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Fetal Thoracic Circumference and Lung Volume and Their Relation to Fetal Size and Pulmonary Artery Blood Flow

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Abbreviations

AC, abdominal circumference; AT, acceleration time; CI, confidence interval; ET, ejection time; FL, femur length; GA, gestational age; GW, gestational weeks; HC, head circumference; ICC, intraclass correlation coefficient; LPA, left pulmonary artery; LV, lung volume; PA, pulmonary artery; pp BMI, prepregnancy body mass index; PreventADALL, Preventing Atopic Dermatitis and ALLergies in Children; PI, pulsatility index; RPA, right pulmonary artery; SD, standard deviation; TAMX, time-averaged maximum velocity; TC, thoracic circumference

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Objective—Research on early origins of lung disease suggests the need for studying the relationships of thoracic and lung size with fetal size and pulmonary circulation. The primary aim of this study is therefore to explore the associations between fetal thoracic circumference, lung volume, and fetal size. We also aim to assess if lung volume and thoracic circumference are associated with fetal pulmonary artery blood flow velocity measures.

Methods—Cross-sectional assessment of singleton pregnancies from the general population ($n = 447$) at 30 gestational weeks (GW) was performed using ultrasound measurement of fetal thoracic circumference, lung volume, head and abdominal circumference, and femur length. We obtained Doppler blood flow velocity measures from the proximal branches of the fetal pulmonary artery. Associations between variables were studied using Pearson's correlation and multiple linear regression analyses.

Results—Both thoracic circumference and lung volume correlated with fetal size measures, ranging from $r = 0.64$ between thoracic circumference and abdominal circumference, to $r = 0.28$ between lung volume and femur length. Adjustment for gestational age, maternal nicotine use, pre-pregnancy body mass index, and fetal sex marginally influenced the associations with abdominal circumference. The correlations of thoracic circumference and lung volume with pulmonary artery blood flow velocity measures were weak ($r \leq 0.17$).

Conclusion—We found moderate to low correlation between thoracic circumference, lung volume, and fetal size at 30 GW. The closest relationship was with the abdominal circumference. We found low correlations of thoracic circumference and lung volume with pulmonary artery blood flow velocity measures.

Key Words—Doppler; fetal; lung volume; pulmonary artery; PreventADALL; thoracic circumference

Several birth cohort studies have found association between infant respiratory health, on the one hand, and fetal size, fetal growth patterns, and blood flow in the fetal pulmonary artery (PA), on the other.[1-3] These findings suggest the necessity of integrating specific thoracic and lung size measures when studying the intrauterine origins of lung disease, particularly the extent to which these specific measures relate with fetal size. Fetal thoracic

circumference (TC) and lung volume (LV) are ultrasound measures suggested as prognostic indicators of survival in fetuses with risk factors of neonatal pulmonary hypoplasia.[4,5] Research on these variables in the general population is limited.

In studies performed within a large gestational age (GA) range, from early- or mid-pregnancy to term, fetal TC and LV correlated strongly with the fetal size measures.[6-8] Studying these relationships in a large population within a narrow gestational interval will reduce the dominant influence of GA.

The growth of airways and pulmonary blood vessels is closely related.[9] Blood flow to an organ may be associated with the organ size, as shown in studies on fetal kidneys and liver.[10,11] Different PA blood flow velocity variables have been associated with pulmonary hypoplasia.[12-14] In healthy fetuses, Doppler blood flow velocity variables in the PA are related to the gestational age.[15-17] This might be due to increased organ size and also the physiological changes in the vascular wall or the ventricular contractility throughout the pregnancy. To our knowledge, no studies have yet examined the relationship between fetal pulmonary circulation and LV in presumably healthy human fetuses.

Our primary aim was to explore the association of fetal TC and LV with standard measures of fetal size (head and abdominal circumference, and femur length) at 30 gestational weeks (GW). Our secondary aim was to explore the associations of LV and TC with Doppler blood flow velocity measures in the right and left proximal fetal PA branches.

