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Poor early childhood growth is associated with impaired lung function: Evidence from a Ghanaian pregnancy cohort

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Abstract

Objectives: Nearly 40% of African children under 5 are stunted. We leveraged the Ghana randomized air pollution and health study (GRAPHS) cohort to examine whether poorer growth was associated with worse childhood lung function.

Study Design: GRAPHS measured infant weight and length at birth and 3, 6, 9,12 months, and 4 years of age. At age 4 years, $n = 567$ children performed impulse oscillometry. We employed multivariable linear regression to estimate associations between birth and age 4 years anthropometry and lung function. Next, we employed latent class growth analysis (LCGA) to generate growth trajectories through age 4 years. We employed linear regression to examine associations between growth trajectory assignment and lung function.

Results: Birth weight and age 4 weight-for-age and height-for-age *z*-scores were inversely associated with airway resistance (e.g., R_5, or total airway resistance: birth weight $\beta = -0.90$ cmH2O/L/s, 95% confidence interval [CI]: −1.64, −0.16 per 1 kg increase; and R_{20}, or large airway resistance: age 4 height-for-age $\beta = -0.40$ cmH2O/L/s, 95% CI: −0.57, −0.22 per 1 unit *z*-score increase). Impaired growth trajectories identified through LCGA were associated with higher airway resistance, even after adjusting for age 4 body mass index. For example, children assigned to a persistently

Abbreviations: AX, area of reactance; BMI, body mass index; CO, carbon monoxide; Fres, resonant frequency; GA, Gestational Age; GRAPHS, Ghana randomized air pollution and health study; HAZ, height-for-age *z*-score; IOS, impulse oscillometry; LCGA, latent class growth analysis; LMICs, low- and middle-income countries; R_{20}, resistance at 20 Hz; R_5, resistance at 5 Hz; R_{5-20}, the difference in resistance between 5 and 20 Hz; WAZ, weight-for-age *z*-score; WHZ, weight-for-height *z*-score; X_5, reactance at 5 Hz.

stunted trajectory had higher R_5 (β = 2.71 cmH2O/L/s, 95% CI: 1.07, 4.34) and R_{20} (β = 1.43 cmH2O/L/s, 95% CI: 0.51, 2.36) as compared to normal.

Conclusion: Children with poorer anthropometrics through to age 4 years had higher airway resistance in early childhood. These findings have implications for lifelong lung health, including pneumonia risk in childhood and reduced maximally attainable lung function in adulthood.

KEYWORDS

growth, impulse oscillometry, low- and middle-income country, stunting

1 | INTRODUCTION

Lung function in early life is a critical determinant of lung health over the life course. Children with poorer lung function are at increased risk for pneumonia,[1,2] a leading cause of morbidity and mortality in children under 5,[3] and persistently low lung function over childhood.[1,4] Despite the importance of early life lung function, there is a paucity of data from low- and middle-income countries (LMICs) on lung function in early childhood and an incomplete understanding of modifiable risk factors that are associated with poorer lung health, which may differ from those in high-income countries.[5] A better understanding of conditions that increase risk of poorer lung health is critical to inform LMIC-specific public health interventions to mitigate risk.

Stunting and wasting, defined as a height-for-age *z*-score (HAZ) or weight-for-height *z*-score (WHZ), respectively, less than −2, and fetal growth restriction result in 2.2 million deaths and 21% of the total disability adjusted life years in children under 5.[6] Sub-Saharan African children are disproportionately affected—an estimated 40% (56.9 million) are stunted, 3.9% are severely wasted (5.6 million) and 21% are underweight (defined as weight-for-age *z*-score [WAZ] less than −2; 31 million).[6] Children with impaired growth who survive early childhood have far-reaching health consequences.[7] Emerging evidence suggests that childhood undernutrition may impair lung growth and increase risk for poorer lung health over the life course.[8–10]

Studies largely from high-income countries suggest that low birth weight and fetal growth restriction are associated with higher risk for poorer lung function suggestive of a restrictive impairment.[11] Supporting evidence from LMICs is sparse and with mixed results. Higher birth weight and larger infant size were associated with better lung function in South African infants aged 5–17 weeks.[12] Lower birth weight has been associated with lower lung function as measured by spirometry in Indian adults aged 38–59 years old. However, in Brazilian adult males aged 18 years, low birth weight and preterm birth were not associated with lung function.[13,14]

Postnatal lung growth may be further impaired by poor nutrition and inadequate somatic growth in childhood, although evidence is limited to cross-sectional, unadjusted analyses.[15] A cross-sectional study of Ethiopian children aged 6–9 years found that children who were underweight or stunted had lower forced expiratory volume in 1 s (FEV_1) than those who were not underweight or stunted.[16] A multicenter study from Angola, DR Congo, and Madagascar found that children with body mass index (BMI) *z*-score of less than −2 had symmetrically reduced FEV_1 and forced vital capacity, suggestive of a restrictive ventilatory defect.[17] Conversely, a study of lung function at age 9 in survivors of severe acute malnutrition events found no difference in lung function as compared to controls, although on average all groups had HAZ and WAZ less than −1.[18]

We hypothesized that poorer anthropometry and growth over early childhood is associated with worse lung function. We used a rural Ghanaian pregnancy cohort, followed prospectively with repeated anthropometric measures over childhood and lung function (impulse oscillometry [IOS]) at age 4 years. IOS is an effort-independent modality that requires minimal patient cooperation and therefore is suitable for lung function evaluation in young children. First, we analyzed associations between birth weight and length and being born small for gestational age (GA), considered separately, and age 4 lung function. Next, we analyzed cross-sectional associations between age 4 World Health Organization (WHO) WAZ, HAZ, and WHZ, again considered separately, and lung function at age 4. Finally, we employed latent class growth analyses (LCGA) to construct *z*-score growth trajectories over early childhood and assigned each child to a WAZ, HAZ, and WHZ trajectory. We then analyzed associations between *z*-score trajectory assignment and age 4 lung function.

