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Third trimester fetal lung volume, thoracic circumference, and early infant lung function

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Abstract

Background: We aimed to investigate the relationship between fetal third trimester lung volume (LV), thoracic circumference (TC), fetal weight, as well as fetal thoracic and weight growth, and early infant lung function.

Methods: Fetal LV, TC and estimated weight were measured with ultrasound at 30 gestational weeks in 257 fetuses from the general population-based prospective cohort study Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL). Fetal thoracic growth rate and weight increase were calculated using TC and estimated fetal weight measured by ultrasound during pregnancy, and TC and birthweight of the newborn. Lung function was assessed by tidal flow-volume measurement in awake infants at 3 months of age. The associations between fetal size (LV, TC, and estimated weight) and growth (thoracic growth rate and fetal weight increase) measures and the time to peak tidal expiratory flow to expiratory time ratio (t_{PTEF}/t_E) as well as tidal volume standardized for body weight (V_T/kg) were analyzed using linear and logistic regression models.

Results: We observed no associations between fetal LV, TC or estimated fetal weight and t_{PTEF}/t_E as a continuous variable, t_{PTEF}/t_E < 25th percentile, or V_T/kg. Similarly, fetal thoracic growth and weight increase were not associated with infant lung function. Analyses stratified for sex showed a significant inverse association between fetal weight increase and V_T/kg ($p = 0.02$) in girls.

Conclusion: Overall, fetal third trimester LV, TC, estimated fetal weight, thoracic growth rate and weight increase were not associated with infant lung function at 3 months of age.

KEYWORDS

fetal growth, lung function, lung volume, PreventADALL, thoracic circumference, tidal breathing

1 | INTRODUCTION

There is increasing evidence of early origins of asthma, one of the leading chronic diseases in children. Lung function trajectories persist from early infancy throughout childhood[1,2] and previous studies demonstrated an association between reduced infant lung function and childhood asthma.[3,4] Different antenatal exposures, mainly maternal smoking, but also alcohol intake and air pollutants,[5–8] as well as hypertensive pregnancy complications,[5] have been linked to impaired lung function in children. Reduced fetal size and growth have also been associated with lower infant lung function,[9–12] whereas less consistent associations were observed with symptoms related to asthma in infancy and childhood.[9–13] A newly published study showed an inverse association between mid-pregnancy thoracic circumference (TC), adjusted for femur length as a TC/femur length ratio, and infant lung function.[14] Ultrasound measures related to fetal lung size, such as lung volume (LV) or lung area, as well as TC, have a predictive value for neonatal respiratory outcome and survival in certain pathological conditions such as diaphragmatic hernia and skeletal dysplasia.[15–17]

To our knowledge, in contrast to general fetal size and growth, no previous study has investigated potential associations between fetal LV or thoracic growth and measures of postnatal lung function. In contrast to earlier stages of pregnancy, third trimester is characterized by the most rapid fetal growth and larger interindividual differences in fetal size.[18] TC in relation to infant lung function has however only been investigated in the second trimester of pregnancy.[14]

In early infancy there are few available methods of measuring lung function. Earlier studies have used maximal expiratory flow at functional residual capacity (VmaxFRC), a method that usually requires sedation. Thus, an alternative lung function measurement is tidal flow-volume (TFV) loops, feasible from birth in both awake and sleeping infants. The method has demonstrated reduced lung function after in utero exposure to cigarette smoking[6] as well as augmented lung function in a randomized clinical trial using vitamin C to protect the fetus against adverse effects of nicotine.[19] Impaired lung function by TFV is reflected particularly in a lower ratio of the time to peak tidal expiratory flow to expiratory time (t_{PTEF}/t_E),[5,6] a measure that correlates with VmaxFRC.[20]

We aimed to investigate intrauterine origins of early infant lung function by exploring the associations between third trimester fetal LV, TC, as well as estimated fetal weight and TFV measures at 3 months of age. Our secondary aim was to study the effect of third trimester fetal thoracic growth and weight increase on the same lung function measures.

