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Relation of early childhood growth and wheezing phenotypes to adult lung function

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Summary

Rationale—Several studies have reported associations between indicators of birth size and postnatal growth rates with levels of pulmonary function achieved as adults. The objective of this study was to determine if levels and/or rates of weight gain, measured in early life (birth–6 yrs), are associated with FVC or FEV1 levels achieved in young adulthood and if these associations differ by early childhood wheezing phenotypes.

Methods—We used data from participants in the Tucson Children's Respiratory Study (CRS), a prospective birth cohort study. Weight was measured quarterly up to age 3 yrs and again at age 6 years. Pulmonary function was assessed at ages 16 and 22. Mean weight and slope of weight growth between 3 and 6 yrs were estimated using standardized residuals. Longitudinal models were used to determine predictors of FVC and FEV1 at ages 16 and 22 yrs.

Results—There were 127 non-Hispanic white subjects that had at least 4 weight measures and one or more pulmonary function measures as young adults. After adjusting for sex, height, and age, the standardized slope of weight growth, (between 3 and 6 years), was positively associated with higher levels of FVC at age 16 and 22 years ($p=0.0001$) among subjects who did not have pre-school wheezing. However, this association was completely absent among subjects who had wheezing lower respiratory tract illnesses in the first three years of life. Similar trends were found for FEV1.

Conclusion—The rate of weight gain between 3–6 yrs is significantly positively related to adult FVC and FEV1 and this association is modified by early wheezy phenotypes.

Keywords

Growth velocity; allometric; adulthood lung function

Introduction

Several studies have reported associations between indicators of birth size and postnatal growth rates with levels of pulmonary function achieved as young adults ^{1–6}. These associations held true after adjustment for height as assessed at the time that lung function was measured, indicating that tracking of body size from birth to adult age can not be the only explanation for these findings. An alternative explanation is that intrauterine and early postnatal body growth are the result of developmental processes that are also critical for a

concurrent proportional (also called “allometric”) maturation of the lungs and the airways⁷. In this framework, factors that influence these processes early in life could in turn affect predisposition for adult chronic lung diseases, thus explaining the strong links that have been reported between birth weight and growth patterns in childhood on one side, and respiratory and cardiovascular morbidity and mortality on the other⁸⁻¹⁰.

In this scenario, factors that selectively impact early developmental processes in the airways might be associated with later lung function deficits by leading to dysanaptic lung growth and severing the connection between the above mentioned proportional body, lung parenchymal, and airways' growth. One such potential factor is wheezing lower respiratory tract illness in early life, since children who wheeze in the first three years of life have lower lung function at age 16 years¹¹. In another study, bronchial biopsies demonstrated airway remodeling in wheezy preschool children by age three, but not in younger wheezing infants¹². These results suggested that the remodeling changes may be acquired in the first 2-3 years of life in children with recurrent, (usually viral) illnesses⁷. However, whether these early insults, which impact lung development in children with early wheezing, may alter the direct correlation between early body growth and subsequent lung function remains to be determined.

The objective of the current study is to ascertain if weight or rates of weight gain measured in early life (birth-6 yrs) are associated with subsequent levels of FVC and FEV1 achieved by ages 16 and 22 years, and if these associations are modified by early childhood wheezing phenotypes.

Methods

Population

Healthy infants, born to parents using the pediatric services of the largest health maintenance organization in Tucson, were enrolled between May 1980 and October 1984 as part of the Tucson Children's Respiratory Study (CRS)¹³. Follow-up is ongoing with questionnaire and clinical data being collected at regular intervals. Data on early growth was obtained prospectively during well child visits at approximately 3-4 month intervals from birth through three years of age. Weight was measured at each well visit. This analysis is limited to subjects that had at least 4 well visit weight measures, who were of non-Hispanic white ethnicity, and who had at least one acceptable pulmonary function test at age 16 or 22 years. Informed consent was obtained from the parents for the children, or by enrollees themselves if appropriate. The Institutional Review Board of the University of Arizona approved the study.

