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Obesity, Tidal Volume, and Pulmonary Deposition of Fine Particulate Matter in Children with Asthma

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ABSTRACT

Background: Obese children with asthma are more vulnerable to air pollution, especially fine particulate matter ($PM_{2.5}$), but reasons are poorly understood. We hypothesized that differences in breathing patterns (tidal volume, respiratory rate, and minute ventilation) due to elevated body mass index (BMI) may contribute to this finding.

Objective: To investigate the association of BMI with breathing patterns and deposition of inhaled $PM_{2.5}$.

Methods: Baseline data from a prospective study of children with asthma was analyzed (n=174). Tidal breathing was measured by a pitot-tube flowmeter, from which tidal volume, respiratory rate, and minute ventilation were obtained. The association of BMI z-score with breathing patterns was estimated in a multivariable model adjusted for age, height, race, sex, and asthma severity. A particle dosimetry model simulated $PM_{2.5}$ lung deposition based on BMI-associated changes in breathing patterns.

Results: Higher BMI was associated with higher tidal volume (adjusted mean difference [aMD] between obese and normal-range BMI of 25 mL, 95% confidence interval [CI] 5–45 mL) and minute ventilation (aMD 453 mL/min, 95%CI 123–784 mL/min). Higher tidal volumes caused higher fractional deposition of $PM_{2.5}$ in the lung, driven by greater alveolar deposition. This translated into obese participants having greater per-breath retention of inhaled $PM_{2.5}$ (aMD in alveolar deposition fraction of 3.4%; 95%CI 1.3—5.5%), leading to worse $PM_{2.5}$ deposition rates.

Conclusions: Obese children with asthma breathe at higher tidal volumes that may increase the efficiency of $PM_{2.5}$ deposition in the lung. This finding may partially explain why obese children with asthma exhibit greater sensitivity to air pollution.

ABBREVIATIONS

aMD	Adjusted mean difference
ATAQ	Asthma Therapy Assessment Questionnaire
BMI	Body mass index
FEV1	Forced exhaled volume in the first second
FVC	Forced vital capacity
MPPD	Multi-path particle deposition
$PM_{2.5}$	Fine particulate matter
TB	Tracheobronchial
TLC	Total lung capacity
URT	Upper respiratory tract

INTRODUCTION

Exposure to air pollution, particularly $PM_{2.5}$ (fine particulate matter with an aerodynamic diameter smaller than 2.5μm), is harmful to pulmonary health[1–3]. In children, it is a known driver of chronic bronchitis, incident asthma, and asthma exacerbation[4,5].

Obesity may increase susceptibility to air pollution. Epidemiologic associations between ambient air pollution and respiratory symptoms are stronger among obese versus normal weight children and adults[6,7]. Obese children with asthma report worse symptoms with equivalent levels of exposure to indoor $PM_{2.5}$ and secondhand smoke[8,9].

Increased susceptibility to equal indoor concentrations of $PM_{2.5}$, via greater deposition of inhaled particles, is a potential pathway to at least partly explain disparate asthma morbidity in obese versus non-obese children. Bennett and Zeman reported among 36 healthy children that obesity was associated with greater fractional deposition of inhaled particles in the respiratory system during tidal breathing, and that this relationship was most strongly related to obese children having higher tidal volumes[10]. However, breathing patterns in children with asthma are unknown. Further, changes in anatomic location of particle deposition within the respiratory system due to obesity have not been examined.

The objective of this study was to examine the association of (1) BMI to respiratory patterns, (2) breathing patterns to $PM_{2.5}$ particle deposition characteristics, and (3) BMI to $PM_{2.5}$ particle deposition characteristics within a cohort of children with asthma. We hypothesize that obese children with asthma will breathe at higher tidal volumes, that higher tidal volumes will translate to more efficient deposition of $PM_{2.5}$ in the respiratory system, and that obese children will therefore receive a greater “dose” of inhaled particles compared with normal weight children.

METHODS

Study cohort

AIRWEIGHS is a single-center, randomized, parallel-assignment, quadruple-masked clinical trial of an air purifier intervention for obesity-associated asthma (NCT02763917). A pre-specified secondary objective of the study was to examine breathing patterns in normal weight and obese children with asthma. Participants were 8-17 years of age, non-smokers, and had physician-diagnosed asthma by National Asthma Education and Prevention Program (NAEPP) criteria with at least one exacerbation in the prior year[11]. Those who were underweight or had other significant cardiopulmonary disease were excluded. The study was approved by the Institutional Review Board of Johns Hopkins University School of Medicine (IRB00074171). All participants gave assent, and all primary caretakers gave written informed consent.

Potential participants who lived within the Baltimore, Maryland region were identified from patients seen in Johns Hopkins outpatient clinics and the pediatric emergency department, community engagement activities, recruitment flyers posted in public locations, and a registry of previous study participants. Enrollment was not explicitly stratified by obesity as similar proportions of non-obese and obese children were anticipated based on historical recruitment data from our research center. Baseline characterization and measurement of breathing patterns occurred as part of the lead-in period prior to randomization, and thus this study includes participants who were lost to follow-up or disenrolled prior to randomization. A diagram of participant flow is included as eFigure 1.

Participant characterization

Sociodemographic information was obtained by participant or caregiver report. Asthma control was represented by the maximum symptom day (the maximum of the number of days in the prior

two weeks a participant had slowed activity, wheezing, or coughing or chest tightness due to asthma) and by the Asthma Therapy Assessment Questionnaire (ATAQ) score, which ranges from 0-4, with scores ≥1 indicating uncontrolled asthma[12,13]. Body weight and height were measured in triplicate and each averaged, from which body mass index (BMI) was calculated and converted to a normalized z-score based on the 2000 Centers for Disease Control growth charts[14,15]. We chose z-score instead of percentile due to substantial negative skew in the BMI percentile distribution from a high proportion of obese participants. Gravimetric concentration of $PM_{2.5}$ in the participant's bedroom was measured by a Personal Environmental Monitor (model 200, MSP Corporation; Shoreview, MN) containing a 37-mm polytetrafluroethylene filter (Teflo R2PI025, Pall Corporation; New York, NY) connected to a personal aerosol sampling pump (model AFC 400S, BGI Incorporated; Waltham, MA) running at 4 L/min. Sampling was performed prior to randomization for one week.