2 | STUDY DESIGN AND METHODS

2.1 | Study participants

Participants were from the Ghana randomized air pollution and health study (GRAPHS).[19,20] As has been described in detail elsewhere,[9,20,21] between August 2013 and March 2016, GRAPHS recruited n = 1414 nonsmoking women pregnant with a singleton fetus at gestational age (GA) less than 24 weeks from Kintampo North Municipality and Kintampo South District of Ghana. GA at enrollment was established by ultrasound.[22] The primary objective of GRAPHS was to understand associations between cookstove

interventions to reduce household air pollution exposure and (1) birth weight; and (2) pneumonia risk over the first year of life. GRAPHS follow-up concluded after the age 1-year study visit. In July 2017, additional funding was obtained for lung function measurement in $n = 700$ children beginning at age 4 years. The analyses presented herein include those children who attended the age 4 visit. All pregnant women and, subsequently, mothers provided written informed consent. The study was approved by the regional ethics committees at each participating institution and regulatory authorities in Ghana. The funding agencies played no role in study design nor data analysis.

2.2 | Anthropometric measures

As previously described, trained fieldworkers measured infant anthropometrics including weight and length, once within 72 h of birth[23] and at ages 3, 6, 9, and 12 months of age.[9] Length was measured to the nearest 0.1 cm (Ayrton Infantometer Model M-200; Ayrton Corp.) and weight was measured to the nearest 0.1 kg (Tanita digital scale model BD-590; Tanita Corp.). We created Ghanaian-specific birth weight for gestational week curve following methodology described by the WHO.[23] We considered an infant small for GA if the infant was born alive with a birth weight less than the 10th percentile for that specific week gestation.

At the age 4 lung phenotyping visit, we performed duplicate measures of weight (Seca 803 Clara Digital Floor Scale) to the nearest 0.1 kg and height (Seca 213 Portable Stadiometer) to the nearest 0.1 cm. We calculated HAZ, WAZ, WHZ at 3, 6, 9, 12 months, and 4 years of age using the 2006 WHO child growth standard reference for age and sex.[23] Stunting, underweight or wasting was defined as an infant or child with an HAZ, WAZ, or WHZ, respectively, less than two standard deviations below the WHO child growth standard reference median for age and sex.

2.3 | Impulse oscillometry

IOS was performed at age 4 years by a trained study pediatrician in community clinics using the MasterScreen IOS with Jaeger pneumotach (Vyaire Medical) following American Thoracic Society/European Respiratory Society guidelines.[24] The IOS device was calibrated daily with a standard 3-L syringe. Lung function parameters included resistance at 5 Hz, R_5, a measure of total airway resistance, and 20 Hz, R_{20}, a measure of large airway resistance; the difference in resistance between 5 and 20 Hz, R_{5-20}, a measure of small airway resistance; reactance at 5 Hz (X_5), a measure of small airway elastance; resonant frequency (Fres) or the frequency at which the total reactance is null, and area of reactance (AX) or total reactance at all frequencies between 5 Hz and Fres. Children were tested while standing, with a nose clip in place and cheeks firmly supported following standardized operating procedures. Three acceptable tests free from artifact and reproducible with within session coefficient of variability of Rrs of ≤15% were performed and IOS variables were averaged across these three tests.[25] All studies were overread by the study pulmonologist.

2.4 | Covariates

Maternal ethnicity (categorized into four groups: 1, 2, 3, 4) was determined by questionnaire at GRAPHS enrollment. The main ethnic groups in the study area were Mo, Akan, Konkonba, and other Northern ethnic tribes. Secondhand tobacco smoke exposure at the household level (categorical, yes or no) was determined by any report of secondhand tobacco smoke exposure via questionnaires at GRAPHS enrollment and again at the age 4 lung function visit. Questionnaires administered at GRAPHS enrollment identified household assets (e.g., number of livestock) which were employed to create an asset index, an index of relative socioeconomic status (continuous variable).[26] Fieldworkers visited pregnant women weekly over pregnancy and queried the number of antenatal visits attended (dichotomous variable, categorized as ≥4 visits vs. fewer). During pregnancy, four 72-h personal carbon monoxide (CO) exposure assessments occurred to characterize integrated air pollution exposures.[21] As previously reported, linear interpolation was used to estimate an average prenatal CO exposure (continuous, in parts per million).[10] Child sex was recorded at delivery (categorical, male vs. female) and child age (continuous, in years) at the IOS session. Breastfeeding duration was determined by questionnaires administered every 3 months over the first year of life. Specifically, mothers were asked, "Are you still breastfeeding your baby?" We categorized breastfeeding duration (3, 6, 9, or 12 months) based on when the mother last reported breastfeeding her child. BMI, a measure of size and somatic height at the time of lung function, was calculated from height and weight measured at the IOS session. No imputation for missing data was performed.

2.5 | Statistical analyses

First, we examined associations between birth weight and length and small for GA (yes/no), considered separately, and age 4 lung function. We then examined the cross-sectional associations between age 4 WAZ, HAZ, WHZ, considered separately, and age 4 lung function. We used bivariate and multivariable generalized linear regression models for these analyses, adjusting for child sex, ethnicity, BMI and age at IOS, asset index, maternal age, number of antenatal visits and GA at delivery (Model 1). We then additionally adjusted for environmental exposures including secondhand smoke exposure and average prenatal CO exposure (Model 2).

