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Association between lung function and cognition among children in a prospective birth cohort study

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Abstract

Objectives—While a growing number of studies have demonstrated a relationship between lung function and cognition among adults, this relationship has not been studied among children. We examined the relationship between lung function and cognition among children in the Maternal-Infant Smoking Study of East Boston, a prospective cohort of women and children enrolled prior to 20 weeks of gestation.

METHODS—At 6 years of age, children completed lung function tests. At 9 years of age, the Wide Range Assessment of Memory and Learning (WRAML) and Kaufman Brief Intelligence Test (K-BIT) were administered. Linear regression was used to assess the relationship between cognition and lung function adjusting for race, maternal education, child's gender, age, height, birthweight, asthma, allergies, lower respiratory infections, blood lead level, in utero and second hand tobacco exposure.

RESULTS—The sample of 165 children included 53% girls and 52% Hispanic. Mean (± SD) forced expiratory volume in one second (FEV1) was 1.26L + 0.2; mean forced vital capacity (FVC) was 1.37L + 0.2. In multivariate regression, a one percent increase from expected FEV_1 was associated with increases in the matrices and composite subscales of the KBIT ($p < .05$), and in the verbal and learning subscales of the WRAML ($p < .10$). FVC was associated with increases in the composite and matrices subscale of the KBIT and in the visual and learning subscales of the WRAML (all $p < .05$).

CONCLUSION—Increased lung function was associated with increased cognitive development among children after adjusting for tobacco exposure, birthweight and peak blood lead. Lung and cognitive function may operate under common regulatory processes and thus have shared vulnerabilities to a host of environmental factors during development.

Keywords

cognitive function; lung function; children

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Introduction

An increasing number of cross-sectional (1–3) and longitudinal studies (4–7) have linked lung function and cognition in middle-aged and older adults. In the MRC National Survey of Health and Development (The British 1946 birth cohort study) lower levels of forced expiratory volume in one second (FEV_1) at 43 years of age was associated with slower psychomotor speed at the same age and slower decline in psychomotor speed ten years later (5). Sanchdev et al (8) recently showed a relationship between lung function and structural abnormalities in the brain using Magnetic Resonance Imaging (MRI) in the Personality and Total Health (PATH) through Life Project, a longitudinal cohort based in Australia (8). Furthermore, in this middle-aged community sample, lung function was significantly associated with information processing speed and fine motor dexterity. A similar relationship has also been found in the McArthur studies of Successful Aging (6) wherein a decreased peak expiratory flow rate was associated with adverse changes in neurocognitive function (verbal and nonverbal memory, language and visuospatial ability) in adults over 65 years of age (6). It has been suggested that the relationship between lung function and cognition likely reflects shared (and interactive) neural and endocrine regulatory processes as well as overlapping vulnerabilities to similar environmental exposures throughout development.

The developmental trajectory, and therefore vulnerability to environmental exposures, for the respiratory system as well as neurodevelopment begins very early in life, even before birth (9). Evidence suggests that the respiratory and neurological systems may be susceptible to prenatal, neonatal and early childhood interferences. Longitudinal studies of the natural history of lung function have shown that a number of earlier life risk factors including lower socioeconomic status (10), asthma (11), active and passive smoking prenatally, during childhood and adolescence (12, 13), atopy (14), lower respiratory infections (15), and perinatal factors including birthweight, gestational age, and nutrition (16, 17) are associated with reduced lung function over the life course. A number of these factors have also been linked to neurodevelopment and cognition. Asthma and allergy, both due to uncontrolled symptoms and adverse effects from medications, may diminish cognitive function and learning in childhood (18). Asthma may be more directly linked to cognitive function through the systemic propensity toward TH2 pro-inflammatory nueroimmunomodulation or repetitive intermittent hypoxia (even when mild) [e.g., adverse effects of reactive oxygen species, vasodilatation or vasoconstriction related to catecholamine release or nitric oxide release] (19, 20). Inflammatory mediators involved in allergy and asthma are multifunctional cytokines that also may play important roles both in normal central nervous system (CNS) development and in the response of the brain to diverse forms of injury (21). Systemic immune responses have been implicated in cognitive impairment (22, 23). Furthermore, environmental neurotoxicants such as lead and tobacco smoke exposure have been linked to both cognitive development and lung function (24–26). In-utero exposure to tobacco smoke as well as secondhand tobacco smoke exposure can affect neurodevelopment (24, 27–29). In addition to prior research linking blood lead and cognition (25), increased blood lead levels have been associated with reduced lung function (30, 31).