2 | METHODS

2.1 | Study design and study population

The included infants are participants in the Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL) study, a Scandinavian multicenter, prospective, population-based birth cohort study that enrolled 2697 pregnant women (2701 pregnancies) at an antenatal visit between 16 and 22 gestational weeks (GW) from December 2014 to October 2016. In the Oslo cohort, 449 women with singleton pregnancies were randomly selected for ultrasound examination at 30 GW. Healthy infants born at minimum 35.0 GW were enrolled at birth. Detailed information on the study population has been published previously.[21]

The present exploratory study includes all 257 infants from the PreventADALL cohort with available fetal ultrasound examination at 30 GW as well as infant lung function measurement in the awake state at 3 months of age (Figure 1).

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 was registered at ClinicalTrials.gov (number NCT02449850). Informed consent was signed by the pregnant women at enrollment and by both parents at newborn inclusion.

2.2 | Data collection

Our previous publication provides detailed description of the ultrasound methodology.[22] Fetal TC was measured with ultrasound 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. Fetal LV was calculated from the right and left lung area and length. The equipment used was a GE Voluson E8 ultrasound system (GE Medical Systems, Zipf) with a 4–8 mHz curved array ultrasound transducer (RAB4-8-D abdominal transducer). Combs formula[23] was used to calculate estimated fetal weight based on the head and abdominal circumferences as well as the femur length. All ultrasound measurements were conducted by one dedicated and experienced operator (K. H.) to minimize measurement error.

Trained study personnel measured infant TC, not later than 3 days after birth, with a measuring tape placed around the infant's chest with the lower part in line with the most caudal part of the xiphoid process. We report the average value of three consecutive measurements. Birthweight was measured by hospital staff. Study personnel measured infant weight and length at the 3 months follow-up visit.

Fetal third trimester thoracic growth rate was calculated using fetal TC measured at 30 GW and infant TC at birth: (TC at birth [mm]—TC at 30 GW [mm])/interval between the two TC measurements (days). Similarly, we calculated fetal weight increase using estimated fetal weight at 30 GW and birthweight: (birthweight [g]—estimated fetal weight at 30 GW [g])/interval between the two weight measurements (days).

Lung function was measured by TFV loops as described in detail elsewhere.[24] Measurements were performed by trained study personnel in awake, calmly breathing infants in the supine position using a close-fitting face mask attached to an ultrasonic flow meter (Exhalyzer® D; ECO MEDICS AG, Switzerland), equipped with a dead space reducer. Post-processing analysis focused on shape and reproducibility of the TFV loops. The main outcome variables are t_{PTEF}/t_E as a continuous variable and t_{PTEF}/t_E < 25th percentile. The secondary outcome is tidal volume standardized for infant weight (V_T/kg).