Next, we constructed WAZ, HAZ, and WHZ trajectories using LCGA, without consideration of lung function.[28–30] This data-driven approach allows us to identify characteristics of growth over 4 years of life and group study participants not by predefined groups but rather on data-defined classes (trajectories).[31] Specifically, we used

WAZ, HAZ, WHZ measured at ages 3, 6, 9, 12 months, and 4 years to create *z*-score-specific trajectories. Children with data at ≥1 time-point and who were 48 ± 6 months ($n = 609$) at the age 4 assessment were included. For each *z*-score, we constructed models with two to six trajectories where different models are defined by the number of trajectories. For each *z*-score, the best model (e.g., number of trajectories) was determined by: (1) Akaike information criteria and Bayesian information criterion where smaller numbers indicate better fit; (2) entropy where larger numbers (range 0–1) suggest better class separation; and (3) the number of children in each trajectory.

Following model selection and for each *z*-score trajectory, children were then assigned to the class for which they had the highest probability of correct assignment. Growth trajectory assignments were given a continuous, ordinal number zero to three, where zero was assigned the largest/highest trajectory and three the smallest/lowest trajectory. We then fit bivariate and multivariable generalized linear regression models (Models 1 and 2) to assess associations between WAZ, HAZ, WHZ trajectory assignments and age 4 lung function. Sensitivity models additionally adjusted for breastfeeding duration.

We used Stata version 14, *zscore06* module to calculate *z*-scores. We constructed latent class growth trajectories using Mplus version 7.4. Regression analyses were performed in R software version 3.6.0. Collinearity was assessed in all regression models using the *mctest* package.

3 | RESULTS

GRAPHS enrolled $n = 1414$ pregnant women, resulting in $n = 1306$ (92%) live births. $N = 683$ GRAPHS children attended the lung phenotyping visit. Of these, 567 (83%) performed acceptable and reproducible IOS. Mother–child dyads from a range of ethnic groups, including Akan, Gonja, Dagarti, Mo, Konkomba, and others were enrolled. Approximately half of the children were female ($n = 289$, 51%) and aged a median of 4 years (interquartile range [IQR]: 3.9, 4.2) at the time of IOS (Table 1). Baseline characteristics amongst children who attended the lung phenotyping visit and performed acceptable and reproducible IOS versus the rest of the GRAPHS cohort are shown Table S1. On average, mothers of children included in these analyses were slightly older, attended more antenatal visits, and had lower average prenatal CO exposures.

3.1 | Associations between birth weight and length and small for GA and age 4 lung function

Of the children who performed acceptable and reproducible IOS, $n = 553$ (99%) had valid birth weight and length measurements within 24 h of birth. The Pearson's correlation between birth weight and length was $r = 0.34$, $p < 0.01$. Multivariable models (Model 2, Table 2) found that birth weight was inversely associated with R_5 ($\beta = -0.90$ cmH2O/L/s, 95% confidence interval [CI]: −1.64, −0.16 per 1 kg increase in birth weight), R_{20} ($\beta = -0.50$ cmH2O/L/s, 95% CI: −0.92, −0.08 per 1 kg increase in birth weight), Fres ($\beta = -2.14$ Hz, 95% CI: −3.69, −0.60) and AX ($\beta = -6.93$ cmH2O, 95% CI: −11.84, −2.03). Regression analyses did not identify an association between birth length or small for GA and lung function.

TABLE 1 GRAPHS cohort characteristics ($N = 567$)

Maternal age, median (IQR) (years)	27.6	(23.3, 33.8)
Asset index, median (IQR)	−0.43	(−1.3, 0.7)
Ethnicity, *n* (%)		
1	84	14.8%
2	85	15%
3	371	65.3%
4	27	5%
Number of antenatal visits, *n* (%)		
Missing	3	
Four or more	412	72.8%
Prenatal CO, median (IQR) (ppm)	0.95	0.58, 1.57
Secondhand smoke exposure, *n* (%)[a]	111	19.6%
Preterm birth (GA < 37 weeks), *n* (%)	20	3.5%
Child sex, female, *n* (%)	289	50.9%
Birth weight, median (IQR) (kg)	2.95	2.64, 3.20
Missing, *n* (%)	14	2.4%
Birth length, median (IQR) (cm)	46.8	44.3, 49.0
Missing, *n* (%)	14	2.4%
Small-for-gestational age, *n* (%)	122	22%
Missing, *n* (%)	15	2.6%
Impulse oscillometry (IOS)		
Age at IOS, median (IQR) (years)	4.05	3.87, 4.23
Height at IOS, median (IQR) (cm)	98	95.4, 101.2
Weight at IOS, median (IQR) (kg)	14.6	13.6, 16
Height-for-age *z*-score, median (IQR)	−1.11	−1.71, −0.41
Weight-for-age *z*-score, median (IQR)	−0.75	−1.33, −0.16
Weight-for-height *z*-score, median (IQR)	−0.23	−0.78, 0.43
Body mass index, median (IQR) (kg/m^2)	15.08	14.4, 16
R_5, median (IQR) (cmH2O/L/s)	14.3	12.3, 16.4
X5, median (IQR) (cmH2O/L/s)	−3.4	−4.5, −1.9
R_{20}, median (IQR) (cmH2O/L/s)	8.4	6.9, 9.6
R_{5-20}, median (IQR) %	71.7	50.4, 100.3
Fres, median (IQR) (Hz)	28.2	24.3, 32.9
AX, median (IQR) (cmH2O/L)	5.7	4.5, 7.2

Abbreviations: AX, area of reactance; CO, carbon monoxide; Fres, resonant frequency; GA, gestational age; IQR, interquartile range; ppm, parts per million.

[a]Secondhand smoke exposure determined by questionnaire.