Materials and Methods

Study Design

This is a sub-study of the Scandinavian multicenter, prospective, general population-based birth cohort study Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL). It included 2701 pregnancies by 2697 women enrolled from December 2014 through October 2016. The PreventADALL study included women at the routine ultrasound examination at approximately 18 GW. Exclusion criteria were pregnancy with more than two fetuses, severe fetal malformations or disease and insufficient Norwegian or Swedish language skills. Detailed information on the PreventADALL study may be found elsewhere.[18]

In the present cross-sectional sub-study, we included 458 out of 1732 PreventADALL participants with singleton pregnancies giving birth at Oslo University Hospital. These women were invited for an additional ultrasound assessment at 30 GW. Priority was given to participants with fetal TC measured at the routine ultrasound examination (84% of the Oslo University Hospital PreventADALL cohort). We excluded women carrying fetuses with severe fetal growth restriction and those with chronic maternal disease or on medication with a potential to affect fetal growth and hemodynamics. One woman withdrew from the study and 10 were excluded due to trisomy 21 ($n = 1$), genetic syndromes ($n = 2$), severe intrauterine growth restriction resulting in delivery within 1 week after the ultrasound examination ($n = 2$), maternal diabetes mellitus type 1 ($n = 2$), and chronic hypertension ($n = 3$). We did not exclude the women that developed pregnancy induced hypertension, pre-eclampsia, or gestational diabetes mellitus after 30 GW ultrasound data collection.

We obtained baseline characteristics from interviews and measurements at study inclusion, electronic questionnaires at 18 and 34 GW, and medical records.

The PreventADALL study was approved by the Regional Committee for Medical and Health Research Ethics in South-Eastern Norway (2014/518) and in Sweden (2014/2242-31/4), and the study was registered at ClinicalTrials.gov (number NCT02449850). All participants signed informed consent at the inclusion.

Ultrasound Measurements

We determined gestational age for the present study by measurement of head circumference (HC) at the second trimester routine ultrasound examination.[19] The 30 GW ultrasound examinations were performed by a single operator (K.H.) using a GE Voluson E8 ultrasound system (GE Medical Systems, Zipf, Austria) with a 4 to 8 mHz curved array ultrasound transducer (RAB4-8-D abdominal transducer). The women were placed in a semi-recumbent position. Standard fetal biometry measurements included HC, abdominal circumference (AC), and femur length (FL).[19]

Thoracic circumference was measured in the axial plane at the level of the four-chamber view of the heart, parallel with the ribs, by placing an ellipse around the bony thorax. Lung area was measured in

the same plane by tracing the contours of the right and left lung separately. The right and left lung length was measured in the parasagittal plane that did not include the heart, by placing calipers on the apex of the lung and the dome of the diaphragm (Figure 1). The majority of the measurements were performed during fetal quiescence. If fetal breathing movements were persistent, TC and lung measures were obtained at the expirium. The LV was calculated as 1/3 × lung area × lung length, as described by Moeglin et al.[20] We modified their method by using the length of both lungs instead of the right only. Total LV was defined as the sum of the left and right LV. For all biometric measures, we used the mean value of at least three measurements.

We sampled fetal PA Doppler measures from the right and/or left proximal pulmonary branches, as close as possible to the pulmonary bifurcation, as previously described.[21] We sought to sample at least one of the PA branches. We recorded the following measures: time-averaged maximum velocity (TAMX), pulsatility index (PI; defined as the difference between peak systolic velocity and maximum end-diastolic velocity, divided by TAMX), fetal heart rate, acceleration time (AT; defined as time from the onset of the systole to the systolic peak), and ejection time (ET; defined as the duration of the systole).

Statistical Analysis

We report continuous variables as mean with either standard deviation (SD) or 95% confidence interval (CI), or as median with 25th and 75th percentiles if not normally distributed. Categorical variables are reported as frequency and percentage. The intra-rater reliability of thoracic and lung measurements was tested by intraclass correlation coefficient (ICC) analysis of two repeated measurements (two-way mixed model, consistency correlation of single measures) in a group of randomly selected study participants and volunteers at 30 GW.