While there is some evidence that a relationship between lung function and cognition may be present even earlier in the lifecourse (5), this association has not been studied in early childhood. We examined the relationship between lung function and cognitive ability among a group of children in a prospective cohort and examined the influence of adjusting for several of these shared vulnerability factors thought to influence both lung function and cognition (i.e., socioeconomic status, birthweight, height, allergies, asthma, respiratory infections, tobacco smoke exposure and lead).

Methods

Study Population

Mother's and their children were voluntary participants in the ongoing Maternal-Infant Smoking Study of East Boston a prospective cohort originally designed to study the effects of pre- and postnatal tobacco smoke exposure on childhood lung growth and development and respiratory health. The study has been described in detail previously (12) with only relevant components discussed here. In brief, pregnant women receiving prenatal care, (< 20^{th} week of gestation) at an urban community health center in Boston, MA between March 1986 and October 1992 were eligible for enrollment. Women who did not speak either English or Spanish, who did not plan to have pediatric follow-up at the clinic, and who were less than 18 years of age at the time were excluded. Of the 1,000 pregnant women initially enrolled, 848 delivered a full term infant and remained eligible for postnatal follow-up with 498 mother-child pairs continuing follow-up at age 6 to 7 years when they were approached for lung function testing. Of those, 330 agreed to pulmonary function testing for their children. In November 1996 new study initiatives were implemented, including neurocognitive assessment; all subjects were approached to participate albeit given practical limitations (i.e., funding and staffing) 175 children were brought in and completed neurocognitive assessments in this phase of the study. Notably, among the children who completed the lung function tests, there were no significant differences between those who participated in the cognitive assessment and those who did not based on race/ethnicity, maternal education, lung function measures, height, birthweight or tobacco smoke exposure. The study was approved by the human studies committees at the Brigham & Women's Hospital and the Beth Israel Deaconess Medical Center.

Lung Function Measures

Lung function was measured using a Morgan spirometer (P.K. Morgan, Andover, MA) when children were between 6 and 7 years of age, within one year of the neurocognitive assessment. Standing height without shoes was measured prior to spirometry. The lung function protocol was developed by an experienced pulmonologist and pediatric pulmonary function technologist. Furthermore, the children were not naïve to spirometry as they had been participating in lung function testing from the time they were 4 years old in anticipation of formal testing at age 6 to 7 years. A trained pulmonary function technologist instructed children during testing and monitored the flow-volume curve to ensure good effort. Maneuvers were repeated to obtain three acceptable curves; data from each technically acceptable effort were stored following established guidelines (32, 33). Forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and forced mid-expiratory flow rate ($FEF_{25–75\%}$) were measured from the best acceptable blow (32).

Cognitive Measures

Approximately three years after lung function testing, a battery of cognitive tests was administered. A single test administrator trained by an experienced neuropsychologist (David Bellinger PhD) administered all neurocognitive assessments. A random sampling of 5% of tests were directly observed for quality assurance. The cognitive battery included the Kaufman Brief Intelligence and the Wide Range Assessment of Memory and Learning. The Kaufman Brief Intelligence Test (K-BIT) is an individually administered test of verbal and nonverbal intelligence (34). Two subscales, vocabulary and matrices, comprise the test as well as a composite IQ score. The K-BIT has acceptable correlation with the widely used Wechsler Verbal, Performance and Full-Scale Scores of the Wechsler Intelligence for Children Third Edition (WISC-III) (35); validation studies are reported for children less than 7 years of age with normative data available (36). The Wide Range Assessment of Memory and Learning (WRAML) is a well-standardized psychometric instrument, which allows

evaluation of a child's ability to actively learn and memorize a variety of information (37, 38). Three subscales, verbal memory, visual memory and learning comprise the test. The WRAML is normed for children aged 5 to 17 years and based on racial sub-categories including minorities. All measures are expressed as standardized scores, which represent the score of the individual taking the test relative to scores obtained by children of the same age and gender in the standardization sample. All scores have a mean of 100 and standard deviation of 15.