Wheeze Phenotypes

Upon enrollment into the study, parents were asked to take their child to a pediatrician if the child had any symptoms of a lower respiratory illness (LRI) before the age of 3 years. In addition, parents completed questionnaires for each child at age 6 years which determined current wheeze. In this analysis we included wheezing phenotypes that were defined based on reported LRIs, before 3 years of age, and wheezing status at 6 years of age. Four phenotypes were defined¹⁴ as: 1) Never Wheezing, no LRI and no wheezing at 6 years, 2) Transient Early Wheezing, wheezing LRI during first 3 years but no wheezing at age 6 years, 3) Persistent Wheezing, early LRI and current wheezing at 6 years, and 4) Late onset, no early LRI but currently wheezing reported at 6 years.

Pulmonary Function Tests

For this analysis, lung function measured at ages 16 and 22 years were used. Pulmonary function was measured using a portable Schiller Spirovit SP-1 spirometer, (Schiller AG, Baar, Switzerland), using standardized spirometric techniques (American Thoracic Society 1995). The system was calibrated with a Jones syringe, (Jones Medical Instrument Co., Oak Brooke, IL). Participants were asked not to use short acting bronchodilators within 4 hours of the test, or long acting bronchodilators in the previous 12 hours. The participant's height, weight, and age at the time of the test were also recorded. Percent predicted values for pulmonary function measures were calculated using prediction equations published by Knudson RJ, et al that use each subjects' sex, age, and height to standardize the measures ¹⁵.

Birth Size Indices

Birth weight and length was obtained from the newborn medical record. The Ponderal Index (PI), defined as the birth weight (gm) times 100, divided by length (cm) cubed was calculated as a measure of an infant's leanness.

Statistical Methods

All weights obtained at well child visits and at age 6 years were standardized for age and sex. Standardization was achieved by fitting a multiple regression model to the weights at each visit, with age and sex as independent variables, and utilizing the corresponding standardized residuals for calculating level and slope estimates. Slope of weight gain for the first three years was then calculated by fitting a simple linear regression to the well visit residuals within each subject. The slope of weight gain between 3 and 6 years was calculated by taking the difference in weight standardized residuals, between 6 and 3 years, divided by the change in time. The longitudinal FVC and FEV1 observations at ages 16 and 22 were fitted using a Linear Mixed Model (LMM) with subject, as a random effect to remove any serial correlation related to the repeated measures and sex, height, and age as covariates. LMM allows subjects to have missing observations that can be at unequal time intervals. The fixed portion of the LMM is interpreted the same as that from fitting linear regression, namely that coefficients for continuous predictor variables represent the amount of the output changes for a one unit change in the predictor variable. Likewise, the coefficients for categorical variables represent the amount of change in the output variable relative to the reference category. Approximately 30% of the subjects meeting the inclusion criteria were missing the information to calculate ponderal index. To prevent those subjects from being excluded in subsequent analyses, PI was categorized into tertiles and an additional category was included for those missing data. Demographic variables were compared between subjects included and not included in the analysis by unpaired "t" tests and Chi Square tests. Relations were sought, between the weight and growth variables, in the first 6 years of life and lung function at 16 and 22 using LMM, overall and stratified by wheezing phenotypes. In addition, all interaction terms between weight slope and wheezing phenotypes were also tested. All statistical comparisons were made at the $\alpha = 0.05$ significance level, assuming a two tailed comparison. All statistical analyses were done using STATA version 10.0.

Results

Of the subjects who had at least one pulmonary function test at age 16 or 22 years of age (N=583), 357 were non-Hispanic white. Of this group 127 also had at least 4 well visit weight measurements. Among the 127 subjects included, almost half had 7 or more well visits (44%, N=56). To assess the ability to generalize our results, comparisons were made between those included and not included in the primary analysis (among those who had at least one PFT at age 16 or 22 years of age). There were slightly more males (55.1%) than

females (44.9%) among those included (Table 1B). Subjects included in the analysis had higher rates of weight gain between 3 and 6 years of age, were heavier at birth and were taller at lung function testing than those not included but this is likely due in part to the higher proportion of males in the included group (Table 1A). There were no statistically significant differences between groups in the remaining variables. Of the subjects included in the analysis, 65% had FVC and FEV1 observations at both ages 16 and 22, while 22% had lung function data only at 16 and 13% only at 22. Demographics were also compared between early wheezing (early, late, and persistent combined) and non-wheezing subgroups and the only significant difference was in the percent predicted FVC, which was lower among the wheezing subjects (results not shown). In addition, there were no statistically significant differences between wheezing phenotypes in the mean rates of weight gain for either birth-3 years ($p = 0.127$) or between 3-6 years ($p = 0.249$). Comparisons of demographics and growth rates were also made between children with and without Ponderal Index (PI) information. The only variable found to differ significantly was the slope of weight gain 0 – 3 years, where those missing the PI had slower rates of growth.

