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Fetal thoracic circumference in mid-pregnancy and infant lung function

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Abstract

Background and Aim: Impaired lung function in early infancy is associated with later wheeze and asthma, while fetal thoracic circumference (TC) predicts severity of neonatal lung hypoplasia. Exploring fetal origins of lung function in infancy, we aimed to determine if fetal TC in mid-pregnancy was associated with infant lung function.

Methods: From the prospective Scandinavian general population-based PreventA-DALL mother–child birth cohort, all 851 3-month-old infants with tidal flow-volume measurements in the awake state and ultrasound fetal size measures at 18 (min–max 16–22) weeks gestational age were included. Associations between fetal TC and time to peak tidal expiratory flow to expiratory time (t_{PTEF}/t_E) were analyzed in linear regression models. To account for gestational age variation, we adjusted TC for simultaneously measured general fetal size, by head circumference (TC/HC), abdominal circumference (TC/AC), and femur length (TC/FL). Multivariable models

were adjusted for maternal age, maternal asthma, pre-pregnancy body mass index, parity, nicotine exposure in utero, and infant sex.

Results: The infants (47.8% girls) were born at mean (SD) gestational age of 40.2 (1.30) weeks. The mean (SD) t_{PTEF}/t_E was 0.39 (0.08). The mean (SD) TC/HC was 0.75 (0.04), TC/AC 0.87 (0.04), and TC/FL 4.17 (0.26), respectively. Neither TC/HC nor TC/AC were associated with infant t_{PTEF}/t_E while a week inverse association was observed between TC/FL and t_{PTEF}/t_E ($\hat{\beta}$ = −0.03, 95% confidence interval [−0.05, −0.007], p = 0.01).

Conclusion: Mid-pregnancy fetal TC adjusted for fetal head or abdominal size was not associated with t_{PTEF}/t_E in healthy, awake 3-month-old infants, while a weak association was observed adjusting for fetal femur length.

KEYWORDS

femur length, fetal size, infant lung function, infant sex, pregnancy, PreventADALL, respiratory function test, thoracic circumference, tidal breathing, t_{PTEF}/t_E, tidal flow-volume loops, tidal volume, ultrasound

1 | INTRODUCTION

Impaired lung function in infancy predicts lower lung function values later in life[1–4] and is associated with an increased risk of wheeze and asthma,[3,5–7] indicating in utero origins of aberrant lung function development.

Lung development starts with lung budding in the fourth week of fetal life.[8,9] At 22–24 weeks' gestational age (GA), alveolar ducts with small amount of surfactant make gas exchange possible.[10] As the alveoli grow in size and number, the lung volume and function increase until a peak in early adulthood.[8,9]

Lung function can be measured from birth, both in the awake and sleeping state, by tidal flow-volume (TFV) loops. The TFV ratio of time to peak tidal expiratory flow to expiratory time (t_{PTEF}/t_E) correlates with forced exhalation outcomes that usually require sedation in infants,[7,11,12] making TFV loops a suitable measure of infant lung function. Exposure to maternal smoking in utero[13,14] and a family history of asthma[13,15] increase the risk of low t_{PTEF}/t_E, and t_{PTEF}/t_E values in the lower range are associated with airway hyper-responsiveness and asthma.[1,7,16] Infant boys tend to have lower t_{PTEF}/t_E than girls,[9,17] but no clear cutoff value of t_{PTEF}/t_E indicates impaired lung function.

Lower tidal volume (V_T) in infancy is associated with prematurity[18] and with more severe outcome in infants with lung hypoplasia.[19] While infant t_{PTEF}/t_E values decrease during the first weeks of life, tidal volume (V_T) increases with age.[20]

Fetal size and growth trajectories have been associated with respiratory health.[21] In a British cohort from the general population, children who in fetal life had large first-trimester crown-rump-length, had higher lung function values at 5 and 10 years of age, as well as lower risk of wheeze and asthma.[22,23]

Fetal thoracic circumference (TC) measured by ultrasound indicates fetal lung size.[24] Fetal TC, particularly in relation to abdominal circumference (AC), as the TC/AC ratio, predicts postnatal outcome in pregnancies with increased risk of neonatal lung hypoplasia and is important for prenatal diagnosis of this disease.[25–27] In older children and adults, TC has been positively related to lung function.[28,29]

We hypothesize that fetal TC may be positively associated with infant lung function and we are not aware of previous studies relating fetal TC and future lung function in healthy infants.

