ONLINE DATA SUPPLEMENT

PATHOPHYSIOLOGIC FACTORS FOR THE OBSTRUCTIVE SLEEP APNEA SYNDROME IN ADOLESCENTS

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METHODS

Data were obtained from a comprehensive study examining the pathophysiology of the obstructive sleep apnea syndrome (OSAS) in adolescents, and some components of this study have been published individually.[1-4] The current manuscript included all participants participating in the overall study who successfully performed both MRI and Pcrit measurements. The Institutional Review Board at the Children's Hospital of Philadelphia approved the study. Informed consent was obtained from the parents/guardians of the participants, and assent from the participants.

Study Group

Obese adolescents with OSAS and obese controls without OSAS were studied. Adolescents, aged 12-16 years, were recruited from the Sleep Center at the Children's Hospital of Philadelphia (OSAS only), and from the hospital's Healthy Weight Program as well as the general population via advertisements (OSAS and controls). All controls were non-snorers without symptoms of OSAS, as determined by a negative Brouillette questionnaire.[5] Participants with OSAS were eligible if they were obese and had an AHI >5 events/hour, i.e., mild to moderate pediatric OSAS, and control participants were eligible if they had an AHI<1.5 events/hour.[6-9] Obesity was defined as a body mass index (BMI) >95th percentile.[10] Lean adolescents with OSAS were not included as OSAS is very uncommon in lean individuals in this age group.[11] Patients with chronic illnesses (other than mild, intermittent asthma) were excluded. Participants with OSAS were all newly-diagnosed and had not received prior treatment such as adenotonsillectomy or continuous positive airway pressure.

The sample (42 OSAS and 37 controls) was restricted to those participants with available data on the primary predictors of interest (ATV on MRI and activated and hypotonic Pcrit). 79 (81%) participants of the original sample of obese participants with OSAS and obese controls were included. 18 subjects were excluded due to dropouts who did not wish to continue in the study after their baseline PSG (N=3), lack of MRI data (MRI not done due to orthodontic braces [N=3], other metallic implants [N=1] or claustrophobia [N=3]; MRI technically unsatisfactory due to motion artifact [N=4]) or lack of Pcrit data (refused [N=1], scheduling issues [N=1] or technically unsatisfactory due to poor sleep [N=2]). Included participants had a lower AHI compared to excluded patients (median 5.1 *vs*. 9.3, p=0.023). We note that exclusion of patients with more severe OSAS would be expected to make it harder to find significant associations with disease status. There were no significant differences in age, gender or race between the original sample and the current sample.

Due to the extensive resources required for testing hypercapnic ventilatory responses (HCVR), genioglossal electromyogram (EMGgg) and CO_2 responses during sleep, including the need for a physician to be present, these tests were performed only on consecutive initial subsets of the population (N shown in Table 1). When comparing the demographic characteristics of subsets of patients with and without these data from the overall study sample (N=79), patients who underwent CO_2 testing were less likely to be African American compared to those who did not (67% vs. 89%, p=0.014). There were no other statistically significant differences in gender, age, BMI Z-score or AHI between patients with and without these measures in the study sample.

Polysomnography
Baseline polysomnography was performed using standard pediatric recording and scoring techniques,[12] as previously described for our laboratory[2].

Magnetic resonance imaging (MRI)
T1 and T2-weighted upper airway images were obtained during wakefulness using a 3 Tesla MRI scanner (Sonata, Siemens, Malvern, PA) equipped with a prototype enhanced gradient system. Detailed methods of image acquisition and analysis have been published previously.[4] The technician performing the image analyses was blinded to the polysomnography results.

Hypercapnic ventilatory response testing (HCVR)
Ventilatory responses to hypercapnia were measured during wakefulness using a modification of the Read hyperoxic hypercapnic rebreathing technique,[13] as described previously.[2] The participant was seated and breathed through a mouthpiece. End-tidal CO_2 was measured by infrared capnometry (Novametrix Medical System, Inc., Wallingford, CT). Flow was measured using a heated pneumotachograph (Hans Rudolph, Inc., Shawnee, KS) and transducer (ADInstruments, Colorado Springs, CO). Minute ventilation was obtained by analog integration of the flow signal. All outputs were recorded on a PowerLab system (ADInstruments, Colorado Springs, CO). The participants rebreathed from a bag filled with 70 ml/kg of a gas mixture with the initial composition of 95% O_2 and 5% CO_2. The participants breathed room air through the mouthpiece for several minutes to establish baseline values. The inhalation valve was then switched at the end of a normal expiration so that the participant rebreathed the hypercapnic mixture. The participants were asked to take three deep breaths after the valve was switched, and then breathe normally. They were encouraged to continue until end-tidal CO_2 reached 65 mmHg. Please see figure 2 in reference.[2] All tests were completed within 4 minutes so that significant respiratory acidosis would not occur.[14] Ventilatory responses to hypercapnia were expressed as $\dot{V}_E$ versus end-tidal CO_2.