To better understand the associations between potential predictor variables (birth weight, gestational age, slope of weight gain 0-3 years, and slope of weight gain 3-6 years) and to insure that there were no problems with collinearity, we estimated the correlation matrix between them. Two pairs had statistically significant correlations. As expected, birth weight was positively correlated with gestational age. Slope of weight gain 0-3 years had a significant inverse association with slope of weight gain at 3-6 years indicating that children who experienced more rapid rates of growth later in life (3-6 years) had slower rates of growth earlier in life. This suggests that these two variables should be treated independently in the modeling.

Table 2 shows the results of cross-sectional analysis testing for linear trends in mean percent predicted FVC and FEV1¹⁵, across tertiles of potential predictor variables, including birth weight, ponderal index, and slope of weight gains 0-3 years and 3-6 year, (stratified by age). Slope of weight gain between 3 and 6 years had a statistically significant linear trend across tertiles for both FVC and FEV1 at ages 16 and 22 years. This suggests that on average, children who gained weight more rapidly, between 3 and 6 years of age, achieved higher pulmonary function by adolescence, which persisted into early adult life. Ponderal index was also positively correlated with both pulmonary function measures at ages 16 and 22 years, but the associations with FVC and FEV1 only reached statistical significance at age 22. Neither birth weight nor slope of weight gain, between birth and 3 years, were significant predictors of FVC or FEV1.

The results of fitting linear mixed models to the data for FVC and FEV1, at ages 16 and 22 years, are shown in Tables 3 and 4. In the best fitting model, the ponderal index showed a linear relation with FVC, but the difference was only statistically significant for the highest tertile of ponderal index (Table 3). Children in the highest tertile of PI, at birth, had on average 240 mL greater FVC levels as adults, compared to those in lowest tertile.

As shown in Model 1, the slope of weight gain, (3-6 years), was a highly significant predictor of FVC ($p=0.0001$) among children who never wheezed, with a one unit increase in the slope associated with a corresponding increase of 664 mL in FVC levels.

Wheezing phenotypes (in early life) significantly modified this positive association between childhood growth rates and lung function outcomes, which was observed among non-wheezers. The interactions between wheezy phenotypes and slope of weight gain are very striking, as illustrated in Figure 1. The highly significant positive association observed between FVC (at age 16-22 years) and slope of weight gain, (between ages 3 and 6 years)

that was seen in non-wheezers, completely disappeared among those with wheeze in early life. The interaction with slope of weight gain on FVC, was statistically significant both for Early Transient and Persistent wheezers. This is suggesting that among those with physician-diagnosed wheezing and lower respiratory illnesses before age 3, the rate at which they grow between 3-6 years no longer has a positive association with levels of FVC achieved as an adult. Thus, in contrast to the FVC increase of 664 mL per unit, change of slope of weight gain, between 3-6 years, observed among non-wheezing subjects with transient early wheezing had essentially no change in FVC associated with slope of weight gain. These findings indicate that for early wheezers, weight gain between 3-6 years has no impact on FVC level achieved as adults. The findings for late wheezers are similar in magnitude but did not achieve statistical significance because of the small sample size (N=15).

The results for FEV1 are shown in Table 4. As was the case for FVC, the relations of slope of weight gain (between 3-6 years) and PI to FEV1 levels are statistically significant with magnitudes that are slightly less than those estimated for FVC. Similarly, the magnitude of these effects tended to be smaller among subjects with active wheezing phenotypes in early life although none of the interaction terms between the wheezing phenotypes and the slope of weight gains (between 3-6 years) was statistically significant. We also fit the LMM to the FEV1/FVC data and there were no statistically significant associations with birth or growth rate measures. Both gestational age and maternal smoking during pregnancy were included in the FEV1 and FVC models but neither reached statistical significance.

To test for sex differences we conducted analyses both stratified by sex and including sex by wheeze by slope interactions. The results for FVC and FEV1 were for the most part similar to those reported herein but were no longer statistically significant because of the reduced sample sizes. We are dealing with relatively small cell sizes in the wheezing phenotypes and stratifying them by sex reduces further the sample size and thus the statistical power.