Breathing patterns

Up to ten minutes of at-rest breathing were measured by a calibrated flow meter while participants passively watched videos on a multimedia device[16]. The apparatus was comprised of a pitot-tube flow sensor connected to a full-face neoprene mask. The design allowed integrated continuous measurements of oral and nasal airflow, minimized mechanical dead space, and allowed participants to breathe to their comfort.

Breath-by-breath tidal volume and respiratory rate were calculated from the airflow waveforms utilizing a semi-automated time-series analysis (WaveMetrics; Portland, OR), from which tidal volume and respiratory rate were measured. Minute ventilation was derived as the product of tidal volume and respiratory rate. More details are included in the supplement.

Particle deposition

We applied the multi-path particle dosimetry (MPPD) model version 3.04 (Applied Research Associates; Raleigh, NC) to estimate the effects of breathing patterns on $PM_{2.5}$ deposition. This computational model estimates region-specific particle deposition characteristics in a five-lobe respiratory system by applying theoretical equations of particle impaction, sedimentation, and diffusion, which are described in more detail elsewhere[17]. The model incorporates age-specific differences in airway morphometry originally described by Mortensen and colleagues[18,19]. MPPD estimates have been shown to agree with empirical measurements of total deposition among individuals aged 3 months to 21 years old, and it is a commonly-used model in dosimetry research in children[20–22].

We input each participant's own tidal volume and respiratory rate into the model. Other parameters, chiefly body position and functional residual capacity (FRC), were left at default values. Estimates of fractional deposition (ratio of particles deposited to particles inhaled) and deposition rate (particle mass deposited per minute) for the upper respiratory tract (URT), defined as nose to trachea; tracheobronchial (TB), defined as trachea to the 16^{th} airway generation; and alveolar regions were calculated. To allow between-participant comparisons of deposition rate attributable to BMI, calculations of deposition rate assumed a constant indoor air $PM_{2.5}$ concentration equal to the mean observed in-home concentration.

We performed sensitivity analysis of two key model assumptions. First, the model estimates participant FRC using an age-specific equation based on the work of Hoffman[23]. Because obesity in children is associated with a reduction in FRC, we performed a parallel analysis by forcing a 20% reduction in model-estimated FRC among obese participants, which is the approximate magnitude based on a meta-analysis of studies[24]. Second, due to lack of empirical data specifically for nasal deposition efficiency in children, the model assumed different values for

nasal deposition efficiency among children <12, 12-15, and ≥16 years of age. We initially stratified estimates by age group and investigated if this assumption caused systematic differences in the relationship of BMI to deposition characteristics between age groups. After determining that they were not, unstratified estimates were reported. Further details are included in the supplement.

Statistical analysis

Univariable comparisons between obese and non-obese participants were performed with unpaired t-tests for continuous variables and chi-square tests for categorical variables. The association of BMI z-score with tidal volume, respiratory rate, and minute ventilation was estimated by multivariable linear regression. We adjusted for covariates predictive of lung function – age, age^2, height, height^2, sex, and race – as well as asthma severity by NAEPP criteria[25]. Because there was a non-linear association between BMI z-score and respiratory rate, BMI was represented as a linear and squared term. Statistical association was assessed by a Wald test against the hypothesis that the coefficient of BMI z-score and BMI z-score^2 were jointly equal to zero. Contrasts between an obese (BMI z-score of 2.2, corresponding to the median z-score among obese participants in this study) and normal weight participant (z-score of 0) were estimated. For deposition analysis, statistical relationships between BMI z-score, respiratory pattern, and deposition pattern were estimated by univariable regression.

All statistical analyses were performed in Stata 15 (StataCorp; College Station, TX). A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

Cohort description

One-hundred and seventy-four participants had available anthropometry and respiratory pattern data for inclusion in this study (Table 1). Mean age was 11, and the majority were of male sex and Black race. Despite most participants receiving moderate-to-high doses of inhaled corticosteroids, 81% of the 155 participants with recorded ATAQ scores had uncontrolled asthma. The mean in-home $PM_{2.5}$ concentration was 20.1 $\mu g/m^3$. The BMI z-score range was -1.7 (5^{th} percentile) to 2.9 (>99^{th} percentile), and approximately half of the participants were obese by CDC criteria. When stratified by obesity, there were no differences in baseline characteristics in univariable comparisons except for higher minute ventilation among obese participants.

Association of BMI with tidal volume, respiratory rate, and minute ventilation

As shown in Figure 1, we identified a linear relationship between increasing BMI and increasing tidal volume (adjusted mean difference [aMD] between obese and normal-range BMI of 25 mL, 95% confidence interval [CI] 5–45 mL). Respiratory rate had a U-shaped relationship with BMI, with those at the extremes of observed values having higher respiratory rates. However, the magnitude of change in tidal volumes outweighed the change in respiratory rate, such that the relationship of BMI to minute ventilation remained approximately linear, with increasing BMI associated with increasing minute ventilation (aMD 453 mL/min, 95% CI 123–784 mL/min). A child at the 99^{th} percentile for BMI (z-score of 2.2) was predicted to have approximately 17% higher minute ventilation compared to a child at the 50^{th} percentile (z-score of 0).

Tidal volume and respiratory rate have opposing effects on alveolar fractional deposition

MPPD analysis demonstrated that higher tidal volumes were associated with greater fractional deposition of inhaled $PM_{2.5}$ within the respiratory system (eFigure 2, open circles). This was predominantly driven by more efficient deposition within the alveolar region, where for every 100 mL increase in tidal volume, fractional deposition in this region increased by approximately 4% (eFigure 2, closed circles). Associations with other regions are listed in eTable 1.