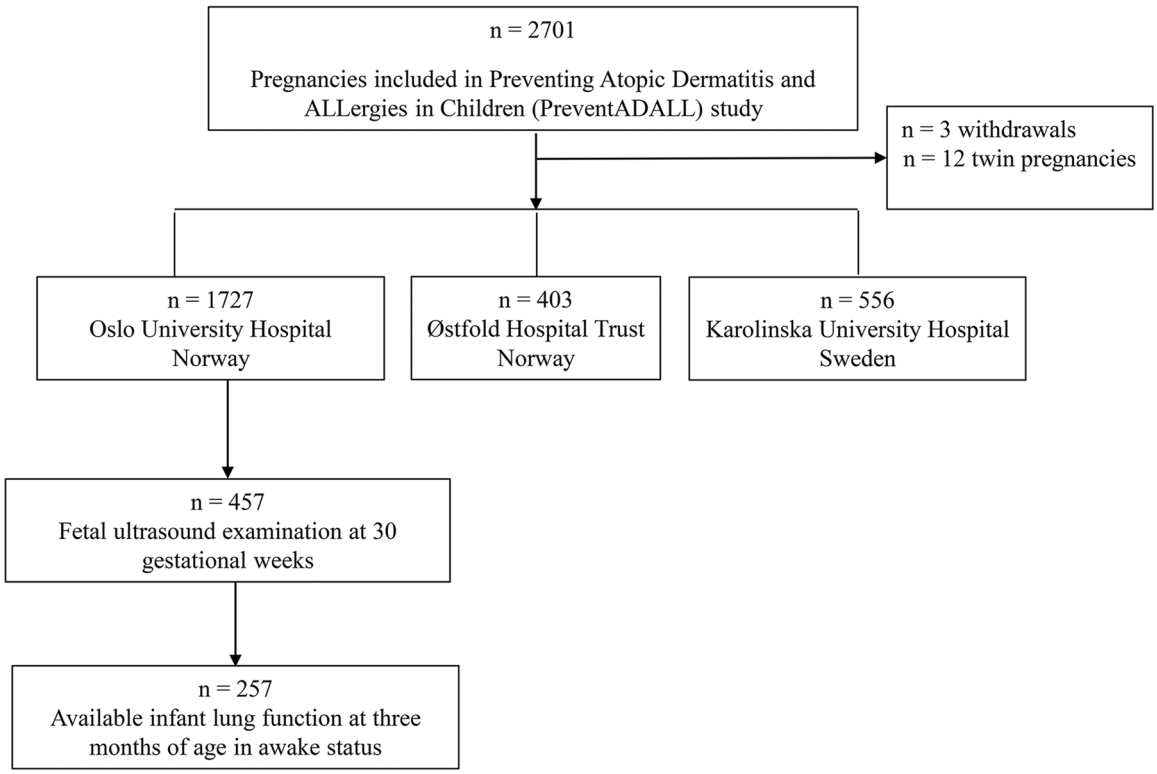

FIGURE 1 Flowchart of participants included in the study.

Background characteristics were collected from interviews and measurements at study inclusion, electronic questionnaires at 18 and 34 GW, at 3 months postnatal age, and from medical records.

2.3 | Statistical analyses

We report continuous variables as the mean and standard deviation (SD) or as the median with first and third quartile, according to variable distribution, unless otherwise stated. Categorical variables are reported as frequencies and percentages. Results from the regression analyses are presented as regression coefficients or odds ratios (OR) with 95% confidence intervals (CI) and *p* values. Student's *t*-test, Mann–Whitney *U* test, χ^2 test, and one-way analysis of variance test were used for group comparisons. Correlations were analyzed by Pearson's correlation. Linear regression analyses were used to explore if third trimester fetal size measures (TC, LV, and estimated weight at 30 GW) and third trimester fetal growth measures (thoracic growth and weight increase)—were associated with t_{PTEF}/t_E and V_T/kg. Logistic regression analyses were applied in the models with t_{PTEF}/t_E < 25th percentile as outcome variable. All multivariable regression models were adjusted for infant sex, use of nicotine in pregnancy, and hypertension in pregnancy, previously shown to be associated with both fetal size and growth[25–27] as well as infant lung function.[5,6,28] Multivariable models with third trimester fetal thoracic growth rate and weight increase as exposure variables were also adjusted for fetal TC and estimated weight at 30 GW, respectively. To account for possible effect modification of fetal exposure variables on lung function by sex, based on previous findings of sex-determined structural and functional differences in the respiratory system[29] as well as fetal growth,[18] we included an interaction term with sex in the regression analyses.