Discussion

In this study, we found weight gain between age 3 and 6 years to be a strong and independent positive predictor of size-adjusted FVC and FEV1 values, at both ages 16 and 22 years. However, this association was present only among children who did not wheeze in the first three years of life, whereas among those who had physician-ascertained wheezing lower respiratory tract illnesses in early life, there was no association between preschool weight gain and lung function at ages 16 and 22 years.

Weight gain between ages 3 and 6 years is, at least partly, an indicator of the rate of bodily development in pre-school years, during which dramatic growth of lung and airway size also occurs. Therefore, the correlation between early weight gain and lung function in young adult life may indicate an allometric development of the lungs in the first years of life, which is directly related to the entire bodily growth and tracks over time into adult life. This scenario is consistent with previous observations from the 1966 Northern Finland Birth Cohort⁴, in which weight gain during the first year of life was found to be positively related to both FVC and FEV1 levels at age 31 years. After adjusting for covariates (including birth weight), each 1-kg increase in weight gain, during the first year of life, was associated with 30-ml and 51-ml increases of FVC in adult life, among females and males respectively. In a subsequent report from the Dunedin Multidisciplinary Health and Development Study¹, weight gain between birth and age 3 years was also associated with increased levels of FVC at 32 years of age, although this association was true only among males. It is unclear why weight gain between birth and age 3 years showed no significant association with

subsequent lung function in the current study, although statistical power to detect small effect sizes may have been insufficient in our study.

The most important finding of our study is that any correlation between early weight gain and lung function at ages 16 and 22 years was completely lost among children who had wheezing episodes in the first three years of life. This observation was valid for both FVC and FEV1, although the interaction term between weight gain and wheezing phenotypes was significant only for the former. One possible explanation for these findings is that the presence of wheezing early in life can somehow alter the mechanisms involved in the above mentioned allometric growth of the lungs. Whether this alteration is due to the effects of environmental and/or genetic factors (which could be responsible for predisposing to early wheezing), or rather is a consequence of the airway inflammation and possible lung remodeling that may accompany and follow episodes of early wheezing, remains unknown. Either way, these data indicate that wheezing in pre-school age children is associated with impaired lung development in relation to bodily growth, and in turn with achieving sub-maximal ventilatory capacity as an adult. These findings are consistent with previous observations by our group indicating that children with transient and persistent wheezing (i.e., children with wheezing in the first three years of life) have consistently reduced maximal expiratory flows as compared with their peers throughout 16 years of age¹¹. Another possible explanation for the observed difference could be that the results were driven by differences in the range of slope estimates in the wheezing phenotypes however tests for mean differences between wheezing phenotypes using ANOVA showed that there were no significant differences ($p=0.127$) suggesting this likely was not the case.

Most likely, the links between weight gain and lung function are strongly dependent on age and developmental stages. Several studies have found inverse, rather than direct, correlations between weight gain and lung function when both are assessed in infancy^{16,17}. In a cohort of 154 infants from Perth, Australia that was assessed at 1 and 12 months, weight gain was inversely correlated with change in maximal flow at functional residual capacity during the same period¹⁷. These negative effects on early lung function may be related to the inverse relation of early weight gain to birth weight or to the direct impact of elevated body mass index on lung function measurements in infancy. However, in the long-term, these effects appear to reverse as children age into the early school years. Consistent with this scenario, in the Perth study cited above, weight gain during the first 12 months of life tended to be positively associated with the mid expiratory flow that was measured in the same children at age 11 years¹⁷.

In our study, the association between early weight gain and subsequent lung function was independent of sex, height, and age as assessed at the time of lung function measurement and ponderal index. This observation is particularly important in light of the previously reported^{1,4,5,18-20}, although still debated²¹⁻²³, link between low birth weight and impaired lung function in adulthood. Although we did not find a significant correlation between birth weight and subsequent lung function, children in the highest tertile of ponderal index had FVC and FEV1 values at ages 16 and 22 years were on average over 200 ml higher than those of children in the lowest tertile of ponderal index ($p=0.04$). Thus, our data supports the importance of *in utero* growth to achieve maximal ventilatory capacity in adulthood and indicates that these pre-natal effects are supplementary to those of post-natal weight gain. As expected, unlike the effects of weight gain between ages 3 and 6 years, the effects of ponderal index on subsequent lung function were not modified by the presence of wheezing in early life.