Higher respiratory rates were associated with the opposite effect. With increasing respiratory rate, total fractional deposition decreased (eFigure 3, open circles), which was again driven by decreased alveolar fractional deposition (eFigure 3, closed circles). Higher respiratory rate was also statistically associated with lower fractional deposition in TB region and higher fractional deposition in the URT region, but these were of negligible magnitude (eTable 1).

Overall, the effect of obesity was an increase in total and alveolar fractional deposition (Figure 2, open and closed circles). An obese child was predicted to have a 12% higher alveolar fractional deposition compared to a normal-weight child, corresponding to an adjusted mean difference of 3.4% (95% confidence interval 1.3—5.5%). We did not find a relationship between BMI and fractional deposition within the TB or URT regions.

We next reduced FRC among obese participants and found that associations between BMI and worsened fractional deposition were maintained (eFigure 4). The difference in alveolar fractional deposition between an obese and normal-weight child was qualitatively similar at 5.2% (95% CI 2.7—7.7%). In more comprehensive sensitivity analyses (not shown), we found that inferences were insensitive to perturbations in FRC.

Obesity is associated with higher rates of particle deposition

We next modeled rates of $PM_{2.5}$ deposition at a concentration of 24.1 $\mu g/m^3$ for each participant, the mean indoor $PM_{2.5}$ concentration from the 148 available measurements in this cohort (eFigure 1). As shown in Figure 3 (open circles), higher BMI was strongly associated with higher rates of particulate deposition within the respiratory system. This was driven predominantly by higher rates of deposition within the alveolar region (Figure 3, closed circles), where an obese child was predicted to have a 29% higher rate of $PM_{2.5}$ deposition compared to a normal weight child, corresponding to an adjusted mean difference of 7.1 ng/min (95% CI 3.9—10.2 ng/min), with smaller increases in deposition rates within the URT and TB regions (eTable 2).

DISCUSSION

In this study of children with asthma, we found positive associations between BMI and tidal volume, respiratory rate, and minute ventilation. We identified that obesity was associated with higher tidal volume and higher minute ventilation, which were in turn associated with greater breath-to-breath efficiency and higher rate of $PM_{2.5}$ deposition in the lung. These results provide evidence for a unique mechanism which may partially explain why obese children with asthma demonstrate greater susceptibility to air pollution.

To our knowledge, this is the first study to examine obesity-related changes in breathing patterns among children with asthma. The combination of obesity precipitating a higher respiratory rate, with each breath being more efficient in depositing $PM_{2.5}$ in the lung, outlines a "dual hit" scenario whereby obese children with asthma are cumulatively exposed to greater amounts of airborne particulate matter than their normal weight counterparts even when breathing the same ambient air.

Our results are consistent with a small experimental study in healthy children by Bennett and Zeman showing that increased BMI was associated with higher total fractional deposition of inhaled fine particles, which was in turn most associated with higher tidal volumes[10]. Our results extend this study by examining a larger number of children, focusing on those with prevalent asthma, and incorporating estimates of regional in addition to total fractional deposition. Additionally, we utilized a novel flow meter that allowed direct measurement of both oral and nasal flows. This device increased ventilatory measurement accuracy by minimizing mechanical dead space and avoided the need for a nose clip, which has been shown to alter breathing patterns[26].

We utilized the MPPD model to predict consequences of BMI-associated changes in breathing patterns, which to our knowledge is the first application of a dosimetry model for this purpose. In this manner, we were able to relate obesity to more deleterious particle deposition characteristics. We emphasize that this inference was made indirectly through an analysis of tidal volumes *in silico*. An implicit assumption in this approach is that the effect of obesity on particle deposition occurs predominantly through changes in breathing patterns. Although we showed that the model was not particularly sensitive to perturbations in FRC, and we did not identify any other configurable parameter that may be conceivably altered by obesity, our study should not be interpreted as conclusive. Direct physiological measurement of regional particle deposition characteristics in non-obese and obese children with asthma is an important next step.

Due to increased metabolism and CO_2 production, an increase in minute ventilation with higher BMI is perhaps unsurprising[10,27]. However, our study suggests that this was due in part to an increase in tidal volume, which is not immediately intuitive. Among adults, obesity has been associated with lower tidal volumes at rest and exercise, findings attributed to decreased

respiratory system compliance and differences in autonomic regulation of breath timing[27–30]. These would seem consistent with well-described associations of obesity with a restrictive pattern on pulmonary function testing, characterized by reduced total lung capacity (TLC), FRC, and in cases of morbid obesity, a reduction in forced vital capacity (FVC). However, literature from adult bariatric studies have related weight-reduction surgery with a decrease in tidal volume despite an increase in FVC and reversal of other impairments seen in pulmonary function testing, reinforcing that lung function does not necessarily correlate with breathing patterns and suggesting that our finding may not be limited to children[31,32]. Further, in children, despite similar reductions in TLC and FRC, morbid obesity does not significantly affect FVC, suggesting that respiratory mechanics remain more preserved in youth[24].

An obese child at the 99th percentile for BMI was predicted to have a 29% higher rate of alveolar $PM_{2.5}$ deposition compared to a normal weight child the 50th percentile. Although the extrapolated difference of 10.2 μg per day is small, this estimate is conservative as it assumes calm, tidal breathing in an indoor environment at modest concentrations of $PM_{2.5}$. In children with asthma, small differences in indoor $PM_{2.5}$ concentration are associated with large differences in asthma symptoms, highlighting that asthma control is especially sensitive to environmental changes[33]. This may be explained by the particular harms of $PM_{2.5}$, which by virtue of their small size are able to deposit deeper within the respiratory tree, exposing a large surface area of airway epithelium to inflammatory injury[34].

The direct measurement of breathing patterns and application of the MPPD model to predict consequences of their changes due to obesity are key novelties of this investigation. However, some limitations are noted. Although we have shown that estimates from the MPPD model were robust to changes in assumed inputs, the model does not explicitly simulate airway obstruction.