TABLE 2 Association between birth outcomes and age 4 impulse oscillometry (IOS), linear regression ($n = 553$)

	Bivariate analyses ($n = 553$)			Model 1 ($n = 552$)			Model 2 (Nn = 542)		
IOS variable	PE	95% CI	*p* value	PE	95% CI	*p* value	PE	95% CI	*p* value
Birth weight									
R_5, cmH2O/L/s	−0.92	−1.61, −0.23	<0.01	−1.03	−1.78, −0.29	<0.01	−0.90	−1.64, −0.16	0.02
X_5, cmH2O/L/s	0.20	−0.25, 0.65	0.39	0.03	−0.46, 0.53	0.89	0.04	−0.46, 0.54	0.88
R_{20}, cmH2O/L/s	−0.48	−0.87, −0.09	0.02	−0.53	−0.95, −0.10	0.02	−0.50	−0.92, −0.08	0.02
R_{5-20}, %	−3.04	−10.71, 4.62	0.44	−3.00	−11.44, 5.44	0.49	−2.11	−10.61, 6.38	0.63
Fres, Hz	−2.22	−3.65, −0.79	<0.01	−1.96	−3.53, −0.39	0.01	−2.14	−3.69, −0.60	<0.01
AX, cmH2O/L	−7.33	−11.81, −2.85	<0.01	−6.99	−11.90, −2.09	<0.01	−6.93	−11.84, −2.03	<0.01
Birth length									
R_5, cmH2O/L/s	−0.03	−0.12, 0.06	0.49	−0.02	−0.11, 0.06	0.59	−0.03	−0.11, 0.06	0.57
X5, cmH2O/L/s	−0.01	−0.07, 0.05	0.79	−0.02	−0.08, 0.04	0.51	−0.01	−0.07, 0.05	0.74
R_{20}, cmH2O/L/s	−0.02	−0.07, 0.03	0.51	−0.01	−0.06, 0.04	0.58	−0.02	−0.08, 0.03	0.33
R_{5-20}, %	−0.18	−1.16, 0.79	0.71	−0.13	−1.13, 0.88	0.81	0.11	−0.91, 1.12	0.84
Fres, Hz	0.05	−0.13, 0.24	0.56	0.10	−0.09, 0.29	0.30	0.08	−0.11, 0.26	0.42
AX, cmH2O/L	−0.09	−0.66, 0.48	0.75	0.07	−0.52, 0.65	0.83	0.03	−0.55, 0.61	0.92
Small for gestational age									
R_5, cmH2O/L/s	0.13	−0.62, 0.88	0.73	0.19	−0.57, 0.95	0.63	0.06	−0.69, 0.81	0.87
X5, cmH2O/L/s	−0.18	−0.66, 0.31	0.47	−0.09	−0.58, 0.41	0.73	−0.10	−0.60, 0.41	0.71
R_{20}, cmH2O/L/s	0.12	−0.30, 0.54	0.57	0.14	−0.29, 0.56	0.52	0.12	−0.30, 0.55	0.58
R_{5-20}, %	0.00	−0.08, 0.09	0.91	0.00	−0.08, 0.09	0.95	−0.01	−0.09, 0.08	0.91
Fres, Hz	0.70	−0.86, 2.25	0.38	0.65	−0.93, 2.23	0.42	0.91	−0.66, 2.48	0.26
AX, cmH2O/L	0.14	−0.34, 0.62	0.57	0.16	−0.32, 0.65	0.51	0.18	−0.31, 0.67	0.47

Note: Weight is per 1 kg increase in birth weight. Length is per 1 cm increase in birth length. Small for gestational age (yes vs. no) defined as a child born alive with a birth weight less than the 10th percentile for the specific gestational week at delivery after creating a Ghanaian specific curve using methodology described by the World Health Organization. Model 1 adjusts for child sex, ethnicity, body mass index and age at time of IOS, asset index, maternal age, number of antenatal visits, and preterm delivery. Model 2 additionally adjusts for prenatal secondhand tobacco smoke exposure and prenatal household air pollution exposure as indexed by personal carbon monoxide exposure monitoring.

Abbreviations: AX, area of reactance; CI, confidence interval; Fres, resonant frequency; IOS, impulse oscillometry.

3.2 | Associations between age 4 anthropometrics and lung function

All children who performed acceptable and reproducible IOS had valid cross-sectional height and weight measures. Median age 4 WAZ, HAZ, and WHZ were −0.75 (IQR: −1.33, −0.16), −1.11 (IQR: −1.71, −0.41), and −0.23 (IQR: −0.78, 0.43), respectively. In multivariable models, on average WAZ and HAZ were inversely associated with measures of airway resistance (Table 3). Specifically, in Model 2, children with higher WAZ and HAZ had lower R_5 (WAZ $\beta = -0.97$ cmH2O/L/s, 95% CI: −1.41, −0.53; HAZ $\beta = -0.84$ cmH2O/L/s, 95% CI: −1.15, −0.53 per 1 unit *z*-score increase), R_{20} (WAZ $\beta = -0.50$ cmH2O/L/s, 95% CI: −0.75, −0.25, HAZ $\beta = -0.40$ cmH2O/L/s, 95% CI: −0.57, −0.22 per 1 unit *z*-score increase) and AX (WAZ $\beta = -5.64$ cmH2O/L/s, 95% CI: −8.57, −2.71; HAZ $\beta = -4.70$ cmH2O/L/s, 95% CI: −6.77, −2.63 per 1 unit *z*-score increase). No associations were seen with WHZ and IOS parameters.