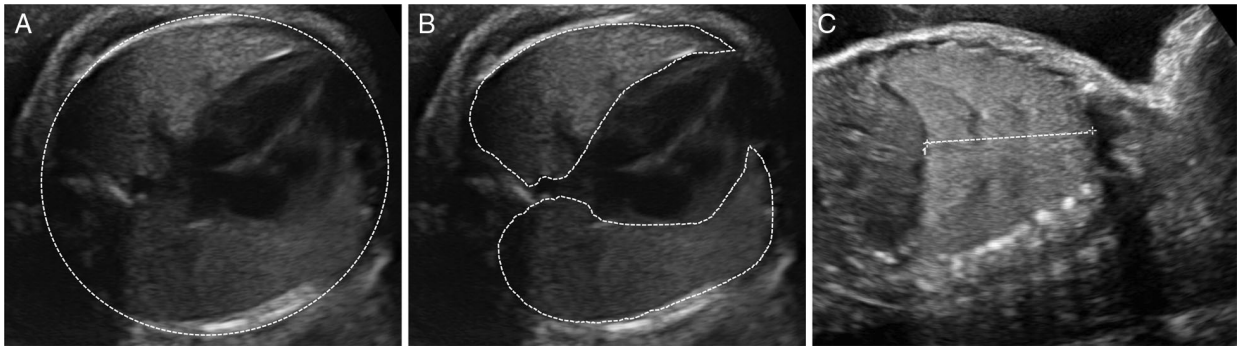
To assess correlation between fetal measures, we used Pearson's correlation test. The main outcome variables were TC and total LV. Their associations with maternal factors, fetal sex, and GA were calculated by Pearson's correlation test and Student's *t*-test. Variables with $P < .2$ in the univariate analyses were included in the multiple linear regression models with TC or total LV as outcome variables. To determine the associations between TC or total LV and fetal size, we performed linear multiple regression analyses, including covariates and potential confounders. Right and left lung area, length, and volume were compared by paired samples *t*-test.

We conducted all statistical analyses with IBM® SPSS® statistics version 25.0 (SPSS Inc., Chicago, IL, U.S.A.) using $P < .05$ as statistically significant.

Results

Baseline characteristics for the 447 subjects are given in Table 1. Except for a higher educational level, the women included in this study did not differ from the total PreventADALL study group (Table 1). Nicotine use during pregnancy was low; of the 56 users, 54 stopped when recognizing their pregnancy. The mean GA at ultrasound examination was 30.0 weeks (SD 0.50), ranging from 28.9 to 31.3 weeks.

Figure 1. Ultrasound images demonstrating the measurement of the thoracic circumference (**A**), lung area (**B**), and lung length (**C**). Lung volume was calculated from lung area and lung length.



Thoracic circumference was successfully obtained in all cases while lung volume calculation was possible in 440 fetuses, missing in 7/447 (1.6%) cases due to poor visualization. The ICC for TC ($n = 17$) was 0.85 (95% CI 0.62, 0.94) and 0.86 (95% CI 0.66, 0.95) for total LV ($n = 16$).

The fetal biometric measures are shown in Table S1. The right lung area was significantly larger than the left lung area [mean 972.4 mm^2 (95% CI, 961.5–983.3) versus 658.7 mm^2 (95% CI, 649.8–667.7), $P < .001$]. The right lung volume was significantly larger than the left lung volume [mean 12.6 ml (95% CI, 12.4–12.8) versus 8.7 ml (95% CI, 8.6–8.9), $P < .001$]. On the other hand, the right lung length with a mean of 38.7 mm (95% CI, 38.3–39.1) was significantly shorter than the left lung length with a mean of 39.6 mm (95% CI, 39.2–40.0), ($P < .001$).

Both TC and total LV were positively correlated with fetal biometric measures (HC, AC, and FL) ($r = 0.28$ to 0.64, $P < .001$ for all correlations). The strongest correlation was observed between TC and AC and the weakest between total LV and FL (Table 2).

In univariate analysis, TC was not significantly different in female and male fetuses ($P = .26$), fetuses exposed versus not exposed to maternal use of nicotine at any time during the pregnancy ($P = .08$), among mothers who were para ≥1 compared to nullipara ($P = .33$), in mothers with or without hypertensive disorders in pregnancy ($P = .97$), or gestational diabetes ($P = .66$). In equivalent analyses, total LV was not affected by fetal sex ($P = .16$), parity ($P = .54$), nicotine exposure ($P = .15$), hypertensive disorders in pregnancy ($P = .70$), or gestational diabetes mellitus ($P = .88$).

Maternal age was not significantly correlated with TC ($r = 0.04$, $P = .36$) or total LV ($r = -0.01$, $P = .89$). Maternal pre-pregnancy body mass index (pp BMI) showed a low positive correlation with TC ($r = 0.17$, $P < .001$), but not with total LV ($r = 0.04$, $P = .37$). Gestational age at ultrasound examination correlated positively with TC ($r = 0.34$, $P < .001$) and total LV ($r = 0.28$, $P < .001$).