This limitation, however, is balanced by two factors. First, exposure studies of ultrafine particles in children and fine particles in adults have both shown that asthma is associated with higher total deposition, suggesting that our findings establish a conservative lower bound for estimates of fractional deposition[35,36]. Second, almost all participants with asthma in these other studies had obstruction on spirometry. This was not evident in our population, making significant departures from MPPD estimates less likely overall. Additionally, because AIRWEIGHS did not recruit participants who are underweight, this study cannot be extrapolated to children below the 5th percentile for BMI. Finally, our study population was predominantly Black and recruited from an urban center, with attendant limitations in generalizability to the overall population of pediatric asthma.

CONCLUSION

Among children with asthma, obesity was associated with higher tidal volumes which, in turn, was associated in a particle deposition model with more efficient deposition of $PM_{2.5}$ within the lung generally and alveoli in particular. These findings characterize a mechanism for why obese children with asthma are more susceptible to air pollution, and thus rationale for why obesity is a risk factor for more severe and uncontrolled asthma. Follow-on investigation of particle deposition characteristics in children with asthma is warranted.

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Table 1. Participant characteristics (n=174)

Characteristic	Non-Obese (n=88)	Obese (n=86)	p-value
Age, mean±SD	11.1±2.5	10.9±2.5	0.49
Female sex, n (%)	30 (34)	39 (45)	0.13
Black race, n (%)	74 (84)	75 (87)	0.56
Asthma control, mean±SD			
Maximum symptom day*	4.3±4.4	5.2±4.9	0.20
ATAQ score+	2.2±1.9	2.8±2.0	0.08
Asthma severity, n (%)			0.61
Intermittent	8 (9)	4 (5)	
Mild persistent	29 (33)	26 (30)	
Moderate persistent	37 (42)	39 (45)	
Severe persistent	14 (16)	17 (20)	
Spirometry, mean±SD			
FEV1 (% predicted)	91±15	96±16)	0.02
FVC (% predicted)	99±14	104±15)	0.01
FEV1/FVC	0.81±0.09	0.81±0.08	0.94
Tidal breathing measures, mean±SD			
Tidal volume (mL)	201±80	213±62	0.26
Respiratory rate (breaths/sec)	17.8±3.4	18.9±4.1	0.06
Minute ventilation (L/min)	3.4±1.0	3.9±0.9	<0.01

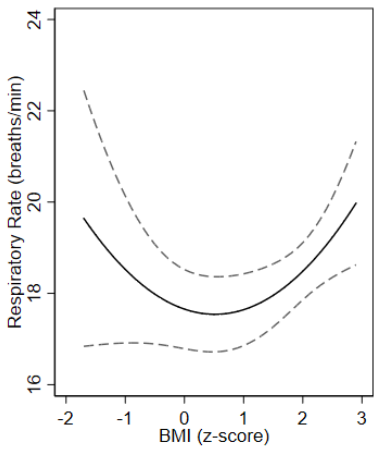
*20/174 missing; +19/174 missing; ATAQ: Asthma Therapy Assessment Questionnaire; SD: standard deviation; FEV1: forced exhaled volume in the first second; FVC: forced vital capacity

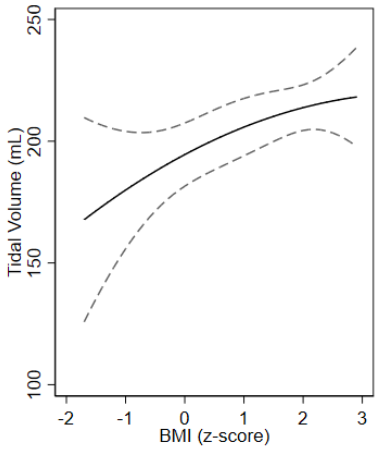
FIGURE CAPTIONS

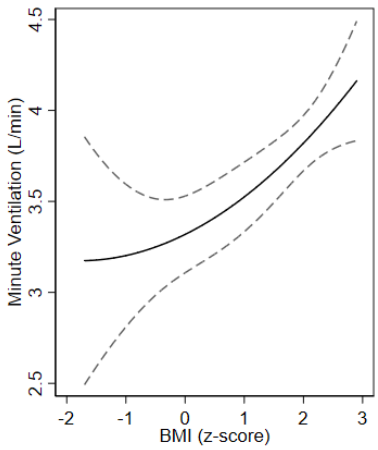
Figure 1. Point estimates (solid line) and 95% confidence intervals (dashed lines) of the association of BMI with respiratory rate, tidal volume, and minute ventilation across the range of observed BMI. Models are adjusted for age, age^2, height, height^2, race, sex, and asthma severity.