Ventilatory response to CO_2 during sleep
Ventilatory responses to CO_2 during sleep were measured during a second polysomnogram, using previously published techniques.[2] Participants wore a full face mask (Philips Respironics, Murrysville, PA) attached to a heated pneumotachometer with a differential pressure transducer. The pneumotachometer was connected to a continuous positive airway pressure device (Philips Respironics, Murrysville, PA).[15, 16] CO_2 was introduced via a port on the mask. Nasal pressure (P_N) was measured at the mask using a pressure transducer. Transcutaneous PCO_2 (Radiometer, Copenhagen) was primarily assessed rather than end-tidal CO_2 as accurate end-tidal measurements could not be obtained during challenges due to the bias flow through the system. Signals were acquired on a PowerLab system and simultaneously displayed on a Rembrandt polysomnography system. During rapid eye movement (REM) and non-REM (NREM) sleep, trials were performed at a holding pressure defined as the nasal pressure just below the pressure at which flow limitation was abolished.[17] Flow limitation was determined by the characteristic waveform pattern, consisting of increasing inspiratory flow followed by a mid-inspiratory plateau.[18, 19] The participants breathed at holding pressure for at least 2 minutes prior to the challenge in order to obtain a stable baseline. CO_2 was then administered at 1 LPM and increased as needed until the transcutaneous PCO_2 increased by 3 mm Hg from baseline, and was then maintained at that level for 1 minute. Please see figure 3 in reference.[2] Trials with changes of

sleep state were excluded. Inspiratory airflow, tidal volume, inspiratory time and total respiratory cycle time were measured for each breath and averaged over the minute preceding the CO_2 challenge, and the last minute of the CO_2 challenge. The changes in ventilatory parameters were expressed as the percentage of baseline values.

Upper airway functional measurements during sleep

Upper airway functional measurements were determined during stable NREM sleep using previously published techniques.[1, 2, 20] These were performed following the CO_2 measurements, after allowing time for normalization of CO_2 and resumption of baseline breathing. In brief, intraoral surface genioglossal electromyogram (EMGgg) was obtained from a dental mouthpiece.[1, 21] P_N was altered in either a positive or subatmospheric direction.[1] For the activated technique, participants slept while receiving a level of P_N sufficient to abolish inspiratory airflow limitation. Once inspiratory flow limitation occurred, P_N was lowered in 2 cm H_2O step-like decrements every 5 breaths until flow approached zero or an arousal occurred. This gradual, stepwise protocol allowed for recruitment of upper airway reflexes, resulting in a neuromuscularly activated airway; the resulting Pcrit represents the upper airway combined structural and neuromotor properties.[20, 22-25] For the hypotonic technique, participants slept at the holding pressure. P_N was then decreased abruptly by 2 cm H_2O for 5 breaths, following which it was rapidly returned to the holding pressure. P_N was dropped repeatedly to incrementally lower levels, with a return each time to the holding pressure, until either flow approached zero or arousal occurred. Previous studies have shown that it takes several breaths at subatmospheric pressure before the upper airway reflexes are activated;[20, 25, 26] thus analyzing only the first 3 breaths provides data on a relatively hypotonic upper airway, and represents primarily structural upper airway properties.[20-22] See figure 1 in reference.[1]

Pressure-flow curves were constructed based on analysis of flow-limited breaths. For activated runs, the average mid-inspiratory flow was measured from the lowest two consecutive breaths at each level of P_N.[20, 27] For hypotonic runs, the mid-inspiratory flow was measured from the first 3 breaths following the pressure drop. Pressure-flow curves were constructed by plotting maximal inspiratory airflow (V_{Imax}) against P_N. P_N *vs* $\dot{V}$ curves were fitted by least squares linear regression. The critical closing pressure (P_{crit}) was defined as the X-axis intercept of the regression line ($V_{Imax} = 0$), i.e., the P_N at which there was zero flow. As the airway of normal children and adolescents is resistant to collapse, a floor threshold value of –25 cm H_2O (the lowest P_N deliverable by our equipment) was applied to P_{crit} data extrapolated to <-25 cm H_2O.[1, 20] Changes in EMGgg in response to decrements in P_N were presented as the slope of EMGgg *vs* P_N, normalized as a percentage of baseline EMGgg during stable NREM sleep.[1] Note that a more negative slope of EMGgg-P_N corresponded to more prominent genioglossal activation.

Statistical analysis

Continuous variables were compared between OSAS and controls using T-tests, and categorical variables using Chi-squared tests. Logistic regression models, both unadjusted and controlling for relevant clinical factors (age, gender, race and BMI Z-score), were used to examine the associations between structural and neuromotor parameters and OSAS status. Results were presented as odds ratios (OR), 95% confidence intervals (95% CIs) and two-sided p-values. To improve comparability of these effect estimates across predictor variables, continuous measures were standardized by subtracting the mean value in the sample and dividing by the standard

deviation (SD). Thus, the OR from the logistic model represents the change in the odds of having OSAS associated with a 1 SD increase in the continuous variable. For binary measures, the OR represents the increased odds of OSAS associated with the indicated group compared to the alternative. In addition, the area under the receiver operating characteristic curve (AUC) was calculated to estimate model predictive ability. The AUC ranges from 0.5-1.0, and can be interpreted as the probability that given randomly a chosen OSAS case and obese control, the model correctly ranks them as to their disease state. An AUC value close to 1.0 demonstrates perfect predictive ability of a model, while a value close to 0.50 indicates a model with poor performance. In this context, the AUC is referred to as a concordance statistic (c-stat).[28]