In the multiple regression models, with TC and total LV as dependent variables, we included AC as the fetal size measure most strongly correlated with these main outcome variables. The relation between TC and AC remained similar after adjusting for GA, nicotine exposure and pp BMI, whereas the relations between TC and GA, nicotine exposure and pp BMI became weaker (adjusted $R^2 = 0.42$) (Table 3A). Likewise, the relation between total LV and AC remained similar after adjusting for GA, nicotine exposure, and fetal sex, whereas the impact of GA, fetal sex, and nicotine

Table 1. Baseline Characteristics of the Study Participants and PreventADALL Participants Not Included in the Present Subcohort

Number of PreventADALL Participants Depending on the Inclusion in the Present Sub-study[a]	*n*	Included *n* = 447	*n*	Not-included *n* = 2251
Maternal age (years)	447	32.9 (3.9)	2251	32.2 (4.3)
Maternal pp BMI (kg/m^2)	440	22.0 (20.6, 24.2)	2183	23.2 (20.7, 24.6)
Nicotine use at any time in pregnancy, *n* (%)	442	56 (12.7)	2084	227 (10.9)
Maternal level of education, *n* (%)				
High and/or primary	398	15 (3.8)	1941	242 (12.4)
Higher education ≤ 4 years		120 (30.2)		637 (32.8)
Higher education > 4 years		262 (65.8)		1061 (54.6)
Other		1 (0.3)		1 (0.1)
Nullipara, *n* (%)	447	291 (65.1)	2243	1302 (58.0)
Pregnancy after in vitro fertilization, *n* (%)	446	32 (7.2)	2245	174 (7.8)
Hypertensive disorders, *n* (%)	447	32 (7.2)	2236	231 (10.3)
Gestational diabetes mellitus, *n* (%)	446	19 (4.3)	2233	86 (3.9)
Birthweight (g)	446	3513 (496)	2231	3545 (550)
Placental weight (g)	430	659 (131)	1578	656 (139)
Male fetal sex, *n* (%)	446	227 (50.9)	2242	1189 (53.0)

Data are presented as mean (SD), median (25th, 75th percentile), or *n* (%).
pp BMI, pre-pregnancy body mass index; PreventADALL, Preventing Atopic Dermatitis and ALLergies in Children; SD, standard deviation.
[a]Out of 2701, three participants withdrew and asked for removal of all data giving total number of pregnancies 2698.

Table 2. Results From Pearson's Correlation Analyses Between Thoracic Circumference, Lung Volume, and Fetal Size Measures at 30 Gestational Weeks

	Head Circumference		Abdominal Circumference		Femur Length	
	r[a]	*P*	*r*[a]	*P*	*r*[a]	*P*
Thoracic circumference	0.44	<.001	0.64	<.001	0.39	<.001
Total lung volume	0.36	<.001	0.53	<.001	0.28	<.001

[a]*r* = Pearson's correlation coefficient.

Table 3. Multiple Linear Regression Analyses of the Determinants of (A) Thoracic Circumference and (B) Total Lung Volume

(A) Thoracic Circumference

	Unadjusted *B* (95% CI)	*β*	*P*	Adjusted *B* (95% CI)	*β*	*P*
AC	0.51 (0.46, 0.57)	0.64	<.001	0.47 (0.41, 0.53)	0.59	<.001
GA at US	0.89 (0.66, 1.12)	0.34	.001	0.29 (0.09, 0.50)	0.11	.006
pp BMI	0.46 (0.20, 0.71)	0.17	<.001	0.25 (0.05, 0.45)	0.09	.02
Nicotine exposure[a]	2.22 (−0.36, 4.81)	0.08	.09	0.42 (−1.58, 2.42)	0.02	.68
Adjusted R^2 of the model = 0.42						

(B) Total Lung Volume

	Unadjusted *B* (95% CI)	*β*	*P*	Adjusted *B* (95% CI)	*β*	*P*
AC	0.17 (0.14, 0.19)	0.53	<.001	0.16 (0.13, 0.18)	0.49	<.001
GA at US	0.29 (0.20, 0.39)	0.28	<.001	0.09 (−0.002, 0.19)	0.09	.05
Fetal sex	−0.49 (−1.18, 0.19)	−0.07	.16	−0.18 (−0.76, 0.41)	−0.02	.56
Nicotine exposure[a]	0.77 (−0.27, 1.80)	0.07	.15	0.26 (−0.62, 1.14)	0.02	.56
Adjusted R^2 of the model = 0.28						

[a]At any time during the pregnancy.
AC, abdominal circumference; *B*, unstandardized regression coefficient; β, standardized regression coefficient; pp BMI, pre-pregnancy body mass index; GA, gestational age; US, ultrasound.