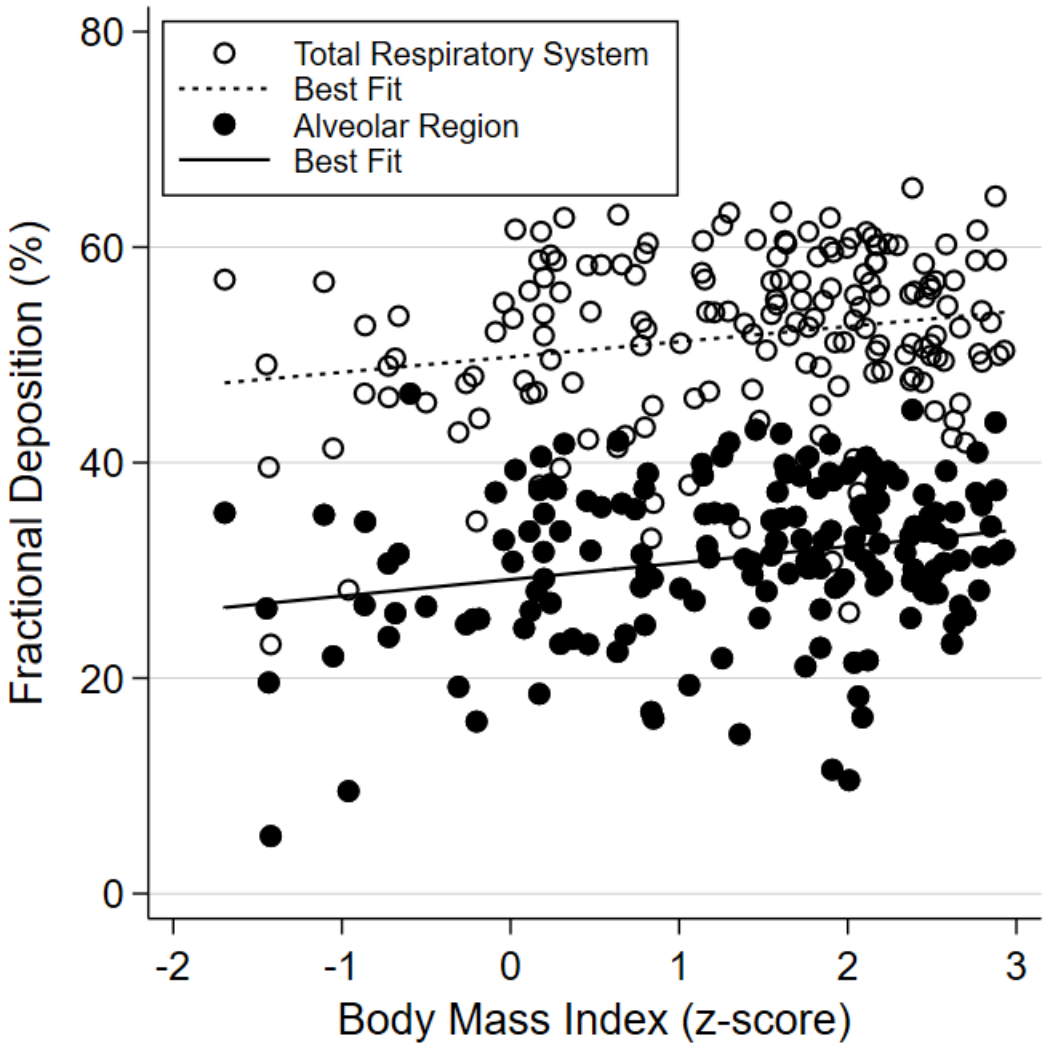
Figure 2. Scatterplot of $PM_{2.5}$ fractional deposition by body mass index for the total respiratory system and alveolar regions, with respective lines of best fit.

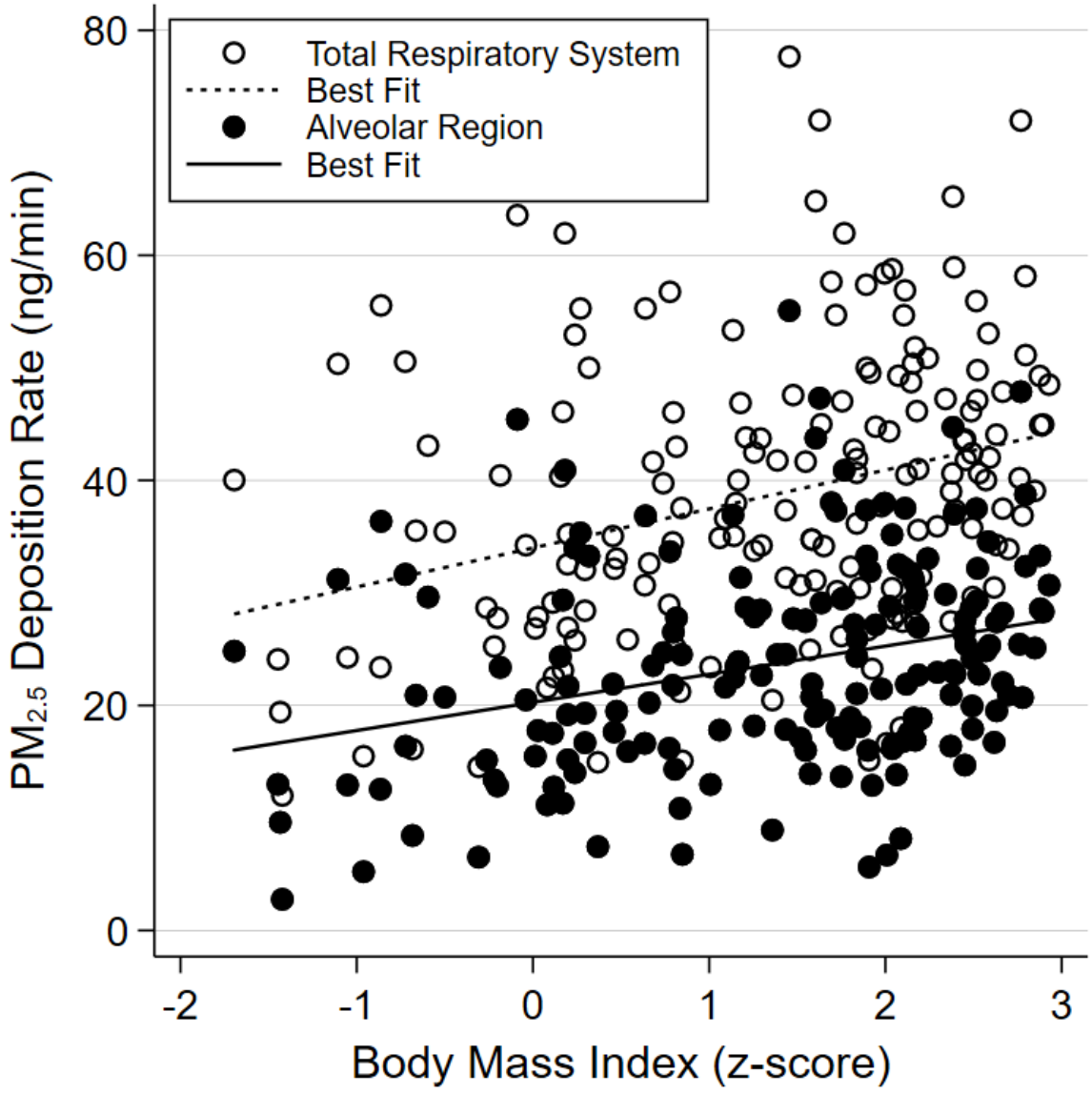
Figure 3. Scatterplot of $PM_{2.5}$ deposition rate by body mass index for the total respiratory system and alveolar regions, with respective lines of best fit.