To determine which variables to include in multivariate models of OSAS risk, bivariate analyses assessing the association between individual predictors and OSAS were performed using all available data, to maximize statistical power. Any variable with $p<0.05$ in bivariate models was carried forward into multivariate analyses; if multiple variables from a given domain (e.g., tonsil volume, adenoid volume, and ATV) met this criteria, the variable with the strongest bivariate association (defined as the smallest p-value) was carried forward. In multivariate analyses, the sample was restricted to those participants not missing any of the variables of interest to allow for direct comparisons of model fit between alternative model definitions. Any variable with $p<0.05$ in multivariate analyses was retained in the final models. Analyses were performed unadjusted, as well as controlling for age, gender, race and BMI Z-score.

To determine the relationship between structural and functional variables and OSAS severity as determined by polysomnographic measures, Pearson's correlations were calculated. Analyses were restricted to OSAS participants, and crude and partial (controlling for age, gender, race and BMI Z-score) correlation estimates were obtained. OSAS severity was characterized using five complementary measures: the AHI, percent sleep time with $SpO_2<90\%$, SpO_2 nadir, peak end-tidal CO_2 and percent sleep time with end-tidal $CO_2>50$ mmHg. As a final step, to assess the impact of multiple variables on OSAS severity, multivariate linear regression analyses were performed including any variables significantly associated in the correlation analyses.

Finally, pairwise interactions and response surface modeling (RSM) were used to examine the simultaneous association of any two factors on the risk of OSAS.[29, 30] Pairwise interactions were assessed by adding a product term ($Var_1 \bullet Var_2$) to the main effects models described above. In general, RSM is used to evaluate the impact on a response variable when multiple predictor variables are changed simultaneously. We employed RSM to evaluate the simultaneous relationship between selected pairs of predictor variables and OSAS risk using multiple logistic regression models that included main effects, interactions and higher order terms for each variable, in order to allow the association with OSAS risk to depend on the variables in linear and non-linear ways. Specifically, a given RSM model for two variables (Var_1 and Var_2) will have the following form:

$$E(\ln[odds\ of\ OSAS]) = \beta_0 + \beta_1 \cdot Var_1 + \beta_2 \cdot (Var_1)^2 + \beta_3 \cdot Var_2 + \beta_4 \cdot (Var_2)^2 + \beta_5 \cdot (Var_1 \cdot Var_2) + \beta_6 \cdot [(Var_1)^2 \cdot Var_2] + \beta_7 \cdot [(Var_2)^2 \cdot Var_1]$$

To evaluate the importance of the overall model and individual model components, we used AUC statistics and likelihood ratio tests of overall model fit comparing the full model to reduced

models excluding specific parameters of interest. For example, the impact of Var_1 on the RSM was evaluated by calculating the change in AUC between the overall RSM and the model without the 5 terms that include Var_1, and a p-value was obtained by performing a likelihood ratio test. The impact of Var_2 was assessed in a similar fashion, while the impact of interaction and quadratic terms was assessed by comparing the overall RSM to models without the 3 interaction terms or 4 terms with squared variable, respectively. Results were illustrated using three-dimensional plots showing the predicted probability of OSAS as a function of the two variables included in the overall RSM. While all data were used to fit the RSM model, to avoid extrapolations beyond the data, we visually examined scatter plots and present the predicted probabilities only over the region where we observed an adequate number of data points (see Figure S1).

It should be noted that the predicted probabilities of OSAS from the logistic regression model depend on the percentage of OSAS cases in our analysis sample, which was roughly 50%. The model-predicted probabilities are expected to be shifted upward or downward when applied to populations with larger or smaller OSAS prevalence, respectively. To increase the generalizability of results, it is possible to adjust model predicted values to reflect the known or estimated prevalence in any target population.[31] This may be done in two steps, using the sample and target population OSAS prevalence estimates. The first step is an adjustment to the formula used to make predictions, including an adjustment to the intercept. These changes convert the usual predicted probabilities into likelihood ratio values[32] that do not depend on the sample OSAS prevalence. The second step involves incorporation of the target population OSAS prevalence, and may be applied using another adjustment to the model intercept or through what is essentially Bayesian updating. The Bayesian updating involves updating the target population prior odds using the model-based, subject specific likelihood ratio values obtained in Step 1 and obtaining posterior odds that may then be converted to posterior probabilities relevant to the target population of interest.[31] Utilizing these steps, results presented in this manuscript can be directly extended to independent adolescent populations with different OSAS prevalence.