Another possible explanation for the strong linear association found among non-wheezers between early weight gain and subsequent lung function (Figure 1), is that children in the

lower quartiles of weight gain had more non-wheezing illnesses, leading to less increase in weight and subsequent lung development. To test for this possibility we looked at the proportions of children with bronchiolitis, croup, pneumonia, or otitis media, across the tertiles of weight gain between 3 and 6 years. There were no significant differences, suggesting that unequal distributions of these illnesses are likely not the cause of the observed linear trend.

An important limitation of our study was that the sample size was relatively small and that only a fraction of all eligible subjects had sufficient data to allow inclusion. When compared with participants who were excluded from the analysis, study subjects were both taller at the time of pulmonary function testing and weighed more at birth. In addition, they had slightly slower increases in weight gain between 3 and 6 years. These differences may have impacted the ability to generalize our findings. However, because no differences were found in lung function between subjects included and excluded from the present study, it is very unlikely that the main findings of our study are simply due to selection bias. This study population offers an almost unique opportunity to evaluate prospectively the links between birth weight, weight gain in infancy, early wheezing phenotypes, and lung function in adult age. The longitudinal nature of these data is critical to minimize potential sources of methodological bias, including the recall bias that may impact differentially the report of early wheezing by young adults, with low as contrasted with normal lung function. In addition, estimates of weight slope between ages 3 and 6 years were based on multiple measurements. All subjects included in this study had at least four weight measurements and almost half of the population had more than seven. This is likely to have reduced measurement error, enhanced precision, and, in turn, increased the statistical power of the study.

In summary, this study demonstrates that both ponderal index and weight gain between ages 3 and 6 years are strong, independent, and positive predictors of lung function levels attained at ages 16 and 22 years. They also indicate that the links of post-natal weight gain to adult lung function are modified by early wheezing, because they are completely lost among children who wheezed in the first three years of life. These findings suggest that the previously reported long-term *sequelae* of early wheezing on subsequent lung function may be partially mediated by alterations in lung development and in its relation to bodily growth during the first years of life.

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Figure 1.

Figure 1 illustrates the predicted FVC values, resulting from fitting the LMM to the longitudinal FVC observations (Table 3), plotted versus rate of weight gain between 3-6 years of age. Subjects that never wheeze (Black line) have a strong positive linear relationship that was completely absent among subjects experiencing any childhood wheeze (Colored lines). There were no significant differences in the predicted FVC values between wheezing phenotypes (tested using linear contrast in the LMM).

Table 1A
Descriptive Statistics for Continuous Variables by Inclusion in Primary Analyses

Continuous Variables	Included (N=127)			Not Included (N=456)		
	N	Mean	SD	N	Mean	SD
Height (cm)[†]	114	172.7	8.42	395	169.8	9.41
Weight (kg)[†]	114	68.3	17.7	395	67.4	17.2
Age[†]	110	16.59	0.48	376	16.70	0.60
Ponderal Index	84	2.69	0.24	345	2.70	0.30
Birth Weight (kg)	127	3.57	0.45	456	3.46	0.47
Slope of Infant Weight Gain 0 – 3 yrs (Z scored)	125	0.183	0.721	115	0.238	0.767
Slope of Infant Weight Gain 3 -6 yrs (Z scored)	127	-0.081	0.34	108	-0.092	0.32
						0.001

[†] At time of pulmonary function testing

Table 1B
Descriptive Statistics for Categorical Variables by Inclusion in Primary Analyses

Categorical Variables	Included (N = 127)		Not Included (N = 456)		P value
	Frequency	Percentage	Frequency	Percentage	
Sex (Male)	70	55.1	217	47.5	0.13
Ethnicity					
Non-Hispanic White	127	100	230	50.4	NA
Other	0	0	226	49.6	
Wheeze [†]					
No	62	48.8	184	48.6	0.97
Early Transient	28	22.1	79	20.8	0.76
Late	15	11.8	68	17.9	0.11
Persistent	22	17.3	48	12.7	0.10

[†] N=379 for subjects not included that also had information to determine wheezing status.