Tobacco smoke exposure

Women were asked at baseline about their past and current smoking status. At each subsequent prenatal visit (median number of visits = 6, range 1–12), women reported current smoking habits. A urine specimen was obtained for determination of a creatinine-corrected cotinine level as previously detailed (12). Mothers were classified as never smokers during their pregnancies if they always reported that they had never smoked on the standardized questionnaire and each of their urine cotinine levels were < 200 ng cotinine/mg creatinine (12). At any visit, if the report of nonsmoking by the mother was contradicted by the urine cotinine, the mother was classified as a current smoker for that interval. We have previously reported that the sensitivity and specificity of self-report of current smoking compared with cotinine-indicated smoking in this sample was high (88.4% and 99% respectively) (39). Maternal reported postnatal second hand smoke (SHS) exposure was assessed through questionnaire (monthly through age 26 months, every 6 months between 26 months and 4 years, and annually thereafter). Children were considered to be exposed to SHS at each follow-up interval if the mother reported personal active smoking or active smoking by any other person living in the household. Postnatal SHS was categorized as early (occurring from birth to 25 months of age) and late (26 months of age or older). The late SHS exposure category includes children exposed both early and late (46 children) and late only (11 children) given that there were relatively few children in the latter category. The child's exposure to maternal smoking during pregnancy was highly correlated with postnatal SHS exposure. Thirty-seven children were exposed to prenatal tobacco smoke, among these only one child was not exposed to SHS after birth.

Medical History

Birthweight and gestational age were obtained from medical record review at the clinic. Early birth was defined as gestational age less than 37 weeks. History of childhood asthma was determined based on parental report of physician diagnosed asthma on the standardized American Thoracic Society (ATS) respiratory questionnaire (40). Mother's were also asked if the children were ever diagnosed with hay fever, eczema or if they received allergy shots. In addition they were asked whether the children had had a lower respiratory tract infection (croup, bronchitis, bronchiolitis or pneumonia) on the monthly follow-up questionnaires administered from birth to the time the child was two years of age. Lower respiratory infections were categorized as none, one to two and three or more. Presence of allergies was dichotomized as none, or one or more (eczema, hay fever or allergy shots).

Blood lead

Children in Massachusetts are mandated by law to have blood lead testing annually starting at 9 months of age until age 4 unless they are considered to be at high-risk (living in pre-1978 housing that is deteriorated or undergoing construction or having a sibling that is lead poisoned) they are then tested annually until age 6. Results are incorporated into the medical records at the community center where the children obtained pediatric follow-up. Using a standardized instrument, blood lead levels were extracted from medical records at the health center by a physician blinded to the study aims. Because the children had varying numbers of blood lead measurements which were dependent on their lead exposure (higher

lead exposed children had more follow-up tests compared to children with lower lead concentrations), we used the highest blood lead level recorded up to 6 years of age, for each child, referred to as the peak blood lead level.