Power and sample size calculations

Data in this study are from a subset of patients with available measures recruited as part of a larger, NIH-funded study (HL58585); thus, *a priori* sample size and power calculations for the current study were not performed. To provide context to the observed associations, we include *post hoc* power calculations using the available sample sizes. Primary measures of adenotonsillar volume, nasopharyngeal airway volume, and activated and hypotonic Pcrit were available on 42 obese OSAS and 37 obese controls. We observed statistically significant mean differences between OSAS and controls for these measures (see Table 1); absolute effect sizes ranged from 0.7 to 0.9 standard deviations (SDs). At an α=0.05, our sample had >85% power to detect an effect size of 0.7 and >95% for an effect size of 0.9. More generally, we had at least 80% power for a difference as small as 0.64 SDs. Similarly, in logistic regression analyses predicting OSAS, we observed odds ratios (with respect to increased risk) ranging from 2.0 to 2.6 for a one SD change in these primary measures. Our study sample had 78% power for detecting an OR=2.0 and 95% power for an OR=2.6, using an α=0.05. For other measures, which were available on 55 (HCVR measures and activated EMGgg slope), 52 (hypotonic EMGgg slope) and 33 (CO_2 response) participants, power for these effects was more limited. For the observed mean differences, we had between 48-69% power at an N=33 and between 71-90% power for N=55;

we had 80% power to detect mean differences of 1.02 and 0.78 for N=33 and 55, respectively. For logistic regression, power ranged from 42% for an OR=2.0 and N=33 to 85% for an OR=2.6 and N=55. We had 80% power for detecting ORs of 3.4 and 2.4 for 33 and 55 patients, respectively.

Table S1: Multivariate models in analysis sample with anatomy and Pcrit measures without covariates

Variable[†]	OR (95% CI)[*]	p[†]
Model 1: Anatomy *N OSAS= 42, N Controls = 37, AUC = 0.766*		
ATV	**2.09 (1.16, 3.78)**	**0.014**
NPAV	**0.55 (0.31, 0.96)**	**0.037**
Model 2: Pcrit *N OSAS= 42, N Controls = 37, AUC = 0.762*		
Activated Pcrit	1.50 (0.87, 2.60)	0.145
Hypotonic Pcrit	**2.18 (1.22, 3.90)**	**0.009**
Model 3: Anatomy + Pcrit *N OSAS= 42, N Controls = 37, AUC = 0.832*		
ATV	1.65 (0.86, 3.19)	0.133
NPAV	**0.47 (0.25, 0.89)**	**0.020**
Activated Pcrit	1.59 (0.86, 2.94)	0.137
Hypotonic Pcrit	**1.96 (1.05, 3.67)**	**0.035**

[*]OR associated with a 1 SD increase in continuous variables or between groups for categorical variables; [†]p from logistic regression model; Significant estimates ($p<0.05$) shown in **bold**.

Abbreviations: OSAS, obstructive sleep apnea syndrome; OR, odds ratio; CI, confidence interval; AUC, area under the receiver operating characteristic curve; BMI, body mass index; ATV, adenotonsillar volume; NPAV, nasopharyngeal airway volume; Pcrit, critical closing pressure.

Table S2: Multivariate models in sample with anatomy, Pcrit and activated EMGgg measures without covariates

Variable	OR (95% CI)*	p†
Model 1: Anatomy *N OSAS= 32, N Controls = 23, AUC = 0.787*		
ATV	**3.10 (1.30, 7.37)**	**0.010**
NPAV	0.72 (0.39, 1.33)	0.292
Model 2: Pcrit *N OSAS= 32, N Controls = 23, AUC = 0.802*		
Activated Pcrit	1.64 (0.83, 3.27)	0.156
Hypotonic Pcrit	**2.43 (1.16, 5.10)**	**0.018**
Model 3: Activated EMGgg *N OSAS= 32, N Controls = 23, AUC = 0.740*		
EMGgg slope (activated)	**5.71 (1.12, 29.1)**	**0.036**
Model 4: Anatomy + Pcrit + Activated EMGgg *N OSAS= 32, N Controls = 23, AUC =*		
ATV	1.88 (0.71, 4.99)	0.205
NPAV	0.55 (0.26, 1.15)	0.111
Activated Pcrit	1.30 (0.55, 3.08)	0.547
Hypotonic Pcrit	2.11 (0.87, 5.11)	0.100
EMGgg slope (activated)	5.53 (0.67, 45.5)	0.112

*OR associated with a 1 SD increase in continuous variables or between groups for categorical variables; †p from logistic regression model; Significant estimates ($p<0.05$) shown in **bold**.

Abbreviations: OSAS, obstructive sleep apnea syndrome; OR, odds ratio; CI, confidence interval; AUC, area under the receiver operating characteristic curve; BMI, body mass index; ATV, adenotonsillar volume; NPAV, nasopharyngeal airway volume; Pcrit, critical closing pressure; EMGgg, genioglossal electromyogram.

