 ± 4.2 | -8.18 ± 4.47 | -7.64 ± 3.44 | -8.29 ± 3.57 |
| **AHI change** | -3.43 ± 9.51 | -2.4 ± 7.84 | -6.41 ± 6.53 | -3.93 ± 3.8 |
| **Arousal Threshold change** | 4.4 ± 4.46 | 3.33 ± 3.81 | 5.38 ± 4.68 | 3.13 ± 3.39 |
| **TA Failure** | NA | NA | 22 (39.3%) | 16 (38.1%) |

**Table 5. ANCOVA for Arousal Threshold and Allostatic Load (n = 183)**

**Total sample**

| | **Arousal Threshold** | | **Allostatic Load** | |
|---|---|---|---|---|
| | F | p | F | p |
| **Race** | 1.1412 | 0.2869 | 2.9486 | 0.0878^ |
| **Sex** | Excluded | Excluded | 1.8962 | 0.1703 |
| **Asthma** | 0.7405 | 0.3907 | Excluded | Excluded |
| **Premature birth** | 0.5203 | 0.4717 | 0.6194 | 0.4324 |
| **Annual income** | 0.1898 | 0.6636 | 0.4304 | 0.5127 |
| **Maternal education** | Excluded | Excluded | 1.9388 | 0.1656 |
| **Paternal education** | 0.257 | 0.8729 | 0.0988 | 0.7537 |
| **Race*Sex** | Excluded | Excluded | 0.0549 | 0.815 |
| **Race*Asthma** | 2.6696 | 0.1041 | Excluded | Excluded |
| **Race*Premature birth** | 1.0690 | 0.3026 | 2.9158 | 0.0895^ |
| **Race*Annual income** | 1.7519 | 0.1874 | 0.8809 | 0.3493 |
| **Race*Maternal education** | Excluded | Excluded | 0.1504 | 0.6987 |
| **Race*Paternal education** | 0.0411 | 0.8396 | 0.1438 | 0.705 |
| Note. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, ^ $p < 0.1$ | | | | |

**Table 6. ANCOVA for Arousal Threshold and Allostatic Load.**

**Surgery Group (n = 98)**

| | **Arousal Threshold** | | **Allostatic Load** | |
|---|---|---|---|---|
| | F | p | F | p |
| **Race** | 5.7444 | 0.0187* | 0.0254 | 0.8737 |
| **Sex** | Excluded | Excluded | 1.1721 | 0.282 |
| **Asthma** | 0.4928 | 0.4846 | Excluded | Excluded |
| **Premature birth** | 0.0055 | 0.9411 | 0.2525 | 0.6166 |
| **Annual income** | 0.9232 | 0.3393 | 0.0005 | 0.9817 |
| **Maternal education** | 0.5673 | 0.4534 | 2.6224 | 0.109 |
| **Paternal education** | 1.5535 | 0.261 | 0.5028 | 0.4802 |
| **Race*Sex** | Excluded | Excluded | 0.0224 | 0.8815 |
| **Race*Asthma** | 0.8795 | 0.351 | Excluded | Excluded |
| **Race*Premature birth** | 0.8986 | 0.3458 | 1.5897 | 0.2108 |
| **Race*Annual income** | 0.7754 | 0.381 | 2.4133 | 0.1240 |
| **Race*Maternal education** | 0.6078 | 0.4378 | 0.3135 | 0.577 |
| **Race*Paternal education** | 0.8758 | 0.352 | 1.0234 | 0.3146 |
| Note. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, ^ $p < 0.1$ | | | | |