Statistical Analysis

One hundred and seventy-five children completed the lung function and cognitive assessment. Our final sample size for these analyses consists of 165 children due to missing data on birthweight, in-utero tobacco smoke exposure and mother's education level. Estimated effects of lung function are reported using percent of predicted lung function (based on height, age, gender and race/ethnicity) as our independent variable. To obtain the predicted lung function values for each child we regressed the log transformed lung function measures against log height, age, gender and race/ethnicity. Bivariate analyses were conducted to determine the association between cognitive outcomes and demographic, environmental and lung function measures of interest. We also tested for associations between the lung function measures and environmental and socio-demographic markers. The effect of percent predicted lung function on cognition was estimated by linear regression while adjusting for child's age at cognitive assessment, gender, race/ethnicity and maternal education as a marker of socio-economic status (model 1). To assess the potential for confounding, we examined the sensitivity of those results to further adjustment of several covariates in cumulative models; pre- and postnatal smoke exposure (model 2), birthweight and height (model 3), diagnosis of allergies and asthma (model 4), lower respiratory infections (model 5) and blood lead levels (model 6). All covariates were selected a priori given evidence already discussed suggesting that they may be shared vulnerability factors for cognition and lung function. All analyses were conducted in SAS version 9.0 (SAS Institute, Cary, NC).

Results

Among the 165 children in this study, 53% were female, 52% were Hispanic and for 39% of the children, the mother's education level was less than high school (Table 1). The children's mean age (mean ± SD) at the time of the lung function testing and neurocognitive assessment was 6.2 ± 0.3 and 9.9 ± 1.6 years, respectively. The mean peak blood lead level was 9.0 ± 6.6. Mean subscale results for the K-BIT subscales were as follows: composite 95.9 ± 13, vocabulary 90.9 ± 16 and matrices 101.8 ± 13; WRAML mean subscale scores were: 85.6 ± 14 verbal memory index; 93.8 ± 14 visual memory index and 101.1 ± 15 learning index. Mean lung function measures were FEV_1 1.26L ± 0.2, FVC 1.37L ±0.2 and $FEF_{25–75\%}$.1.8L/sec ± 0.4.

In bivariate analyses (data not shown) of the lung function and cognitive measures, FVC and FEV_1 were associated with the composite and matrices subscales of the K-BIT and the visual and learning subscales of the WRAML. $FEF_{25–75\%}$ was not associated with any of the K-BIT or WRAML subscales. Race/ethnicity and maternal education were both associated with the composite, vocabulary and verbal memory subscales of the WRAML and K-BIT subscales. FVC and $FEF_{25–75\%}$ were associated with tobacco smoke exposure and FEV_1 was associated with lower respiratory infections before the age of 2.

In multivariate analyses (Tables 2 and 3) adjusting for race/ethnicity, age, gender and mothers education level, a one percent increase in percent of predicted FEV_1 was associated with a 0.23 (95%CI 0.08, 0.38) point increase in the composite scale of the K-BIT and a 0.27 (95% CI 0.10, 0.45) point increase in the matrices subscale of the K-BIT. Percent of predicted FEV_1 was also associated with increases in the verbal (0.17 95%CI −0.01, 0.34), learning (0.20 95% CI 0.00, 0.40) and visual (0.18 95%CI −0.01, 0.37) subscales of the WRAML. Similarly a one percent increase in percent of predicted FVC was associated with

increases in the matrices (0.23 95%CI 0.07, 0.39) and composite (0.19 9%CI 0.05, 0.33) subscales of the K-BIT and in the visual (0.18 95%CI 0.00, 0.35) and learning (0.21 95%CI 0.02, 0.39) subscales of the WRAML. $FEF_{25–75\%}$ was not associated with any of the K-BIT or WRAML subscales. Further adjustment for tobacco smoke exposure, birthweight, height, asthma diagnosis, presence of allergies, lower respiratory infections prior to age 2 and peak blood lead levels only slightly decreased the effect estimates found when only controlling for socio-demographic variables (model 1), with the exception of the matrices WRAML subscale and the visual KBIT subscales where effect estimates slightly increased upon further adjustment for other covariates.

Discussion

In this prospective birth cohort increases in percent predicted FEV_1 and FVC were associated with increased performance on cognitive tests, even after adjusting for socioeconomic status, in-utero and postnatal second hand smoke exposure and other potential confounders. Our results are robust in that both FEV_1 and FVC had a positive association on all the WRAML and K-BIT subscales, even when not reaching statistical significance. We did not detect associations between $FEF_{25–75\%}$ and any of the K-BIT and WRAML subscales, potentially due to the wide variability in repeated $FEF_{25–75\%}$ measures, as reported by the American Thoracic Society (41). Although $FEF_{25–75\%}$ is thought to be a more sensitive measure of small airways narrowing than FEV_1 it is also less reproducible since it is more dependent on individual effort.