3.3 | Latent class trajectory modeling: Identification of the number of trajectories

Distribution of HAZ, WAZ and WHZ across all ages for the $n = 609$ children aged 48 ± 6 months at the age four visit are shown in Figure S1. Data completion was high, with $n = 535$ (88%), $n = 526$ (86%), and $n = 525$ (86%) of children having at least four out of five WAZ, HAZ, and WHZ measurements, respectively. Using LCGA fit data, we determined that four classes was the optimal fit for HAZ, WAZ, and WHZ trajectories (Table S2). Posterior probabilities for LCGA class assignment were overall high (Table S3). Five hundred eight children included in the growth trajectory construction had acceptable and reproducible lung function tests. Data completion amongst this subset was also high. Three hundred sixty-three (71.5%), 353 (69.5%), and 349 (68.7%) children had five; 123 (24.2%), 128 (25.2%), and 133 (26.1%) children had four; 21 (4.1%), 26 (5.1%), and 23 (4.5%) had three; and 1 (0.2%), 1(0.2%), and 3

TABLE 3 Cross-sectional associations between age 4 *z*-scores and impulse oscillometry (IOS), linear regression

	Bivariate analyses (*n* = 567)			Model 1 (Nn= 565)			Model 2 (Nn= 555)		
IOS variable	PE	95% CI	*p* value	PE	95% CI	*p* value	PE	95% CI	*p* value
Weight-for-age *z*-score									
R_5, cmH2O/L/s	−0.58	-0.93, −0.23	<0.01	−1.03	−1.48, −0.59	<0.01	−0.97	−1.41, −0.53	<0.01
X5, cmH2O/L/s	0.26	0.03, 0.49	0.03	0.28	−0.02, 0.58	0.07	0.22	−0.09, 0.52	0.16
R_{20}, cmH2O/L/s	−0.28	−0.47, −0.08	<0.01	−0.48	−0.73, −0.23	0.08	−0.50	−0.75, −0.25	<0.01
R_{5-20}, %	−1.62	−5.57, 2.32	0.42	−2.86	−7.93, 2.20	0.27	−1.80	−6.94, 3.33	0.49
Fres, Hz	−0.57	−1.31, 0.16	0.13	−0.68	−1.62, 0.27	0.16	−0.69	−1.64, 0.25	0.15
AX, cmH2O/L	−0.37	−0.60, −0.14	<0.01	−6.32	−9.23, −3.42	<0.01	−5.64	−8.57, −2.71	<0.01
Height-for-age *z*-score									
R_5, cmH2O/L/s	−0.91	−1.22, −0.61	<0.01	−0.84	−1.17, −0.51	<0.01	−0.84	−1.15, −0.53	<0.01
X5, cmH2O/L/s	0.16	−0.05, 0.37	0.13	0.20	−0.02, 0.42	0.07	0.16	−0.05, 0.38	0.14
R_{20}, cmH2O/L/s	−0.41	−0.59, −0.24	<0.01	−0.34	−0.53, −0.16	<0.01	−0.40	−0.57, −0.22	<0.01
R_{5-20}, %	−2.58	−6.13, 0.97	0.15	−2.96	−6.71, 0.80	0.12	−2.08	−5.73, 1.57	0.26
Fres, Hz	−0.69	−1.36, −0.03	0.04	−0.43	−1.12, 0.27	0.23	−0.62	−1.29, 0.05	0.07
AX, cmH2O/L	−0.53	−0.73, −0.33	<0.01	−4.89	−7.03, −2.74	<0.01	−4.70	−6.77, −2.63	<0.01
Weight-for-height *z*-score									
R_5, cmH2O/L/s	0.11	−0.20, 0.43	0.47	0.08	−0.76, 0.93	0.84	0.13	−0.70, 0.96	0.76
X5, cmH2O/L/s	0.17	−0.03, 0.38	0.09	0.19	−0.37, 0.75	0.50	0.12	−0.45, 0.68	0.69
R_{20}, cmH2O/L/s	0.03	−0.14, 0.21	0.72	−0.13	−0.60, 0.35	0.60	−0.13	−0.60, 0.34	0.60
R_{5-20}, %	0.33	−3.14, 3.81	0.85	2.66	−6.76, 12.08	0.58	3.21	−6.27, 12.68	0.51
Fres, Hz	−0.08	−0.73, 0.58	0.82	0.27	−1.51, 2.04	0.77	0.29	−1.46, 2.05	0.74
AX, cmH2O/L	0.38	−1.68, 2.43	0.72	−0.68	−6.21, 4.84	0.81	−0.06	−5.57, 5.45	0.98

Note: Change in IOS variable per 1-unit *z*-score increase. Model 1 adjusts for child sex, body mass index, ethnicity, asset index, ethnicity, maternal age, number of antenatal visits, and gestational age at delivery. Model 2 additionally adjusts for prenatal secondhand tobacco smoke exposure, and prenatal household air pollution exposure as indexed by carbon monoxide.

Abbreviations: AX, area of reactance; CI, confidence interval; Fres, resonant frequency; IOS, impulse oscillometry.

(0.6%) children had two WAZ, HAZ, and WHZ measurements, respectively. Examination of growth trajectories suggested that the trajectories remain distinct from birth without crossing of lines, although changes in slope are noted (Figure 1). The mean *z*-scores for children assigned to the lowest and second lowest WAZ and HAZ were at or near −2 or −1, respectively, at each timepoint consistent with the definition of underweight and stunted or at-risk for being underweight or stunted. Assignment to these trajectories was common with 48% (*n* = 243) of children in the two lowest WAZ trajectories and 54% (*n* = 275) of children in the two lowest HAZ trajectories.

3.4 | Associations between growth trajectories and age 4 lung function

In multivariable models, on average, children in poorer WAZ trajectories had higher R_5, R_{20}, and AX, as compared to the normal trajectory (Figure 2A and Table S4). Specifically, in Model 2, children in the WAZ "underweight" had R_5 values that were 2.10 cmH2O/L/s (95% CI: 0.75, 3.45) higher, respectively, than children in the "normal" trajectory ($p_{trend} < 0.01$). Children in the WAZ trajectories "at risk" and "underweight" had R_{20} values that were 0.74 cmH2O/L/s (95% CI: 0.11, 1.37) and 1.57 cmH2O/L/s (95% CI: 0.80, 2.34) higher, respectively, than children in the "normal" trajectory ($p_{trend} < 0.01$). Finally, children in the WAZ "underweight" had higher AX ($\beta = 13.09$ cmH2O/L, 95% CI: 3.99, 22.19) than children in the "normal trajectory ($p_{trend} < 0.01$).