Table S3: Unadjusted Pearson correlations with OSAS severity measures among adolescents with OSAS

Variable	N	AHI (events/hr)†		% sleep time with SpO_2<90%†		SpO_2 nadir (%)		Peak $ETCO_2$ (mm Hg)		% sleep time with $ETCO_2$>50†	
		rho	p	rho	p	rho	p	rho	p	rho	p
Age, year	42	0.20	0.193	0.23	0.134	0.09	0.567	-0.16	0.308	-0.17	0.280
Male	42	0.14	0.379	0.29	0.063	-0.20	0.215	0.21	0.191	0.00	0.987
African American	42	-0.24	0.129	-0.16	0.298	-0.01	0.929	0.13	0.423	0.13	0.426
BMI Z-score	42	0.07	0.658	0.15	0.341	-0.07	0.682	-0.14	0.392	-0.04	0.823
Tonsil volume, mm^3	42	**0.52**	**<0.001**	**0.66**	**<0.0001**	**-0.48**	**0.001**	0.20	0.201	0.18	0.244
Adenoid volume, mm^3	42	**0.39**	**0.011**	0.29	0.066	-0.30	0.055	0.08	0.593	0.01	0.960
ATV, mm^3	42	**0.57**	**<0.0001**	**0.60**	**<0.0001**	**-0.49**	**0.001**	0.18	0.253	0.12	0.441
NPAV, mm^3	42	0.01	0.937	0.24	0.123	-0.03	0.835	-0.08	0.621	0.01	0.951
Nasopharyngeal cross-sectional area, mm^2	42	-0.14	0.388	-0.07	0.638	0.02	0.912	-0.11	0.501	-0.07	0.651
Nasopharyngeal minimum area, mm^2	42	-0.22	0.163	-0.11	0.490	-0.04	0.800	-0.09	0.574	-0.07	0.669
Slope of the pressure-flow response (activated), ml/s/cm H_2O	42	0.25	0.108	0.23	0.151	-0.09	0.550	-0.09	0.575	-0.25	0.115
Pcrit (activated), cm H_2O	42	**0.35**	**0.024**	**0.37**	**0.016**	-0.15	0.330	0.01	0.970	-0.11	0.503
Slope of the pressure-flow response (hypotonic), ml/s/cm H_2O	42	0.12	0.449	0.17	0.286	0.04	0.794	0.00	0.980	-0.23	0.151
Pcrit (hypotonic), cm H_2O	42	0.30	0.051	**0.39**	**0.011**	-0.06	0.718	0.17	0.269	0.02	0.895
EMGgg slope (activated), %/cm H_2O	32	0.10	0.576	0.20	0.281	0.00	0.999	-0.01	0.969	-0.02	0.925
EMGgg slope (hypotonic), %/cm H_2O	30	0.14	0.476	0.03	0.882	0.13	0.481	-0.33	0.077	-0.27	0.149
HCVR slope, L/min/mmHg $ETCO_2$	31	0.16	0.398	0.05	0.780	-0.06	0.751	0.02	0.926	-0.08	0.653
HCVR correlation coefficient	31	0.18	0.333	0.15	0.418	-0.06	0.742	-0.30	0.102	-0.28	0.124
CO_2 response during sleep, $\%\Delta V_E$	16	-0.47	0.069	-0.48	0.062	0.50	0.051	-0.09	0.747	-0.14	0.594

†Measure natural log + 1 transformed for normality; significant ($p<0.05$) correlations shown in **bold**.

Abbreviations: AHI, apnea hypopnea index; SpO_2, arterial oxygen saturation; $ETCO_2$, end-tidal carbon dioxide; ATV, adenotonsillar volume; NPAV, nasopharyngeal airway volume; Pcrit, critical closing pressure; EMGgg, genioglossal electromyogram; HCVR, hypercapnic ventilatory response; V_E, minute ventilation

Table S4: Unadjusted multivariate models for OSAS severity measures within adolescents with OSAS

OSAS Measure	Variable	Anatomy Model		Pcrit Model		Full Model	
		β (95% CI)*	**p†**	**β (95% CI)***	**p†**	**β (95% CI)***	**p†**
AHI (events/hr)‡	ATV	0.42 (0.23, 0.61)	<0.0001	–	–	0.39 (0.18, 0.60)	0.001
	NPAV	0.08 (-0.12, 0.29)	0.416	–	–	0.07 (-0.16, 0.30)	0.531
	Pcrit (activated)	–	–	0.20 (-0.08, 0.49)	0.158	0.02 (-0.27, 0.31)	0.877
	Pcrit (hypotonic)	–	–	0.13 (-0.18, 0.43)	0.403	0.15 (-0.12, 0.43)	0.268
% sleep time with SpO_2<90%‡	ATV	0.50 (0.32, 0.69)	<0.0001	–	–	0.51 (0.32, 0.70)	<0.0001
	NPAV	0.29 (0.09, 0.48)	0.005	–	–	0.33 (0.13, 0.54)	0.002
	Pcrit (activated)	–	–	0.19 (-0.11, 0.48)	0.218	-0.16 (-0.42, 0.10)	0.217
	Pcrit (hypotonic)	–	–	0.23 (-0.09, 0.55)	0.147	0.33 (0.09, 0.57)	0.009
SpO_2 nadir (%)	ATV	-3.84 (-5.98, -1.71)	0.001	–	–	-4.08 (-6.50, -1.65)	0.002
	NPAV	-0.94 (-3.22, 1.35)	0.411	–	–	-1.16 (-3.76, 1.45)	0.374
	Pcrit (activated)	–	–	-1.48 (-4.69, 1.72)	0.355	0.61 (-2.73, 3.96)	0.713
	Pcrit (hypotonic)	–	–	0.40 (-3.01, 3.81)	0.813	0.03 (-3.11, 3.17)	0.984
Peak $ETCO_2$ (mm Hg)	ATV	0.79 (-0.69, 2.26)	0.287	–	–	0.97 (-0.67, 2.60)	0.238
	NPAV	-0.25 (-1.82, 1.33)	0.753	–	–	0.11 (-1.65, 1.87)	0.899
	Pcrit (activated)	–	–	-0.7 (-2.62, 1.23)	0.469	-1.12 (-3.38, 1.14)	0.321
	Pcrit (hypotonic)	–	–	1.35 (-0.70, 3.39)	0.191	1.39 (-0.73, 3.51)	0.192
% sleep time with $ETCO_2$>50‡	ATV	0.19 (-0.30, 0.69)	0.435	–	–	0.34 (-0.21, 0.90)	0.215
	NPAV	0.05 (-0.48, 0.58)	0.851	–	–	0.23 (-0.36, 0.82)	0.438
	Pcrit (activated)	–	–	-0.29 (-0.95, 0.36)	0.368	-0.53 (-1.30, 0.23)	0.167
	Pcrit (hypotonic)	–	–	0.22 (-0.48, 0.91)	0.533	0.28 (-0.43, 1.00)	0.428