These results are of comparable magnitude to results found for other environmental neurotoxicants. For example, among children, a 10μg/dL increase in blood lead has been associated with a loss of 1–5 IQ points (24). Children born to mothers' who smoke 10 or more cigarettes per day during pregnancy have an average decrease of 4 IQ points (42). In our cohort a 10% increase in percent of predicted FEV_1 was associated with a 2 point increase in IQ points (K-BIT composite subscale).

Our results are similar to other studies which have found FEV_1 to be associated with several measures of cognition among adults. While this association had not previously been investigated among children, several studies have shown a relationship between childhood height and cognition both during childhood (43, 44) and adulthood (44). Due to the high correlation between height and lung function it is possible that associations previously seen between height and cognition among children can be partially explained by lung function. In contrast, we avoided the converse possibility of confounding by using percent of predicted lung function for a persons height, which eliminates the correlation of height with our lung function measures.

With regard to criteria for causality in this observational study, the current analysis in children adds to the adult literature demonstrating a temporal relationship between lung function and subsequent cognitive measures (4–6). Moreover, the observed associations were robust across a number of cognitive domains and the narrow confidence intervals in the setting of a relatively small sample size reflect the precision of the estimates. Although it remains unclear just how pulmonary function influences cognitive outcomes, a growing literature suggests possible mechanisms and supports the argument for biological plausibility (19–21). We also were able to partially account for alternative explanations. In this cohort, children were instructed on the proper technique of lung function testing procedures and practiced for several months prior to the lung function assessment. Only when they were able to provide reproducible tests were they then scheduled to conduct the assessment. It is then unlikely that the associations found were due to compliance or ability to follow instructions. We were also able to adjust for a number of shared environmental

vulnerability factors that might influence both lung function and cognitive outcomes [i.e. lead, tobacco smoke, asthma, lower respiratory infections, allergies as well as markers of socioeconomic status (race/ethnicity, mother's education level)].

Further research in this area would thus be strengthened by the inclusion of other risk factors that have been linked to neurodevelopment and lung function. Several lines of evidence indicate that chronic stress may also influence lung function. The extant literature implicates factors that induce chronic persistent inflammation (e.g., tobacco smoke exposure in utero and during early childhood, asthma, air pollution, viral infections) as risk factors for reduced lung function (45–47). Imbalance of physiologic processes including hypothalamic-pituitary-adrenal (HPA) axis function, the proteases-antiproteases, and the oxidants-antioxidants can occur both in the face of these known risk factors (47) and under chronic stress (48). In animals, chronic stress has been found to induce atrophy of apical dendrites in the hippocampus, the brain region with the highest density of glucocorticoid receptors (49–51). Animal behavioral studies have confirmed the adverse independent effects of both prenatal and post-natal chronic stress on memory and learning (52–55). In rats, prenatal dexamethasone influences the development of many organ systems, including the lung (56). These findings have more recently been corroborated in humans (57). Altered cortisol expression has been found to be negatively associated with lung function in the Normative Aging Study (58) and the MacArthur Studies of Healthy Aging (6). Future studies should also incorporate biomarker-based assessment of the underlying pathophysiological processes that may influence early lung and brain development.