Similarly, on average children in poorer HAZ trajectories had higher R_5, R_{20}, and AX (Figure 2B and Table S5). Specifically, in Model 2, children in the HAZ "stunted" had R_5, R_{20}, and AX values that were 2.71 cmH2O/L/s (95% CI: 1.07, 4.34), 1.43 cmH2O/L/s (95% CI: 0.51, 2.36), and 13.77 cmH2O/L (95% CI: 2.80, 24.74) higher, respectively, than children in the "normal" trajectory (R_5 and R_{20} $p_{trend} < 0.01$, AX $p_{trend} = 0.02$).

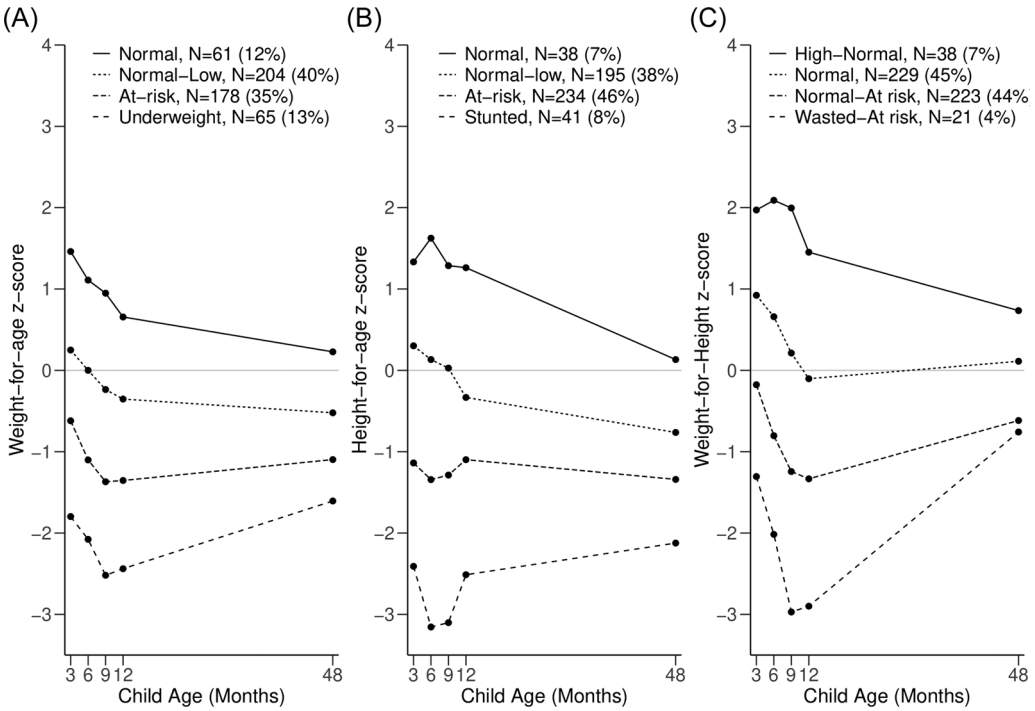

FIGURE 1 Latent class growth trajectories for (A) weight-for-age, (B) height-for-age, and (C) weight-for-height *z*-score trajectories over the first 4 years of life in children with acceptable and reproducible lung function. Height and weight were measured at 3, 6, 9, 12, and 48 months and WHO *z*-scores calculated using the 2006 WHO child growth standards. Latent class growth analyses were employed to construct trajectories for each *z*-score over the first 4 years of life.

No associations were seen between WHZ trajectories and IOS parameters (Figure 2C and Table S6). Sensitivity models additionally adjusting for breastfeeding duration did not substantively change results (data not shown).

4 | DISCUSSION

Despite the fact that approximately 39% of the 141 million African children under the age of 5 are stunted and 21% (31 million) are underweight, the effects of impaired early childhood growth on lung health in this population is poorly defined.[6] In this prospective pregnancy cohort study from rural Ghana, we investigated associations between anthropometry at birth and age 4 years and growth trajectories from birth through age 4 years and early childhood lung function. Overall, we found a consistent association between poorer anthropometry and higher airway resistance independent of current body size as indexed by age 4 BMI, suggesting smaller airway caliber per lung parenchyma, or dysanapsis.[32] Specifically, children with lower weight at birth, lower WAZ and HAZ at 4 years, and lower WAZ and HAZ trajectories over the first 4 years of life had higher R_5, or total airway resistance, and R_{20}, or large airway resistance. Given the importance of early life lung health on respiratory morbidity over the life course, these data add to the urgency of understanding etiologies of poor growth, particularly in sub-Saharan Africa.

Impaired growth prenatally and in early childhood is pervasive in LMICs and inextricably linked to poverty. Between 2000 and 2018, Africa, including West Africa, saw an increase in the number of stunted children under age 5, whereas Asia and Latin America saw a decrease.[33] Indeed, our study WHO *z*-scores suggest an overall frail cohort with study mean below zero (see Figure S1). Our data from Ghana suggest that poorer anthropometry beginning at birth and through age 4 years are independently associated with impaired respiratory mechanics in early childhood. The observed difference in R_5 and AX in children assigned to trajectories consistent with stunting or being underweight as compared to normal is similar to or greater than previously reported for children with uncontrolled asthma and bronchopulmonary dysplasia, as compared to normal children and similar in magnitude to baseline differences predictive of future asthma exacerbations.[34–36] Given the high prevalence of stunting and being underweight in the region, the population at-risk for poorer lung function is significant. Establishing good early life lung function is critical for lung health in childhood and attaining maximal lung health over the life course.[37] These data point to poor early childhood growth as an important and potentially modifiable driver of poor lung health in LMICs.