*Beta coefficient and 95% confidence interval from linear regression model, interpreted as the expected change in outcome for a 1 SD increase in continuous variables or associated with the indicated group for categorical variables; †p-value from linear regression model; ‡measure natural log + 1 transformed for normality; Significant (p<0.05) associations shown in **bold.**

Abbreviations: OSAS, obstructive sleep apnea syndrome; Pcrit, critical closing pressure; AHI, apnea hypopnea index; ATV, adenotonsillar volume; NPAV, nasopharyngeal airway volume; SpO_2, arterial oxygen saturation; $ETCO_2$, end-tidal carbon dioxide.

Table S4: Unadjusted multivariate models for OSAS severity measures within adolescents with OSAS

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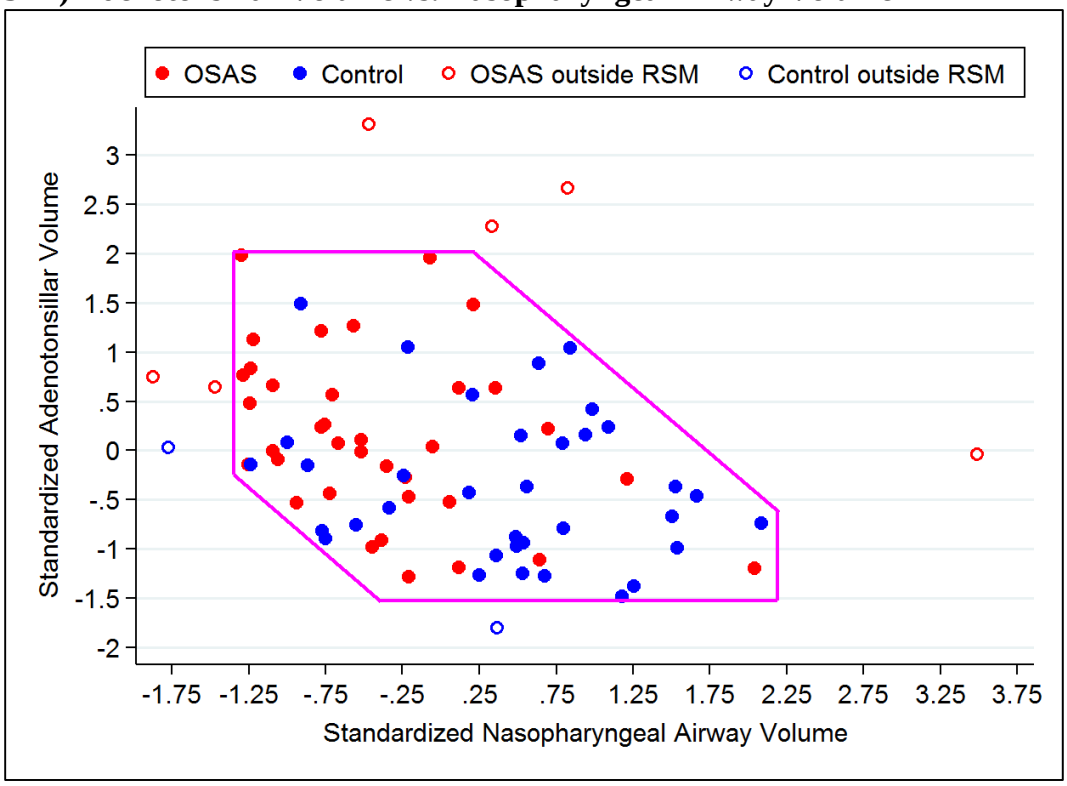
		β (95% CI)*	**p†**	**β (95% CI)***	**p†**	**β (95% CI)***	**p†**
AHI (events/hr)‡	Adenotonsillar volume	**0.39 (0.17, 0.61)**	**0.001**	–	–	0.35 (0.11, 0.60)	**0.006**
	Nasopharyngeal airway volume	0.06 (-0.17, 0.29)	0.596	–	–	0.04 (-0.22, 0.31)	0.748
	Pcrit (activated)	–	–	0.20 (-0.08, 0.49)	0.158	0.01 (-0.34, 0.36)	0.945
	Pcrit (hypotonic)	–	–	0.13 (-0.18, 0.43)	0.403	0.16 (-0.15, 0.47)	0.300
% sleep time with SpO_2<90%‡	Adenotonsillar volume	**0.53 (0.31, 0.74)**	**<0.0001**	–	–	**0.54 (0.32, 0.77)**	**<0.0001**
	Nasopharyngeal airway volume	**0.31 (0.09, 0.54)**	**0.008**	–	–	**0.38 (0.14, 0.62)**	**0.003**
	Pcrit (activated)	–	–	0.19 (-0.11, 0.48)	0.218	-0.23 (-0.55, 0.09)	0.152
	Pcrit (hypotonic)	–	–	0.23 (-0.09, 0.55)	0.147	**0.36 (0.08, 0.64)**	**0.015**