Respiratory Rate (breaths/min)
16
18
20
22
24
-2
-1
0
1
2
3
BMI (z-score)


Tidal Volume (mL)
100
150
200
250
-2
-1
0
1
2
3
BMI (z-score)


Minute Ventilation (L/min)
2.5
3
3.5
4
4.5
-2
-1
0
1
2
3
BMI (z-score)

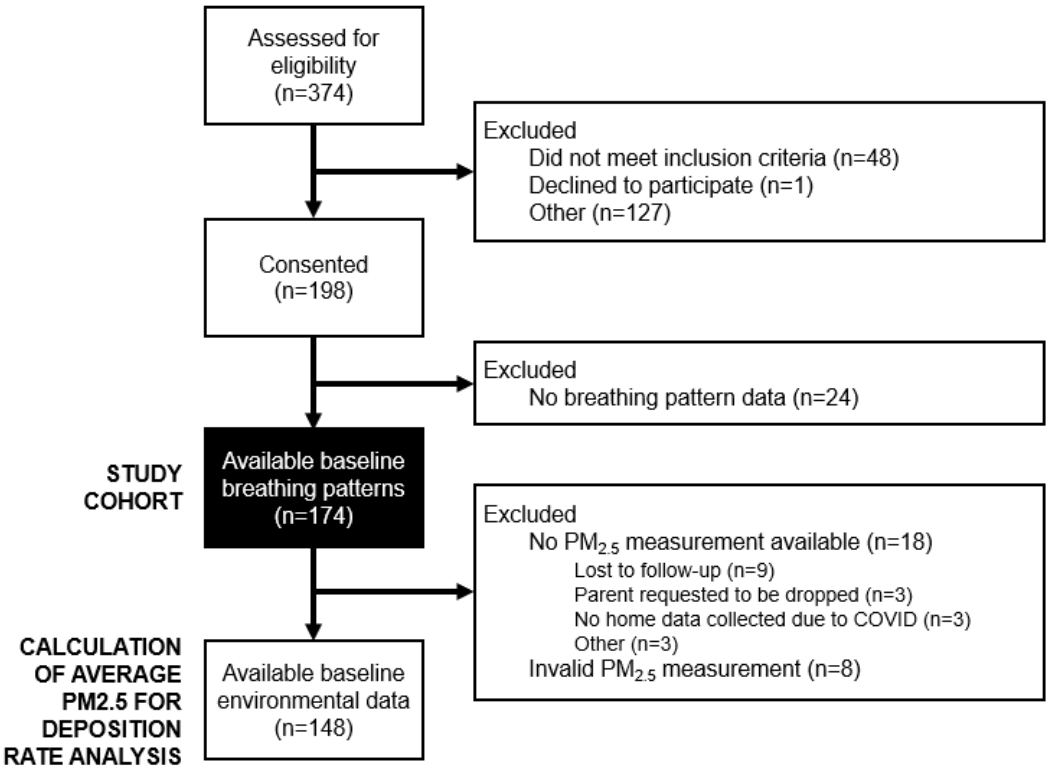

Total Respiratory System
Best Fit
Alveolar Region
Best Fit
Fractional Deposition (%)
80
60
40
20
0
-2
-1
0
1
2
3
Body Mass Index (z-score)


Total Respiratory System
Best Fit
Alveolar Region
Best Fit
80
60
40
20
0
PM2.5 Deposition Rate (ng/min)
-2
-1
0
1
2
3
Body Mass Index (z-score)