We found that infants with lower birth weight have increased R_5, or total airway resistance, and R_{20}, or large airway resistance, at age 4 years, independent of size at the time of lung function testing. Lung development occurs rapidly in utero, beginning at approximately 4 weeks and extending over gestation.[38] Low birth weight reflects

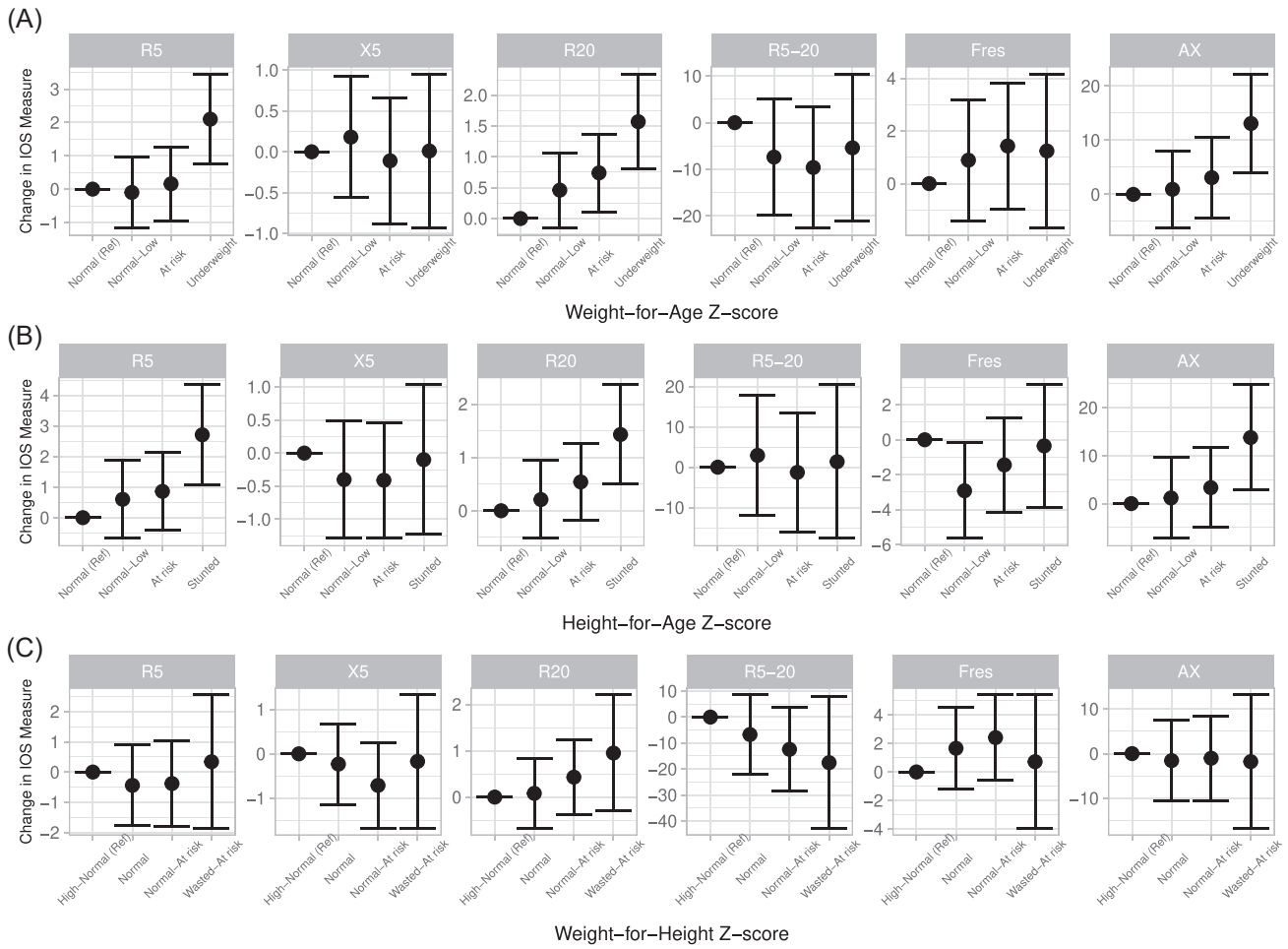

FIGURE 2 Associations between (A) weight-for-age, (B) height-for-age, and (C) weight-for-height *z*-score trajectories through age 4 years and impulse oscillometry. Height and weight were measured at 3, 6, 9, 12, and 48 months and WHO *z*-scores calculated using the 2006 WHO child growth standards. Latent class growth analyses were employed to construct trajectories for each *z*-score over the first 4 years of life. Linear regression models adjust for child sex, ethnicity, body mass index and age at the time of IOS, wealth index, maternal age, number of antenatal visits, preterm delivery, secondhand tobacco smoke exposure and prenatal household air pollution exposure as indexed by carbon monoxide. Abbreviations: R_5, resistance at 5 Hz in cmH2O/L/s; X_5, reactance at 5 Hz in cmH2O/L/s; R_{20}, resistance at 20 Hz in cmH2O/L/s; R_{5-20}, difference between R_5 and R_{20} in %; Fres, resonant frequency in Hz; AX, reactance area in cmH2O/L

impaired global fetal development and these findings suggest altered organ structure and tissue remodeling with wide ranging effects. Infants born with fetal growth restriction and bronchopulmonary dysplasia have altered alveolar and pulmonary vascular development resulting in an increased airway resistance phenotype.[34] Supporting evidence from animal studies suggest that fetal growth restriction results in airway remodeling, thickened airspace walls including increased smooth muscle mass and altered extracellular matrix composition and smaller cross-sectional size of conductive airways.[39–42]