SpO_2 nadir (%)	Adenotonsillar volume	**-4.20 (-6.62, -1.77)**	**0.001**	–	–	**-4.76 (-7.53, -2.00)**	**0.001**
	Nasopharyngeal airway volume	-1.20 (-3.74, 1.34)	0.343	–	–	-1.76 (-4.71, 1.20)	0.235
	Pcrit (activated)	–	–	-1.48 (-4.69, 1.72)	0.355	1.31 (-2.60, 5.22)	0.499
	Pcrit (hypotonic)	–	–	0.40 (-3.01, 3.81)	0.813	0.28 (-3.20, 3.75)	0.872
Peak $ETCO_2$ (mm Hg)	Adenotonsillar volume	0.78 (-0.76, 2.32)	0.309	–	–	0.92 (-0.84, 2.68)	0.294
	Nasopharyngeal airway volume	-0.85 (-2.46, 0.76)	0.290	–	–	-0.59 (-2.47, 1.29)	0.526
	Pcrit (activated)	–	–	-0.70 (-2.62, 1.23)	0.469	-0.84 (-3.33, 1.65)	0.496
	Pcrit (hypotonic)	–	–	1.35 (-0.70, 3.39)	0.191	0.94 (-1.27, 3.15)	0.394
% sleep time with $ETCO_2$>50‡	Adenotonsillar volume	0.18 (-0.35, 0.71)	0.496	–	–	0.34 (-0.26, 0.94)	0.261
	Nasopharyngeal airway volume	-0.16 (-0.72, 0.39)	0.551	–	–	0.02 (-0.63, 0.66)	0.960
	Pcrit (activated)	–	–	-0.29 (-0.95, 0.36)	0.368	-0.47 (-1.32, 0.38)	0.264
	Pcrit (hypotonic)	–	–	0.22 (-0.48, 0.91)	0.533	0.13 (-0.62, 0.89)	0.723

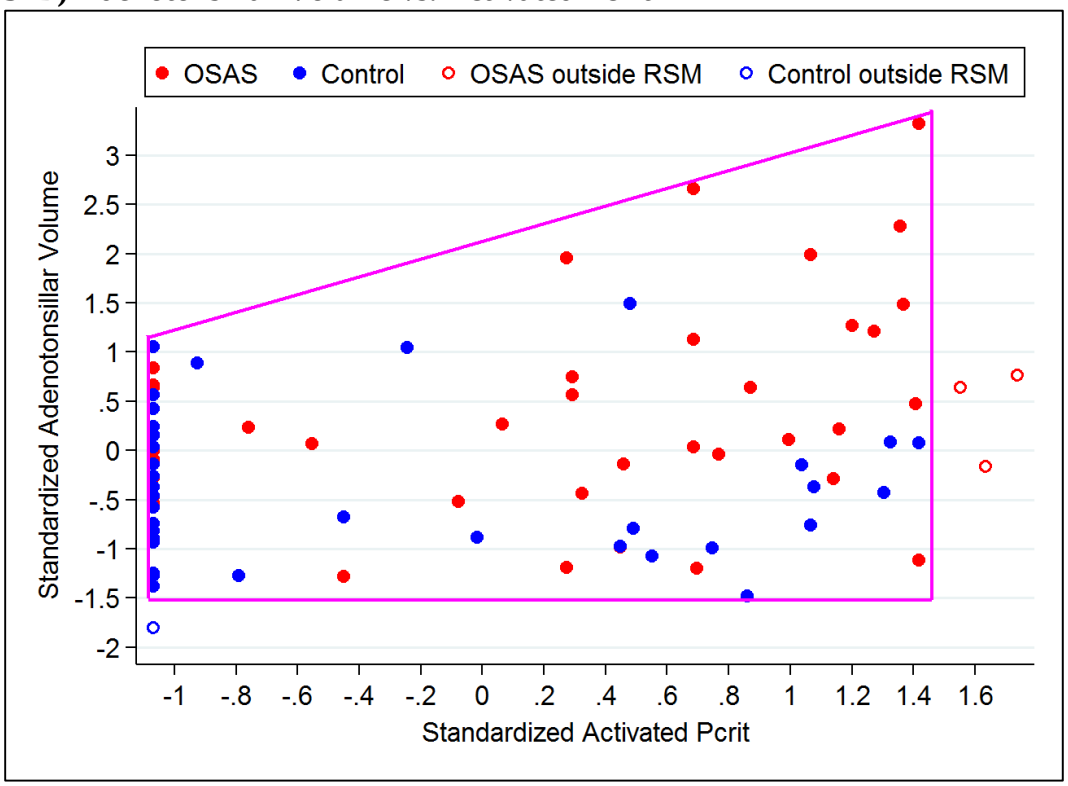
*Beta coefficient and 95% confidence interval from linear regression model, interpreted as the expected change in outcome for a 1 SD increase in continuous variables or associated with the indicated group for categorical variables; †p-value from linear regression model; ‡measure natural log + 1 transformed for normality; Significant ($p<0.05$) associations shown in **bold**; AHI, apnea hypopnea index; SpO_2, arterial oxygen saturation; $ETCO_2$, end-tidal carbon dioxide.