Table 4. Results From Pearson's Correlation Analyses Between Doppler Blood Flow Velocity Measures in the Right ($n = 366$) and Left ($n = 77$) Pulmonary Artery and Lung Volume on the Respective Side, Total Lung Volume, and Thoracic Circumference

	Right Lung Volume		Total Lung Volume		Thoracic Circumference	
	r[a]	*P*	*r*[a]	*P*	*r*[a]	*P*
RPA PI	−0.01	.86	−0.07	.16	−0.06	.27
RPA TAMX (cm/s)	0.10	.06	0.12	.02	0.17	.001
RPA AT/ET	0.11	.04	0.11	.03	0.10	.06
	Left Lung Volume		**Total Lung Volume**		**Thoracic Circumference**	
	r[a]	*P*	*r*[a]	*P*	r[a]	*P*
LPA PI	0.02	.89	0.06	.63	0.19	.10
LPA TAMX (cm/s)	0.10	.40	0.01	.96	−0.01	.96
LPA AT/ET	0.09	.44	0.10	.38	0.04	.74

[a]Pearson's correlation coefficient.
AT, acceleration time; ET, ejection time; LPA, left pulmonary artery; PI, pulsatility index; RPA, right pulmonary artery; TAMX, time averaged maximum velocity; TC, thoracic circumference.

exposure became less pronounced (adjusted $R^2 = 0.28$) (Table 3B).

Pulmonary artery Doppler measurements were successful in 382 fetuses (85.5%), with measurements from the right pulmonary artery (RPA) in 366 fetuses (96%), from the left pulmonary artery (LPA) in 77 (20%) and from both arteries in 62 cases (16%) (Table S2). The lack of PA Doppler measures in 65 fetuses was mainly due to persistent respiratory movements. In univariate analyses of the TC and LV with RPA Doppler measures, we observed several statistically significant correlations although all were weak. The strongest correlation was between TC and RPA TAMX ($r = 0.17$, $P = .001$). No significant correlations were observed between TC, total, and left LV and LPA Doppler measures ($r = -0.07$ to 0.19, $P > .10$) (Table 4).

Discussion

In this cross-sectional study, we found moderate to low correlation between the measures of thoracic and lung size (represented by TC and total LV), and standard biometric measures in 447 presumably healthy fetuses. The novelty of the study is that the measures were obtained in a short gestational age range at 30 weeks. Abdominal circumference was the fetal biometric measure with the strongest correlation with TC and total LV; it remained significant after adjusting for confounders. We observed weak correlation of TC and LV with PA Doppler blood flow velocity measures. To our knowledge, this is the first study combining measurements of fetal TC and LV with PA blood flow velocity waveforms in a general pregnant population without increased risk of neonatal pulmonary hypoplasia.

Our TC measures correspond to those observed at 30 GWs by others,[4,8] although these cross-sectional studies had fewer observations per GW, covered significantly larger periods of pregnancy, and cannot thus be directly compared to this study. Volume and area of the right lung were significantly larger than those of the left lung, as shown previously.[22,23] Contrary to earlier observation of similar right and left lung length,[24] we found significantly shorter right lung length compared to the left. This finding agrees with results from postmortem fetal lung measurements,[25] and seems reasonable as the left side of the diaphragm is placed lower than the right. Our LV measures corresponded to those of Moeglin et al, whose 2D-based method we adapted.[20] According to their observations, results from 2D lung volumetry were highly correlated with those from 3D ($r = 0.92$, $P < 2 \times 10^{-6}$), but were consistently smaller (mean difference of 11.99 ml for measures obtained from GW 20 to 35, $P < 0.1 \times 10^{-6}$). Compared to other studies using 3D volumetry, our LV values are expectedly lower.[22,26] AC, HC, and FL measurements corresponded to reference ranges from both Norwegian and World Health Organization growth charts,[19,27] confirming that the population we studied represented the general pregnant population.