A number of limitations of the current study are worth noting. As is typical with longitudinal studies, there was significant reduction in the sample available from the original cohort over time. The non-participation of many subjects from the longitudinal study may be seen as a limitation albeit there were no differences based on race/ethnicity, maternal education, smoking status, birth weight, or lung function comparing those who had cognition assessed versus those who did not among the participants who also had pulmonary function measures. Thus, this unlikely influenced our findings. Although we had repeated biomarker assessment of prenatal smoke exposure in this sample, postnatal second hand smoke exposure relied on maternal report over time. The sensitivity and specificity of repeated self-report of prenatal smoking with cotinine-indicated smoking was very high in this sample (88.4% and 99%, respectively) (39). This coupled with the fact that women are more likely to underreport smoking status during pregnancy due to social acceptability suggests acceptable reliability of repeated self-reported smoking status assessed to determine second hand smoke exposure postnatally. It is still possible that these results can be attributed to residual confounding or to other shared environmental factors or processes associated with both lung function and cognition which we did not account for (i.e., air pollution exposures, chronic stress).

These data corroborate associations found between lung function and cognition among middle aged and older-adults. We noted similar associations among children even after adjusting for markers of socio-economic status, environmental toxicants, asthma, allergies and lower respiratory infections. Understanding childhood risk factors that contribute to cognitive function is an important area of research as prevention and intervention strategies may be better informed and implemented to prevent more significant problems associated with decreased childhood cognitive ability (i.e. academic achievement, juvenile delinquency, behavioral problems).

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Abbreviations

K-BIT	Kaufman Brief Intelligence Test
WRAML	Wide Range Assessment of Memory and Learning
FEV_1	Forced Expiratory Volume
FVC	Forced Vital Capacity
$FEF_{25–75\%}$	Forced Mid-Expiratory Flow Rate

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Table 1

Demographics, medical history and environmental exposures of the study cohort N=165

Demographics	N(%)
Child's age Mean (SD)	9.9 (1.6)
Child's Gender	
Male	78 (47.3)
Female	87 (52.7)
Child's Race/Ethnicity	
Non-Hispanic†	80 (48.5)
Hispanic	85 (51.5)
Parent's Education Level	
Some College	34 (20.6)
High School Grad/ Tech	66 (40.0)
Less High School/ No Grad	65 (39.4)
Marital Status	
Married/Living with someone	125 (75.8)
Separated/Divorced/Single	40 (24.2)
Medical History and Environmental Exposures	
Gestational Age	
Greater or equal to 37 weeks	112 (67.9)
Less than 37 weeks	53 (32.1)
Tobacco Exposure	
Non Smoker	53 (32.1)
UTS and SHS§	37 (22.4)
Early SHS¶	18 (10.9)
Late SHS#	57 (34.6)
Allergies	
No	147 (89.1)
Yes	18(10.9)
Asthma	
No	135 (81.8)
Yes	30 (18.2)
Lower Respiratory Infections (N=160)	
None	44 (27.7)
One to Two	63 (39.6)
Three or more	52 (32.7)
Peak Blood Lead (N=152)Mean (SD)	9.0ug/dl (6.6)
Birthweight Mean (SD)	3.35kg (0.55)

† Includes 74 white, 2 African-Americans, and 4 identified as other race/ethnicity

§ UTS=In-Utero tobacco exposure; SHS=Second Hand Smoke

[¶] Early SHS= Second Hand Smoke exposure before 26 months of age

[#] Late SHS= Second Hand Smoke exposure after 26 months of age

Table 2

Linear regression model coefficients and 95% Confidence Intervals (CI), showing associations between Forced Expiratory Volume in one second (FEV_1) and WRAML and K-BIT subscales[#] (N=165)