Due to known associations between prematurity and low birthweight with lower lung function[30,31] we performed sensitivity analyses by excluding preterm infants (born between 35.0 and 36.9 GW), as well as infants with birthweight below the 10th percentile for the Norwegian population.[32]

We handled missing data of covariates and outcomes by imputation. For the missing values of nicotine use in pregnancy ($n = 2$) we used best case imputation, as no use was reported by most of the participants (87.8%). We used mean imputation for fetal LV ($n = 5$), as well as sex-specific mean imputation for infant weight ($n = 2$) at 3 months of age. We chose to not impute mean value for missing TC at birth ($n = 12$) due to high variation in gestational age and birthweight. We used IBM® SPSS® statistics version 28.0 (SPSS Inc.) for the statistical analyses. The significance level was set to 5%.

3 | RESULTS

Characteristics of the infants and their mothers are presented in Table 1. The study population was largely representative for the PreventADALL cohort except for higher maternal age and education, lower parity, higher frequency of living in urban areas and higher

TABLE 1 Characteristics of the mothers and infants in the present study population compared to the rest of the Preventing Atopic Dermatitis and ALLergies in children (PreventADALL) cohort.

	Study population		Rest of the cohort		
	n	Mean (SD)/Median (Q1, Q3)/*n* (%)	*n*	Mean (SD)/Median (Q1, Q3)/*n* (%)	*p* Value
Maternal age (years)	257	33.2 (3.8)	2441	32.2 (4.3)	<0.001
Maternal prepregnancy BMI	253	22.9 (20.8–24.2)	2370	23.2 (20.7–24.6)	0.31
Nordic maternal country of origin, *n* (%)	229	207 (90.4)	1931	1745 (90.4)	0.99
Densely populated living area, *n* (%)	229	118 (51.5)	2119	797 (37.6)	<0.001
Nicotine use at any time in pregnancy[a], *n* (%)	255	31 (12.2)	2271	252 (11.1)	0.61
Maternal highest level of education, *n* (%)	229		2110		<0.001
High school and/or primary school		10 (4.4)		249 (11.8)	
Higher education ≤ 4 years		57 (24.9)		700 (33.2)	
Higher education > 4 years		162 (70.7)		1161 (55.0)	
Nullipara, *n* (%)	257	170 (66.1)	2433	1423 (58.5)	0.02
Maternal asthma, *n* (%)	229	37 (16.2)	2119	368 (17.4)	0.65
Hypertensive disorders, *n* (%)	257	19 (7.4)	2398	244 (10.2)	0.16
Pre-eclampsia, *n* (%)		6 (2.3)		60 (2.5)	
Diabetes mellitus, *n* (%)	257	6 (2.3)	2327	99 (4.1)	0.14
Gestational diabetes mellitus[b], *n* (%)		5 (1.9)		95 (4.0)	
Gestational age at birth (days)	257	282.0 (275.0–287.0)	2441	281.0 (274.0–287.0)	0.07
Birthweight (kg)	257	3.52 (0.46)	2420	3.54 (0.55)	0.30
Birthweight < 10th percentile, *n* (%)	257	26 (10.1)	2371	170 (7.2)	0.09
Cesarean delivery, *n* (%)	257	43 (16.7)	2437	423 (17.4)	0.80
Apgar score at 1 min	253	9.0 (9.0–9.0)	2383	9.0 (9.0–9.0)	0.79
Apgar score at 5 min	253	10.0 (9.0–10.0)	2384	10.0 (9.0–10.0)	0.61
Female infant sex, *n* (%)	257	127 (49.4)	2443	1151 (47.1)	0.54
Infant weight at 3 months of age (kg)	255	6.2 (0.8)	1871	6.3 (0.8)	0.28
Infant length at 3 months of age (cm)	250	61.9 (2.2)	1849	61.8 (2.3)	0.97
Breastfeeding at 3 months of age (exclusive or partial), *n* (%)	226	218 (96.5)	1628	1512 (92.9)	0.04

Abbreviations: BMI, body mass index; Q, quartile; SD, standard deviation.

[a]Nicotine (cigarette smoking, use of snus, or both) use was not reported by any participant in the study group after 10 gestational weeks.