The aim of this study was to determine if mid-pregnancy fetal TC was associated with infant lung function, primarily measured as t_{PTEF}/t_E and secondarily as V_T at 3 months of age, and if these potential associations differ by sex.

2 | MATERIAL AND METHODS

2.1 | Study design and setting

Three-month-old infants with available measurements of lung function as well as ultrasound information on mid-pregnancy fetal size, in the prospective general population-based mother–child birth cohort Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL),[30] were included in the present study (Figure 1). Briefly, 2394 infants were antenatally recruited to the PreventADALL study in relation to the routine ultrasound examination at approximately 18 (range 15.7–22.7) gestational weeks in Oslo and the county of Østfold, Norway, and Stockholm, Sweden. Healthy singletons and twins, born from April 2015 to April 2017 at GA of at least 35 weeks, were included at birth and the first follow-up after birth was at 3 months of age. To ensure independence of all participants, the second twin of all twin pairs was consequently excluded from the present study.
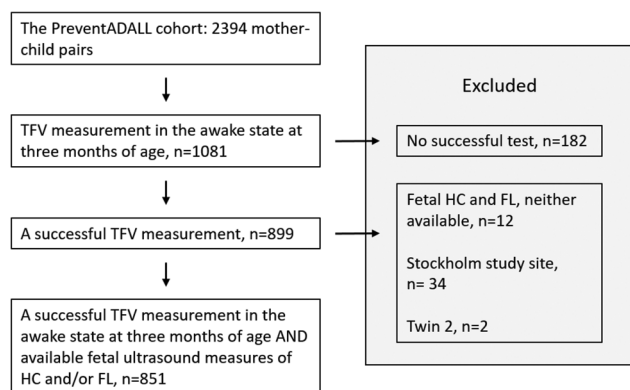
FIGURE 1 Study population. From the PreventADALL mother–child birth cohort, all 851 infants from the Oslo study site with available tidal flow-volume (TFV) measurement in the awake state at 3 months of age as well as mid-pregnancy ultrasound measurements of fetal head circumference (HC) and/or femur length (FL) were included. To ensure independence of all participants, twin 2 was consequently excluded.

Both parents signed an informed consent and the study was approved by the Regional Committee for Medical and Health Research Ethics in Norway (2014/518) and in Sweden (2014/2242-31/4) and registered at clinicaltrial.gov, NCT02449850.

2.2 | Participants

All 851 infants that had TFV measured in the awake state at 3 months of age and available mid-pregnancy ultrasound measures including fetal head circumference (HC) and/or femur length (FL) were recruited in Oslo, the only PreventADALL study site measuring both TFV and fetal TC. The infants included in the present study were similar to the remaining 1543 infants in the PreventADALL cohort, except for somewhat higher frequency of breastfeeding at 3 months of age and fewer being exposed to nicotine beyond the first weeks of fetal life (Supporting Information: Table 1). Compared to the remaining infants, the mothers of included infants were older, had lower pre-pregnancy body mass index (BMI), and were more often nulliparous and highly educated, in line with previously described study site differences in the PreventADALL study.[30]

2.3 | Methods

The ultrasound examination at approximately 18 weeks' GA was performed by specifically trained midwives at the participating hospitals, including HC, AC, and FL as routine measurements of general fetal size. TC was measured by tracing the bony thorax in the axial plane at the level of the four-chamber view of the heart, using an ellipse along the ribs. One fetal medicine obstetrician trained all midwives measuring TC and ensured the quality of random samples of measurements.