Table 2

Cross-sectional analyses testing for linear trends in mean percent predicted FEV1 and FVC by predictor variables, stratified by age for all subjects N=127.

	Age 16 Years		Age 22 Years	
Predictor Variables	PPFVC (%) (Mean, SD)	PPFEV1 (%) (Mean, SD)	PPFVC (%) (Mean, SD)	PPFEV1 (%) (Mean, SD)
Birth Weight				
Lowest	101.7, 13.9	98.6, 13.4	103.2, 14.3	100.6, 13.9
Mid	103.1, 9.1	102.1, 9.1	103.5, 10.6	101.4, 10.5
Highest	104.5, 12.5	100.5, 11.6	106.5, 9.6	99.8, 9.9
Ponderal Index [‡]				
Lowest	101.5, 13.7	98.5, 13.3	100.0, 13.6 [†]	96.9, 11.1 [†]
Mid	103.6, 5.7	101.6, 8.3	105.3, 9.3	102.8, 11.3
Highest	105.4, 11.8	102.9, 11.6	107.9, 8.8	103.9, 9.8
Slope Weight Gain (0 - 3 years)				
Lowest	103.8, 12.3	100.8, 11.4	105.8, 10.6	102.6, 10.4
Mid	101.5, 10.5	101.2, 10.5	103.2, 12.2	100.1, 11.4
Highest	104.7, 12.1	100.0, 12.0	102.6, 13.4	99.3, 11.1
Slope Weight Gain (3 - 6 years)				
Lowest	101.5, 13.0 [†]	98.0, 11.8 [†]	102.6, 13.4 [†]	97.3, 11.2 [†]
Mid	102.5, 8.5	101.5, 9.2	103.8, 8.2	102.4, 10.6
Highest	103.3, 11.5	103.5, 12.0	107.6, 9.7	103.2, 10.4

All Predictor Variables categorized into tertiles (Lowest, Mid, and Highest) PP=Percent Predicted.

[†] P < 0.05 test for linear trend.

[‡] Missing Category not listed

Table 3Linear Mixed Model Results Predicting Forced Vital Capacity (FVC (mL))^{**}

Variable	Model 1 FVC *		
	Coefficient	Standard Error	P-Value
Slope of Weight Gain (3-6 years) z-scored Never-Wheezers	664	173.1	0.0001
Ponderal Index [†]			
Tertile 1	Reference		
Tertile 2	110.7	126.7	0.382
Tertile 3	239.3	116.8	0.041
Wheeze Phenotypes			
Never	Reference		
Early Transient	-81.9	114.6	0.475
Late	-12.4	139.9	0.930
Persistent	-81.5	115.4	0.480
Wheeze X Slope (3-6 years) Interaction			
Never	Reference		
Early Transient	-666.4	330.1	0.044
Late	-535.9	388.9	0.168
Persistent	-668.2	290.9	0.022

^{**} Coefficients indicate change in FVC in mL per one unit change in continuous variables (slope and slope X wheeze) and change in mean level in FVC mL for categorical variables (Wheeze Phenotypes and Ponderal index)

* Adjusted for sex, height, and age.

[†] Missing Category not listed

Table 4

Linear Mixed Model Results Predicting Forced Expiratory Volume in One Second (FEV1 (mL))**

Variable	Model 2 FEV1*		
	Coefficient	Standard Error	P-Value
Slope of Weight Gain (3-6 years) z-scored Never-Wheezers	505	157.3	0.001
Ponderal Index †			
Tertile 1	Reference		
Tertile 2	110.0	115.2	0.339
Tertile 3	217.0	106.1	0.041
Wheeze Phenotypes			
Never	Reference		
Early Transient	-153.4	104.2	0.141
Late	66.0	127.2	0.604
Persistent	-208.4	104.8	0.047
Wheeze X Slope (3-6 years) Interaction			
Never	Reference		
Early Transient	-369.7	299.9	0.218
Late	-261.8	353.5	0.459
Persistent	-229.4	264.4	0.386

** Coefficients indicate change in FEV1 in mL per one unit change in continuous variables (slope and slope X wheeze) and change in mean level in FEV1 mL for categorical variables (Wheeze Phenotypes and Ponderal index)

* Adjusted for sex, height, and age.

† Missing Category not listed