[b]Gestational diabetes mellitus was defined as plasma glucose concentration ≥ 7.8 mmol/L 2 h after an oral glucose tolerance test of 75 g glucose.

frequency of breastfeeding, compared to the remaining participants. Of 255 pregnant women with available data on nicotine use in pregnancy, 31 (12.2%) reported use of nicotine products, but none after 10 GW (21 reported cigarette smoking, nine snus use and one both). Three infants were born preterm (at 35.6–36.9 GW).

Mean (SD) age at ultrasound examination was 30.0 (0.5) GW and median (min–max) gestational age at birth was 40.3 (35.6–42.4) GW. Mean (SD) age at lung function measurement was 92.7 (6.9) days.

At 30 GW mean (SD) LV, TC and estimated fetal weight were 21.3 (3.7) ml, 20.9 (1.0) cm and 1.66 (0.15) kg, respectively. Mean (SD) fetal thoracic growth and weight increase were 1.82 (0.27) mm/day and 26.6 (5.9) g/day, respectively. Supporting Information: Table S1 presents fetal and infant biometric measures, including the differences between girls and boys. Fetal LV and TC were strongly correlated ($r = 0.74$, $p < 0.001$). Fetal LV, TC and thoracic growth were similar in girls and boys. Compared to boys, girls had lower weight at 30 GW, at birth and 3 months of age and lower fetal weight increase. Mean (SD) t_{PTEF}/t_E, V_T and V_T/kg were 0.39 (0.1), 43.9 (12.2) ml, 7.1 (2.0) ml/kg, respectively. Girls had higher t_{PTEF}/t_E compared to boys, whereas V_T and V_T/kg were similar in the two sex groups (Supporting Information: Table S2).

TABLE 2 Linear regression analyses: The association between fetal size and fetal growth variables and infant lung function at 3 months of age.

	Univariable model		Multivariable model	
	Coefficient (95% CI)	*p* Value	Coefficient (95% CI)	*p* Value
Outcome variable: t_{PTEF}/t_E				
Fetal size measures at 30 GW				
Lung volume (mL)	−0.001 (−0.004 to 0.002)	0.40	−0.001 (−0.003 to 0.002)	0.67
Thoracic circumference (cm)	−0.001 (−0.01 to 0.01)	0.82	0.001 (−0.01 to 0.01)	0.90
Estimated fetal weight (kg)	−0.05 (−0.12 to 0.02)	0.15	−0.03 (−0.10 to 0.04)	0.35
Third trimester fetal growth				
Fetal thoracic growth rate (mm/day)[a]	−0.002 (−0.04 to 0.04)	0.92	0.005 (−0.03 to 0.05)	0.79
Fetal weight increase (g/day)[b]	−0.001 (−0.003 to 0.001)	0.44	0.00002 (−0.002 to 0.002)	0.99
Outcome variable: Tidal volume/kg (mL/kg)				
Fetal size measures at 30 GW				
Lung volume (mL)	−0.04 (−0.11 to 0.03)	0.24	−0.04 (−0.11 to 0.03)	0.27
Thoracic circumference (cm)	−0.20 (−0.46 to 0.05)	0.12	−0.20 (−0.46 to 0.06)	0.13
Estimated fetal weight (kg)	−1.43 (−3.05 to 0.20)	0.09	−1.37 (−3.02 to 0.28)	0.10
Third trimester fetal growth				
Fetal thoracic growth rate (mm/day)[a]	0.12 (−0.86 to 1.09)	0.81	0.18 (−0.79 to 1.16)	0.71
Fetal weight increase (g/day)[b]	−0.04 (−0.09 to 0.01)	0.12	−0.03 (−0.08 to 0.03)	0.37

Note: All multivariable models were adjusted for infant sex, maternal nicotine use and hypertension in pregnancy.

Abbreviations: GW, gestational weeks; tPTEF/tE, ratio of the time to peak tidal expiratory flow to expiratory time.

[a]In addition to infant sex, maternal nicotine use and hypertension in pregnancy the multivariable model was adjusted for thoracic circumference at 30 GW.