Figures S1A-C: Pairwise scatter plots of primary predictor variables with indicated regions for response surface modeling (RSM) probability plane estimation. Scatter plots showing the observed values of adenotonsillar volume, nasopharyngeal airway volume, and activated critical closing pressure (Pcrit) are shown. All data were used in determining the RSM model. However, given the increased instability when extrapolating model results at the edges of the observed data, we restricted RSM model predicted probability (see Figure 2A-2C) estimates to the regions that did not include extreme values of the predictors; this region is outlined in magenta. OSAS, obstructive sleep apnea syndrome; Pcrit, critical closing pressure.

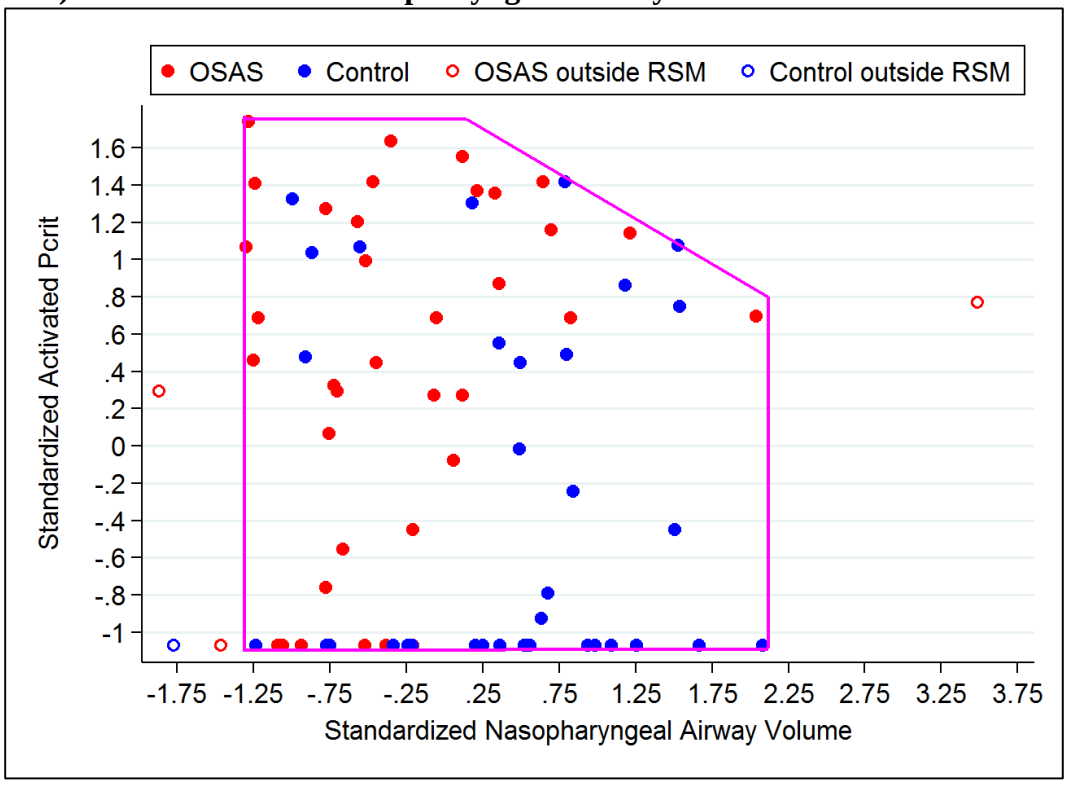
S1A) Adenotonsillar Volume vs. Nasopharyngeal Airway Volume



S1B) Adenotonsillar Volume vs. Activated Pcrit



S1C) Activated Pcrit vs. Nasopharyngeal Airway Volume



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