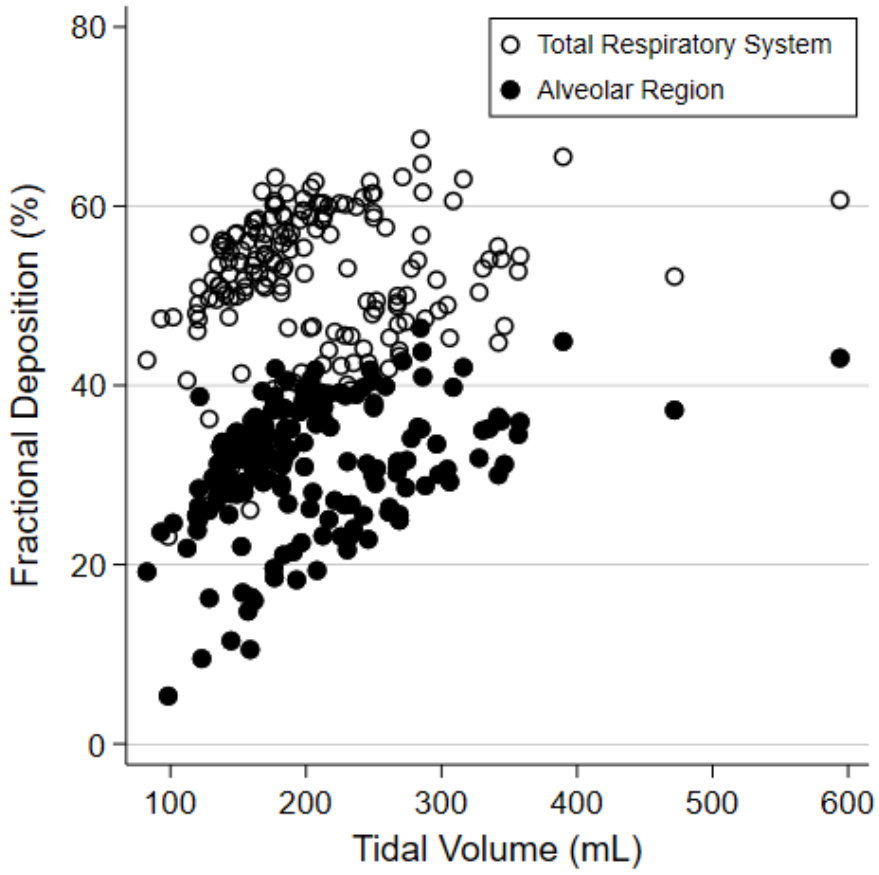
SUPPLEMENTAL MATERIAL

Obesity, Tidal Volume, and Pulmonary Deposition of Airborne Particulate Matter in Children with Asthma

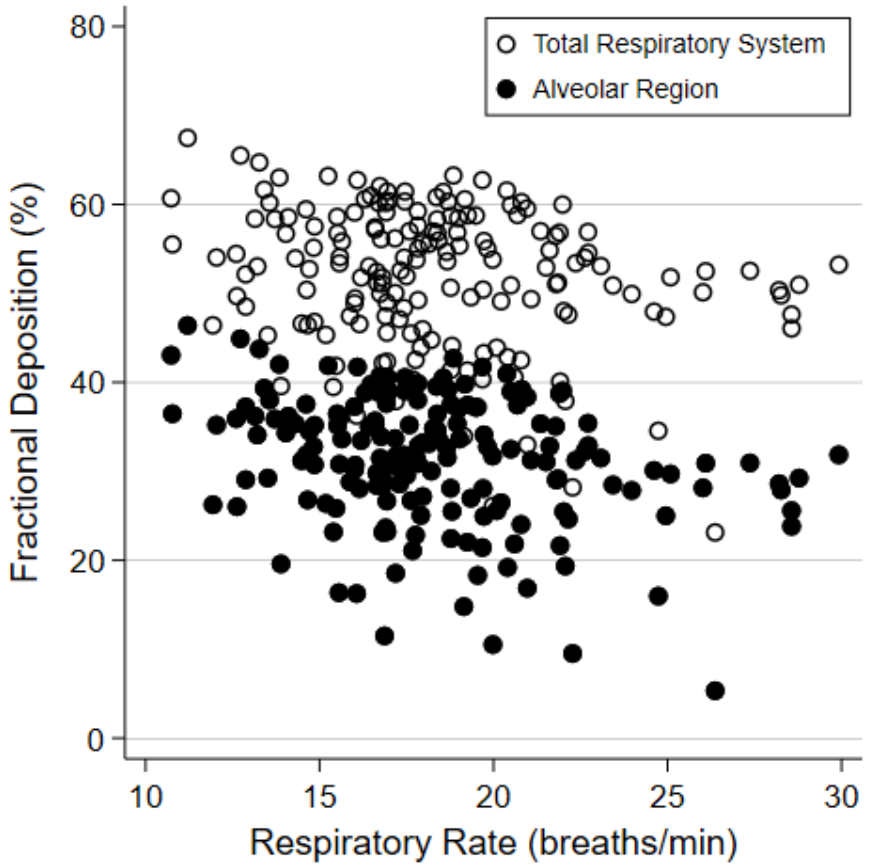
Table of Contents



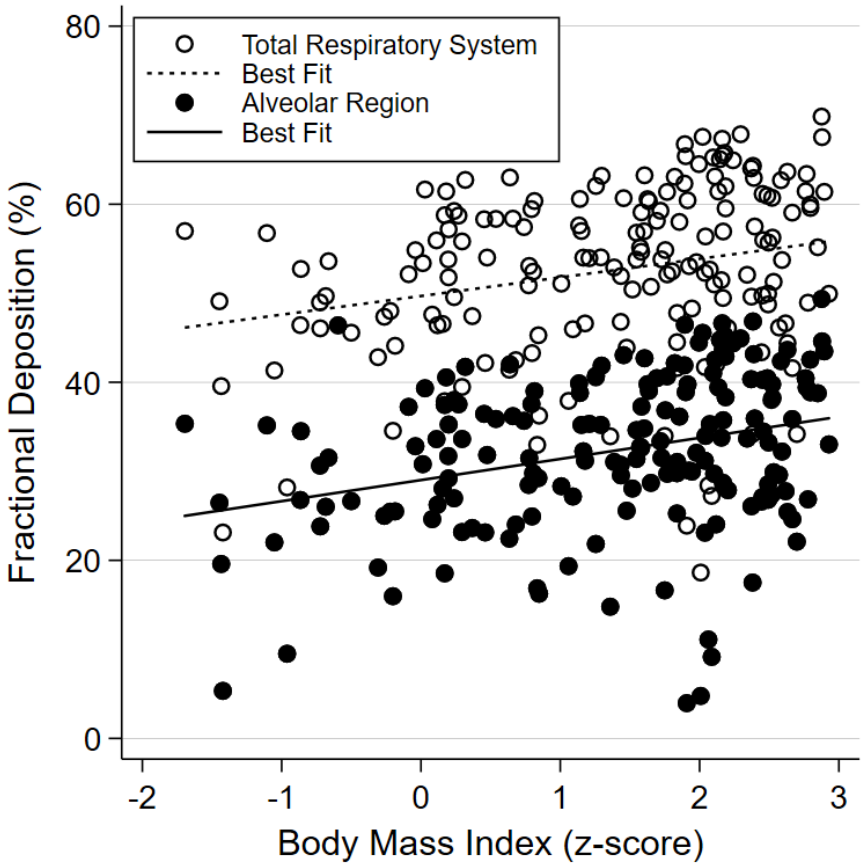
eFigure 1. Participant flow diagram



eFigure 2. Association of tidal volume and fractional deposition for the total respiratory system and alveolar region. Separation is apparent by age <12 and age ≥12 due to model design (see methodology details).