[b]In addition to infant sex and maternal nicotine use and hypertension in pregnancy the multivariable model was adjusted for estimated fetal weight at 30 GW.

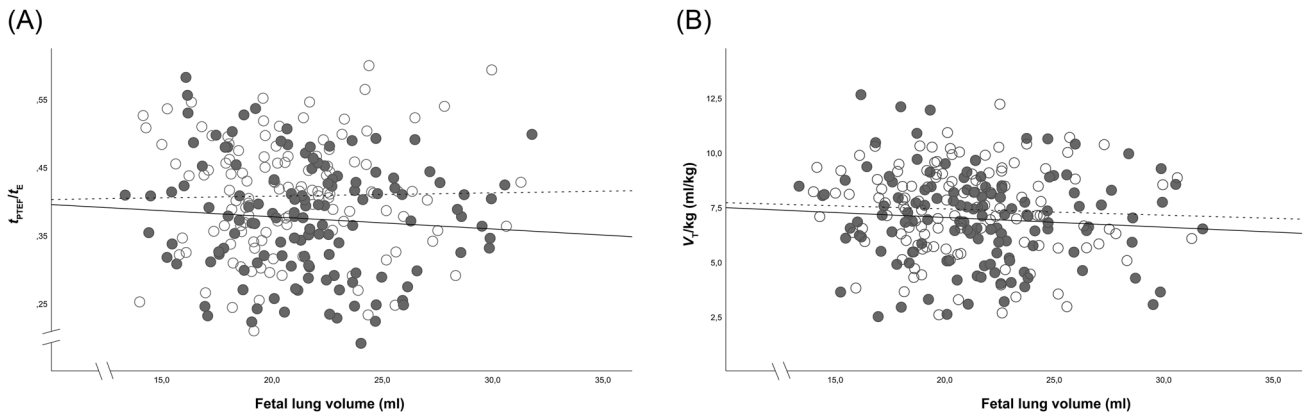

FIGURE 2 Scatterplot of fetal lung volume at 30 gestational weeks and (a) time to peak tidal expiratory flow to expiratory time (t_{PTEF}/t_E) and (b) tidal volume standardized for body weight (V_T/kg) at 3 months of infant age in girls (empty circles and interrupted fit line) and boys (filled circles and full fit line).

Neither fetal size measures at 30 GW (LV, TC, and estimated weight), nor fetal growth measures (thoracic growth and weight increase) were significantly associated with t_{PTEF}/t_E (Table 2 and Figure 2) or with t_{PTEF}/t_E < 25th percentile, corresponding to t_{PTEF}/t_E values below 0.33 (Supporting Information: Table S3). Similarly, no statistically significant associations were observed with V_T/kg (Table 2).

A statistically significant interaction term was shown for fetal thoracic growth rate*infant sex ($p = 0.046$) as well as fetal weight increase*infant sex ($p = 0.03$) in the regression models with t_{PTEF}/t_E < 25th percentile as the outcome (Supporting Information: Figure S1). We observed no statistically significant association between fetal thoracic growth rate or fetal weight increase and

t_{PTEF}/t_E < 25th in analyses stratified for sex (Supporting Information: Table S4). The effect of interaction term fetal weight increase*infant sex was marginally significant in the regression models with V_T/kg as the outcome ($p = 0.05$). In girls, we observed a weak inverse association between fetal weight increase and V_T/kg whereas in boys this association was not significant (Supporting Information: Table S5). The inverse association in girls resulted from the significant correlation between fetal weight increase and infant weight at lung function measurement while fetal weight increase and V_T were in girls, contrary to boys, not correlated (Supporting Information: Figure S2).

After excluding the 26 infants with birthweight below the 10th percentile or the three preterm born infants, no significant associations between the exposure variables and the main outcome variables were observed (results not shown).