Tidal flow-volume (TFV) loops were obtained by trained study personnel at the 3-month follow-up.[31] Using the Eco Medics Exhalyzer® D equipment, TFV loops were collected while the infant was calm, in a supine position on caregivers' lap or in a stroller/bed. The ultrasonic flow head was connected to an appropriately sized face mask with a dead space reducer, a filtering spirette, and a CO_2 adapter with capnostat in between. The mask was placed tightly over the infant's nose and mouth to avoid air leakage. After completion of all 3-month visits, the TFV loops were visually evaluated with focus on shape and reproducibility, and technically successful loops were selected for analysis.

The mothers answered detailed electronic questionnaires on socio-economy, lifestyle, and health, both during pregnancy and 3 months postpartum. Study personnel registered information about the delivery and the newborn infant from hospital registries, as well as infant weight and length at the 3-month follow-up, measured according to the study protocol.

2.4 | Variables

Primary outcome: The t_{PTEF}/t_E ratio as a continuous variable, and partitioned at four different cutoff values, <0.25 and below the 10th (<0.28), 25th (<0.34), and 50th (<0.39) percentiles, to identify infants with lung function in the lower ranges. See Supporting Information for further information.

Secondary outcomes: V_T and V_T adjusted for infant weight in kg (V_T/kg).

Exposures: Fetal TC, relative to fetal HC (TC/HC), AC (TC/AC), and FL (TC/FL).

Covariates: Maternal age, maternal asthma, pre-pregnancy BMI and parity as well as infant sex and in-utero exposure to nicotine were found potentially relevant for analyzing the effect of fetal size on infant t_{PTEF}/t_E, identified using a Directed Acyclic Graph (DAG)[32] before statistical analyses (Supporting Information: Figure 1). To be considered as confounders of the association between fetal TC and infant lung function, variables had to potentially affect both the exposure and the outcome (Supporting Information).

All reported measures of fetal size were measured at the same ultrasound examination in mid-pregnancy, the routine second-trimester ultrasound at approximately 18 gestational weeks. This ultrasound examination also serves as the scan used for setting the date of pregnancy, with GA estimated by fetal HC[33,34] according to the clinical routines of our institution. GA estimated by FL is assumed to be equally reliable at mid-pregnancy while it is less influenced by fetal sex.[35] Simultaneously measured, the measures of fetal size are strongly correlated (Supporting Information: Table 2), and therefore, we could not build regression models with TC alone as the main exposure, adjusting for GA at the time of ultrasound, based on either HC or FL, as a covariate. Instead, we choose to explore TC in relation to general fetal size measures, using the TC/HC, TC/AC, and TC/FL ratios as our exposures, where both TC/HC and TC/FL can be regarded as a proxy for TC adjusted for GA.

2.5 | Statistical analysis

Continuous variables are presented as means with minimum–maximum (min–max) values, standard deviation (SD), or 95% confidence intervals (95% CIs). Categorical variables are presented as counts and percentages.

Associations between the fetal TC ratios and infant lung function were analyzed with linear regression and are presented with regression coefficients (β estimate ($\hat{\beta}$)), 95% CIs, and p values. For dichotomous outcomes, we used logistic regression models, presented with odds ratios (ORs), 95% CIs, and p values. Pearson correlation was used to evaluate the relationship between continuous variables, and R^2 describes the percentage of variability explained by the particular exposure. Supplementary analyses were performed to explore if potential associations between the fetal TC ratios and the continuous lung function outcomes were different when preterm infants (born with GA of 35.0–36.9 weeks) were excluded.

As both fetal size measures and infant lung function have been shown to differ between girls and boys, possible associations between fetal size and infant's lung function were stratified for sex. Differences between the included girls and boys were tested with the independent sample t-test. p values <0.05 were regarded as significant.

IBM SPSS statistics version 27, RStudio version 4.0.3, and Microsoft Excel 2016 were used for statistical analyses.