Our finding that TC had stronger correlation with AC, rather than with HC and/or FL, is in line with previous observations.[6,8] This pattern is more pronounced in our study focused on a specific period of pregnancy. The close relation of thoracic and lung measures with AC could be explained by all being measures of truncal size, in contrast to HC and FL. Moreover, AC is considered the most important single ultrasonographic measure of fetal size.[28] The correlations of TC and total LV with the fetal biometric measures might seem obvious, but were weaker in the present study compared to those shown by others reporting r values of 0.89 or higher.[6-8] However, these operated with considerably larger GA ranges from early- or mid-pregnancy to term. Our results were less influenced by GA, providing a better basis for studying the effect of other background variables on TC and LV. Despite our narrow GA range, the relation between GA and TC was still significant and between GA and LV marginally significant even in our regression analyses. Moreover, adjusting for other variables known to affect fetal growth, including the modifiable variables pp BMI and nicotine exposure[29] did not substantially influence the relation of TC and total LV with AC. We observed significant correlation between maternal pp BMI and TC, but not with total LV. This suggests that maternal variables might influence truncal and lung growth in diverse ways.

Like previous studies have also observed, we had greater success obtaining Doppler measures from the RPA compared with the LPA.[15-17] Our PA Doppler values corresponded to the expected range for 30 GW. Pulsatility index relates negatively to the vascular resistance and TAMX has a positive association with the volume blood flow. Pulmonary artery

AT/ET ratio was significantly lower in children and adolescents with pulmonary hypertension than in healthy controls.[30] Increased PI, reduced TAMX, and AT/ET ratio in fetal PA have been associated with neonatal lung hypoplasia.[12-14] In healthy fetuses, reduced PA vascular resistance and increased blood flow were previously observed with increasing GA, as indicated by a decrease in PI and an increase in TAMX and AT/ET ratio, respectively.[15] The growth of airways and pulmonary vascular bed is parallel and larger total cross-sectional pulmonary vascular bed area in late gestation is believed to result in lower vascular resistance as well as higher perfusion of the lungs, as described by Laudy et al.[31] Our study showed significant, but weak correlations between PA Doppler measures and TC as well as LV. These correlations were significant only for the RPA, possibly reflecting the larger number of observations compared to the LPA. They were in a physiologically plausible direction, that is, increase in flow with increase in organ size. The strength of the correlations suggests, however, that other factors than the lung size, and thereby the size of the pulmonary vascular bed, might be important for the PA blood flow. Our findings are in agreement with a study on fetal lambs, indicating that lung perfusion no longer showed increasing trend with advancing gestation after correcting for the wet lung weight.[32] Vascular bed properties, such as muscular layer thickness or the reactivity of the arterial wall, might be additional factors influencing the pulmonary blood flow Doppler measures.

The strengths of our study are the large number of participants, the prospective design, the performance of all measurements by a single operator, as well as acceptable ICC values of the thoracic and lung measures. Our focus on 30 GW is both a limitation and strength. During the third trimester, fetal growth is rapid and the individual variation of fetal size measures increases. We therefore set up a cross-sectional design with one examination in week 30. We did not select a higher GA due to frequent presence of acoustic shadows, unfavorable fetal position, and respiratory movements reported to limit lung measurements irrespective of method applied.[22,33] A further limitation is that lung volume was calculated from 2D measures. We sought to obtain good quality measures of TC and LV, as well as PA Doppler blood flow velocities. Reports on 3D lung volumetry showed exclusion rates particularly high from GW 30 and onwards.[22] In order to avoid substantial study sample reduction due to unsuccessful recordings of either lung volumes or PA Doppler, we selected a 2D technique based on lung measurement in several dimensions. The diameter of the PAs was not measured. We were therefore unable to calculate volume blood flow to the lungs, representing another limitation of our study. The low proportion of nicotine users limited the possibility of studying the effects of nicotine exposure.

Research has linked fetal size and growth with symptoms or respiratory physiology related to asthma in children.[34] Our findings show moderate to low correlation of thoracic circumference and lung volume with fetal size measures early in the third trimester, in contrast to strong correlation demonstrated in previous reports covering a large period of pregnancy. Future studies of early origins of children's respiratory disease should therefore investigate the relationship between the thoracic and lung size, their growth trajectories, and infant lung function.

In this study, we used the novel approach focusing on a short gestational interval at 30 weeks, reducing the confounding effect of gestational age. We found moderate to low correlation of thoracic circumference and total lung volume with standard ultrasound measures of fetal size. Abdominal circumference was the fetal size measure best correlated with thoracic circumference and lung volume, even after adjusting for gestational age, maternal pp BMI, nicotine exposure, and fetal sex. Correlations of fetal thoracic circumference and lung volume with variables of pulmonary artery blood flow were weak.

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