4 | DISCUSSION

In this exploratory study including 257 infants from a Scandinavian, general population-based birth cohort, third trimester fetal LV, TC and estimated weight were not associated with t_{PTEF}/t_E or V_T/kg at 3 months of age. Similarly, we found no association between third trimester fetal thoracic growth or weight increase with infant lung function. The only exception was a weak negative association between fetal weight increase and V_T/kg in girls.

A recently published study from the PreventADALL cohort, including 851 infants,[14] demonstrated a weak, inverse association between mid-pregnancy fetal TC relative to femur length, but not relative to head or abdominal circumference, and infant t_{PTEF}/t_E at 3 months of age. A weak positive association between TC and V_T was also observed. There are substantial differences between this and the present study. First, TC in the present study was measured by a single operator, during a considerably shorter period of pregnancy. Second, our main exposure was TC alone and not as a ratio including other fetal measures. We thereby concentrated solely on the associations of TC and lung function. Most importantly, these two studies were performed at two different stages of fetal lung development. The relationship between general fetal size, not including specific measures of lung or thoracic size, and lung function in childhood has been investigated in several general birth cohort studies.[9–12,33] In a cohort of 1924 participants, using retrospectively collected ultrasound measures, larger fetal crown-rump length in the first trimester, as well as larger biparietal diameter in the second trimester, were associated with higher lung function values at 5 and 10 years of age.[9,10] Another study observed that femur length (used as a proxy for fetal length) in the third trimester and larger fetal weight in the second and third trimester were associated with lower airway resistance at the age of 6 years.[11] In a later study from the same birth cohort, second and third trimester fetal weight, but not length, were positively associated with spirometry measures at 10 years of age.[12] Direct comparison between these and our study is difficult due to different methodology and age at the lung function assessment. We are not aware of previous studies investigating the relationship between fetal LV and lung function. One study in 80 neonates born at term by elective cesarean section after uncomplicated pregnancies reported significantly smaller fetal LV, measured on the day of delivery, in neonates that developed respiratory distress syndrome compared to those who did not.[34] Although respiratory distress may indicate lower lung function, substantial methodological differences make this study not comparable with ours.

Few studies have explored the associations between fetal growth and postnatal lung function. We are however not aware of any previous study investigating associations between fetal thoracic growth and lung function in infancy or childhood. A study from the Generation R birth cohort, including more than 5000 infants,[12] explored associations between fetal weight and length growth and lung function measures at 10 years of age. In that study, if not adjusted for postnatal growth, restricted fetal weight growth from second trimester to birth, was not associated with lung function. On the other hand, accelerated fetal weight growth was associated with higher forced vital capacity (FVC) and a lower forced expiratory volume in one second/FVC ratio. In another study from the same cohort, at the age of 6 years children with higher airway resistance were found to have reduced fetal weight and length growth from second trimester to birth.[11] Associations between reduced fetal growth and lower lung function were also observed in the studies from the Aberdeen cohort, focusing on fetal growth in the first and second trimester. Children with persistent low fetal growth, having smaller size at both the first and the second trimester, had lower FVC at the age of 5 and 10 years, compared to children with persistent high fetal growth.[9,10] In the present study, we did not observe an association between fetal weight increase and infant lung function measures except for analyses stratified for sex. These showed a weak inverse association between fetal weight increase in girls and V_T/kg. Postnatally, LV in boys is larger than in girls, containing more respiratory bronchioles.[35] We therefore assume that smaller LV in girls combined with higher body weight in boys could account for the different results in the two sex groups.

Different potential mechanisms might impact the early origins of lung development, including antenatal growth, genetic, immunological and nutritional factors as well as exposure to environmental toxins and nicotine in utero.[36] Tidal breathing represents composite measurements of lung function related to the airway size, which might represent the lung size, as well as factors related to lung compliance and neural control of the respiratory muscles.[37] Lung function testing in older children, with a possibility to assess forced expiratory flow parameters, might be more sensitive to detect milder variations in lung function compared to the methods using tidal breathing. The age at lung function measurement might also be important, as more marked associations have been described in older[9] than in younger children.[10] Our secondary analyses pointed to possible sex differences in the associations between fetal factors and infant lung function, in line with previous findings of structural and functional differences in lung and airway development between girls and boys.[29] However, the associations in the present study were

weak and mostly not statistically significant. We are therefore uncertain of their clinical relevance.