	K-BIT			WRAML		
	Matrices	**Vocabulary**	**Composite**	**Verbal**	**Visual**	**Learning**
	Estimate (95% CI)	**Estimate (95% CI)**	**Estimate (95% CI)**	**Estimate (95% CI)**	**Estimate (95% CI)**	**Estimate (95% CI)**
% predicted FEV_1 (standard variables) [##]	0.27 (.10, .45)**	0.14 (−.03, .31)	0.23 (.08, .38)**	0.17 (−.01, .34)*	0.18 (−.01, .37)*	0.20 (.00, .40)*
% predicted FEV_1 (adjust above + smoke)	0.26 (.08, .43)**	0.13 (−.04, .31)	0.22 (.07, .36)**	0.16 (−.02, .33)*	0.18 (−.01, .37)*	0.19 (−.02, .39)*
% predicted FEV_1 (adjust above + birthweight + height)	0.26 (.08, .43)**	0.14 (−.04, .31)	0.22 (.07, .37)**	0.16 (−.01, .34)*	0.18 (−.01, .37)*	0.19 (−.02, .39)*
% predicted FEV_1 (adjust above + asthma +allergy)	0.26 (.08, .43)**	0.14 (−.03, .31)	0.22 (.07, .37)**	0.17 (−.01, .34)*	0.18 (−.01, .37)*	0.18 (−.02, .39)*
% predicted FEV_1 (adjust above + LRI [¶]) (N=159)	0.27 (.09, .45)**	0.13 (−.05, .31)	0.22 (.07, .38)**	0.18 (.00, .35)**	0.18 (−.01, .38)*	0.19 (−.02, .39)*
% predicted FEV_1 (adjust above + lead) (N=145)	0.30 (.12, .49)**	0.12 (−.07, .30)	0.23 (.07, .39)**	0.17 (−.01, .36)*	0.20 (−.01, .41)*	0.21 (−.01, .43)*

[#]Each line is a separate regression model cumulatively adjusting for covariates defined in the previous model. All models adjusted for standard control variables: age, gender race and mothers education

[##]Effect estimates reflect the change in K-BIT and WRAML subscale scores for a one unit change in the percent predicted FEV_1

*p-value<0.10

**p-value<0 .05

[¶]LRI denotes the number of lower respiratory tract illnesses reported for the child prior to the age of 2.

Table 3

Linear regression model coefficients and 95% Confidence Intervals (CI), showing associations between Forced Vital Capacity (FVC) and WRAML and K-BIT subscales[#] (N=165)

	K-BIT			WRAML		
	Matrices	**Vocabulary**	**Composite**	**Verbal**	**Visual**	**Learning**
	Estimate (95% CI)	**Estimate (95% CI)**	**Estimate (95% CI)**	**Estimate (95% CI)**	**Estimate (95% CI)**	**Estimate (95% CI)**
% predicted FVC (standard variables) [##]	0.23 (.07, .39)**	0.10 (−.06, .27)	0.19 (.05, .33)**	0.12 (−.04, .29)	0.18 (.00, .35)**	0.21 (.02, .39)**
% predicted FVC (adjust above + smoke)	0.21 (.05, .37)**	0.10 (−.07, .26)	0.17 (.03, .31)**	0.12 (−.05, .28)	0.18 (.00, .36)**	0.19 (.00, .38)**
% predicted FVC (adjust above + birthweight + height)	0.21 (.04, .37)**	0.10 (−.07, .26)	0.17 (.03, .31)**	0.12 (−.04, .28)	0.18 (.00, .36)**	0.19 (.00, .38)**
% predicted FVC (adjust above + asthma + allergy)	0.21 (.05, .37)**	0.10 (−.06, .27)	0.18 (.04, .32)**	0.12 (−.04, .29)	0.19 (.01, .37)**	0.19 (.00, .39)**
% predicted FVC (adjust above + LRI [¶]) (N=159)	0.22 (.05, .39)**	0.09 (−.08, .25)	0.17 (.03, .32)**	0.13 (−.04, .29)	0.20 (.01, .38)**	0.19 (.00, .39)**
% predicted FVC (adjust above + lead) (N=145)	0.27 (.09, .44)**	0.06 (−.12, .23)	0.18 (.03, .33)**	0.12 (−.06, .29)	0.22 (.02, .42)**	0.22 (.01, .43)**

[#]Each line is a separate regression model cumulatively adjusting for covariates defined in the previous model. All models adjusted for standard control variables: age, gender race and mothers education

[##]Effect estimates reflect the change in K-BIT and WRAML subscale scores for a one unit change in the percent predicted FVC

*p-value<0.10

**p-value<0 .05

[¶]LRI denotes the number of lower respiratory tract illnesses reported for the child prior to the age of 2.