Lung development continues postnatally through adolescence with rapid alveolar expansion and enlargement of airways. These data suggest that children with impaired growth through and at age 4 had altered lung mechanics. Indeed, nutrition and growth play a key role in lung development, directly through lung growth and indirectly through, for example, epigenetic changes that program future lung growth.[43,44] Underlying mechanisms of postnatal growth on lung function impairments are not known, however it has been postulated that growth restricted children may have reductions in airway caliber, a major component of airway resistance, which may result in airway obstruction and predispose to obstructive airways disease.[45]

We observed that lower birth weight, WAZ, and HAZ at age 4 years and being underweight and stunted were associated with increased AX, suggesting increased small airways resistance. All analyses identify consistent associations with R_5; changes in resistance at low frequencies such as R_5 may also be indicative of small airways disease.[46] Spirometry is considered the gold standard for lung function evaluation, however, the forced maneuver may be difficult for young children to perform and does not sensitively evaluate the small airways. Furthermore, signals of small airways impairment may precede spirometry airflow limitation.[47] For

example, Cosio et al. suggest that ~75% of the small airways must be obstructed before changes in forced expiratory volumes are seen.[48]

We also found a lack of association between WHZ at age 4 and age 4 IOS parameters as well as WHZ trajectory and age 4 IOS parameters. Low WHZ is an indicator of acute malnutrition, and this lack of association suggests that lung function is preserved in the acute phase of malnutrition during which tissue remodeling and physiological adaptations may not yet have resulted in dysanapsis. Supporting these findings, a study from Malawi of children surviving acute malnutrition episodes found no association with lung function.[18]

Poorer lung function in early childhood may increase risk for respiratory infection and wheezing,[49] further impairing lung function growth.[50] Diminished lung function may result in reduced maximally attainable lung function[51] with greater predisposition to respiratory disease later in life.[4] The associations observed between weight at birth, WAZ and HAZ at age 4 and WAZ and HAZ trajectories over early childhood and higher airway resistance suggest that smaller children have reduced airway caliber independent of somatic growth and thus conceptually low lung volume, consistent with the definition of dysanapsis,[32,52] a likely critical component of the low early-life lung function phenotype.[53] If replicated, our findings would support impaired early childhood growth as a risk factor for dysanapsis, with implications for lung health over the life course and highlight the need to understand the wide-ranging etiologies[6,9] of poor growth.

We note several study strengths. We leverage GRAPHS, a well-characterized prospective pregnancy cohort with anthropometrics measured every 3 months over the first year of life and again at age 4 years. We employed a validated measure of lung function to allow rigorous examination of associations between anthropometry in early life and lung function. Strengths of IOS include its effort-independent nature making the test ideal for use in small children, ability to characterize small airways, and greater precision in detecting lung mechanics, as compared to spirometry.[54,55] Questionnaires captured a number of important covariates and ultrasound in early pregnancy provided accurate gestational dating. We also note limitations. Anthropometrics in the first year of life were measured only once at each age; repeated measurements may reduce measurement error. Given the young age of study children, we did not perform post-bronchodilator IOS nor spirometry, considered the gold standard of lung function assessment, nor multiple breath washout testing, however these assessments will be important for future evaluations. Comparing lung function in our cohort with a healthy standard would be an important future analysis; to our knowledge no IOS reference lung function equations are available for children from sub-Saharan Africa. These analyses within a rural Ghanaian cohort may not be generalizable to other populations.

4.1 | Implications

In summary, these data suggest that poor anthropometry and growth in early childhood are associated with impaired lung function, with implications for lung health in both childhood and adulthood.

AUTHOR CONTRIBUTIONS

Seyram Kaali: Conceptualization (equal); formal analysis (equal); investigation (equal); writing – original draft (equal); writing – review and editing (equal). **Darby Jack**: Conceptualization (supporting); funding acquisition (equal); investigation (equal); methodology (equal); supervision (equal); writing – review and editing (equal). **Rebecca Prah**: Investigation (supporting); project administration (supporting); writing – review and editing (equal). **Steven N. Chillrud**: Conceptualization (supporting); funding acquisition (supporting); investigation (supporting); methodology (supporting); supervision (supporting); writing – review and editing (equal). **Mohammed Mujtaba**: Investigation (equal); project administration (equal); supervision (equal); writing – review and editing (equal). **Patrick Kinney**: Conceptualization (equal); funding acquisition (equal); investigation (equal); methodology (equal); supervision (equal); writing – review and editing (equal). **Theresa Tawiah**: Investigation (equal); project administration (equal); supervision (equal); writing – review and editing (equal). **Qiang Yang**: Data curation (equal); methodology (equal); supervision (equal); writing – review and editing (equal). **Felix Oppong**: Data curation (equal); formal analysis; writing – original draft (supporting); writing – review and editing (equal). **Carlos Gould**: Formal analysis (supporting); investigation (supporting); writing – review and editing (equal). **Musah Osei**: Investigation (supporting); project administration (supporting); writing – review and editing (equal). **Blair Wylie**: Investigation (equal); project administration (equal); supervision (supporting); writing – review and editing (equal). **Oscar Agyei**: Data curation (equal); investigation (equal); project administration (equal); writing – review and editing (equal). **Matthew Perzanowski**: Conceptualization (equal); funding acquisition (equal); writing – review and editing (equal). **Kwaku Poku Asante**: Conceptualization (equal); data curation (equal); funding acquisition (equal); investigation (equal); project administration (equal); supervision (equal); writing – review and editing (equal). **Alison Lee**: Conceptualization (equal); formal analysis (equal); funding acquisition (equal); methodology (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Anonymized data that underlie the results reported herein are available upon request. Proposals should be directed to kwakupoku.asante@kintampo-hrc.org and to Alison.Lee@mssm.edu; to gain access, data requestors will need to sign a data access agreement.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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