Major strength and novelty of the study are prospectively collected ultrasound measurements at 30 GW, including specific lung and thoracic measures, by one dedicated and experienced operator. All ultrasound measurements were obtained within a short interval of two GW, resulting in an almost equal gestational age for all examinations.[3] Lung function measurements were performed in the awake state in a large population of healthy infants, and they were analyzed according to prestandardized criteria.[24] There are possible limitations of our study. In early infancy we use tidal breathing measurements rather than spirometry, as this was one of few available methods for epidemiological studies, rather than spirometry, which is more commonly used from school age. In two large cohorts of presumably healthy infants tidal breathing method was sufficiently sensitive to identify the associations between intrauterine exposure to maternal smoking and infant lung function.[5,6] Furthermore, in a randomized trial the TFV method demonstrated a beneficial effect on infant lung function by vitamin C supplementation to pregnant women who smoked during the pregnancy.[19] Overall, we therefore believe the lack of significant associations in the present study is unlikely to be a result of the method of lung function assessment. There are no clear cut-off values for low t_{PTEF}/t_E, but we argue that when exploring early origins of health and disease, we look for trends within the normal population, supporting that associations with the lower range of t_{PTEF}/t_E may be important. Our study population had a high prevalence of urban and highly educated women, with the majority (over 90%) born in the Nordic countries, which may limit the generalizability of our results.

For future investigations of early origins of lung function, we suggest exploring the associations between fetal LV, TC as well as fetal growth measures with lung function in older children.

5 | CONCLUSION

In our study population of healthy infants, we found no evidence of associations between fetal third trimester LV, TC, and thoracic growth rate with lung function at 3 months of age. There might be a sex dependent association between fetal weight increase and lung function. To increase knowledge of early origins of childhood lung disease, future studies should investigate the associations between fetal lung and thoracic measures and lung function as well as respiratory symptoms in older children.

AUTHOR CONTRIBUTIONS

Katarina Hilde: Conceptualization; investigation; writing—original draft; methodology; validation; visualization; writing—review and editing; formal analysis. **Hrefna Katrín Gudmundsdóttir**: Investigation; validation; methodology; writing—review and editing; data curation. **Karen Eline S. Bains**: Investigation; validation; writing—review and editing; data curation. **Karin C. Lødrup Carlsen**: Investigation; validation; writing—review and editing; data curation. **Martin Färdig**: Investigation; validation; writing—review and editing; data curation. **Christine M. Jonassen**: Project administration; writing—review and editing. **Ina kreyberg**: investigation; validation; writing—review and editing. **Marissa LeBlanc**: Methodology; writing—review and editing; supervision. björn nordlund: conceptualization; funding acquisition; project administration; writing—review and editing. **Eva Maria Rehbinder**: Investigation; writing—review and editing; validation; project administration. **Marie Cecilie Paasche Roland**: Methodology; writing—review and editing; supervision. **Håvard O. Skjerven**: Project administration; writing—review and editing. **Anne Cathrine Staff**: Project administration; writing—review and editing; conceptualization. **Riyas Vettukattil**: Writing—review and editing; data curation; software; validation. **Guttorm Haugen**: Methodology; validation; funding acquisition; writing—review and editing; supervision; project administration; conceptualization.

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CONFLICTS OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data supporting this study may be provided by the corresponding author upon reasonable request.

ETHICS STATEMENT

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 was registered at ClinicalTrials.gov (number NCT02449850). Informed consent was signed by the pregnant women at enrollment and by both parents at newborn inclusion.

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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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