eFigure 3. Association of respiratory rate and fractional deposition for the total respiratory system and alveolar region. Separation is apparent by age <12 and age ≥12 due to model design (see methodology details).



eFigure 4. Association of BMI z-score with fractional deposition with reduction of FRC among obese participants. Estimates from participants with a BMI z-score >1.645 (corresponding to the 95th percentile) were made with model-predicted FRC reduced by 20%.

eTable 1. Association of tidal volume, respiratory rate, and BMI z-score with total and regional fractional deposition of $PM_{2.5}$

		Regional Fractional Deposition (%)		
Parameter	Total Fractional Deposition (%)	URT	TB	Alveolar
Tidal Volume (per 100mL)	2.3 (0.6, 3.9)	-0.2 (-0.21, -0.14)	0.17 (0.05, 0.29)	3.8 (2.5, 5.3)
Respiratory Rate (per 1 breath/second)	-0.48 (-0.8, -0.17)	0.22 (0.14, 0.30)	-0.13 (-0.14, -0.11)	-0.58 (-0.86, -0.30)
BMI z-score (per 1 unit)	1.42 (0.35, 2.49)	-0.09 (-0.38, 0.20)	-0.27 (-0.11, 0.05)	1.54 (0.58, 2.49)

URT: upper respiratory tract; TB: tracheobronchial; BMI: body mass index

eTable 2. Association of BMI z-score with total and regional deposition rates of $PM_{2.5}$

		Regional Deposition Rate (ng/min)		
Parameter	Total Deposition Rate (ng/min)	URT	TB	Alveolar
BMI z-score (per 1 unit)	4.56 (2.56, 6.55)	0.83 (0.43, 1.24)	0.52 (0.19, 0.84)	3.21 (1.77, 4.64)

URT: upper respiratory tract; TB: tracheobronchial; BMI: body mass index

Methodology details: Flow-time waveform analysis

Flow-time waveforms were uploaded into a time-series analysis program written in Igor Pro (WaveMetrics; Portland, OR). All tracings were manually reviewed by study staff. Periods of artifact (principally those due to sensor noise or if a participant was talking) were discarded. A semi-automated process of breath-to-breath review and quality assurance analysis of airflow waveforms were performed to identify inspiration and expiration. Inspiratory airflow was integrated to derive tidal volume for each breath. Individuals' mean tidal volume for the recording period was then calculated. The total respiratory cycle time (inspiratory + expiratory time) was used to determine mean respiratory rate, calculated as the total number of inhalations over the total time period of recording.

Internal validity was determined by randomized duplicate ventilatory analysis in 10% of the data set by a second investigator. It was determined that the limits of agreement for tidal volumes, respiratory rates, and minute ventilations were within 5%.

Methodology details: Multiple-path particle deposition model

We utilized the multiple-path particle deposition model (MPPD version 3.04; Applied Research Associates, Raleigh NC) to computationally estimate total and regional particle deposition characteristics (fraction and rate). The MPPD computes deposition patterns for particles ranging from 0.01 to 10 μm in size due to sedimentation, diffusion, and impaction mechanisms and is based on lung geometry scans for different age groups. The model splits the respiratory system into three major regions including upper respiratory tract (URT), tracheobronchial (TB), and alveolar region. In this model, the URT is defined as the area from nose down to the trachea. The TB region is the area that extends from the trachea down to the 16^{th} airway generation, and the

alveolar region includes the rest of the child respiratory system that consists of terminal bronchitis, respiratory bronchial, alveolar ducts, and alveolar air sacs.

The MPPD consists of four sub-models including URT deposition modeling, respiratory tract geometry, respiratory tract ventilation, and particle transport modeling. The URT deposition sub-model applies numerical computations based on semi-empirical equations[1,2]. The respiratory tract geometry sub-model includes asymmetric scans of two-dimensional images of the airways that includes 5 lobes[3]. The respiratory tract ventilation sub-model incorporates the steady breathing pattern and air flows, and the particle transport sub-model solves the mass balance equation for each airway using a Eulerian finite element scheme. Further details on the computational schemes used for estimating the deposited particles within each region and verification of all sub-models have been elucidated elsewhere[4–6].

Due to lack of empirical data for nasal deposition efficiency in young children, the MPPD model extrapolated data from adult studies. The designers produced separate estimates of deposition efficiency for children less than 12 years of age, between 12-15 years of age, and 16 years of age or above. In exploratory analysis, we noted that this difference introduced clustering by age strata in the relationships of fractional deposition to tidal volume and fractional deposition to respiratory rate (eFigure 2 and 3). However, correlations were largely similar within each age strata, resulting in model estimates that were not qualitatively different from unstratified analysis in any comparison. Thus, unstratified results are presented.

Volumes of the functional residual capacity (FRC) and the upper respiratory tract are sensitive to the child's age. Therefore, the asymmetric age-specific sub-model with 5 lobes was used for the respiratory tract geometry sub-model. Using the model default values for FRC and URT volumes

for 9 years old children (683 mL and 22.44 mL, respectively) and for 14 years old children (988 mL and 30.63 mL, respectively) the corresponding FRC and URT values for the children ages between 9 to 14 years old were approximated through linear interpolation.

An average count median diameter (CMD) of 44 nm, approximately equivalent to a mass median diameter (MMD) of 78 nm, and an average geometric standard deviation (GSD) of 1.55 were assumed based on a study by Géhin et al[7]. In that study, the aerosol generating sources included a wide list of indoor activities such as a lit candle, a 1000-W electric stove switched on max to cook a piece of meat, and a piece of butter burning in a pan. In all simulations, only the nasal route was considered for the respiratory inhalation. The inspiratory and expiratory periods in a breathing cycle were assumed to be equal with no pause in between. All particles were assumed to be spherical (aspect ratio of 1). The density of all particles was assumed to 1000 kg/m^3.

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