3 | RESULTS

The 851 infants (47.8% girls) were born at a mean (min–max) GA of 40.2 (35.0–42.4) weeks with a mean (min–max) birth weight of 3.6 (1.9–4.9) kg (Table 1). The mean (min–max) GA at the time of ultrasound examination was 18.7 (16.3–22.1) weeks. At the 3-month follow-up, their mean (min–max) age was 93 (74–131) days, weight was 6.3 (4.4–8.9) kg, and length was 61.9 (55.5–70.9) cm.

The mean (SD) t_{PTEF}/t_E was 0.39 (0.08), the 10th percentile was 0.28, while $t_{PTEF}/t_E < 0.25$ was observed in 46 infants (5.4%). The mean (SD) number of TFV loops per infant was 22 (14). Fetal size proportions and correlations in mid-pregnancy are described in Supporting Information: Table 2 and fetal size measurements for girls and boys separately in Supporting Information: Table 3.

Fetal TC relative to head (TC/HC) and abdominal (TC/AC) circumferences were not significantly associated with infant t_{PTEF}/t_E, neither in univariable models nor when adjusted for maternal age, maternal asthma, pre-pregnancy BMI, parity, infant sex and in-utero exposure to nicotine (Tables 2a,b). However, we observed a weak, but significant inverse association between TC relative to fetal femur length (TC/FL) and t_{PTEF}/t_E as a continuous outcome, as well as with t_{PTEF}/t_E below the 10th, 25th, and 50th percentiles, both in univariable and adjusted models (Figure 2, Table 2c).

TABLE 1 Baseline characteristics of the 851 infants included in the present study

Background characteristics	n	Count (%) or mean (SD)
Infant characteristics		
Female	851	407 (47.8)
Age in days (3 months)	851	93 (7)
GA at birth (weeks)	838	40.2 (1.3)
Born with GA <37.0 weeks	838	16 (1.9)
Weight at 3 months (kg)	847	6.3 (0.8)
Length at 3 months (cm)	838	61.9 (2.2)
Birth weight (kg)	849	3.6 (0.5)
Placenta weight (g)	824	668 (131)
BW/PW ratio	823	5.5 (1.0)
Caesarian birth	851	137 (16.1)
Breastfeeding at 3 months of age[a]	742	709 (95.6)
Respiratory distress or cough since birth	742	
No		701 (94.5)
Yes, once		30 (4.0)
Yes, more than once		11 (1.5)
Fetal measures (mid-pregnancy)		
GA at ultrasound, based on HC (weeks)	848	18.7 (0.8)
HC (mm)	848	157.2 (10.1)
TC (mm)	727	117.5 (9.3)
AC (mm)	846	135.1 (10.4)
FL (mm)	846	28.2 (2.6)
Maternal characteristics		
Age in years	851	33.0 (3.9)
Parity (previous deliveries)	851	
Nullipara		542 (63.7)
Pre-gestational BMI (kg/m^2)	831	22.8 (3.2)
Hypertensive disorders of pregnancy	848	71 (8.4)
Any use of nicotine in pregnancy (smoking and/or snus)	851	87 (10.2)
Smoking in pregnancy	851	27 (3.2)
Current smoking at 18 weeks GA	851	1 (0.1)
Snus in pregnancy	851	61 (7.2)
Current snus at 18 weeks GA	851	0 (0)
Family history of asthma,[b] no. (%)		
Maternal asthma	770	132 (17.1)
Paternal asthma	775	104 (13.4)

TABLE 1 (Continued)

Background characteristics	n	Included infants (n = 851) Count (%) or mean (SD)
Sociodemographic factors, no. (%)		
Education	767	
High school only or less		39 (5.1)
Higher education <4 years		205 (26.7)
Higher education ≥4 years		503 (65.6)
PhD		20 (2.6)
Country of origin – mother	770	
Norway		677 (87.9)
Sweden		22 (2.9)
Other Nordic		6 (0.8)
Rest of the world		65 (8.4)

Abbreviations: AC, abdominal circumference; BMI, body mass index; BW/PW ratio, birth weight to placenta weight ratio; FL, femur length; GA, gestational age; HC, head circumference; n, number; SD, standard deviation; TC, thoracic circumference.

[a]Partly or exclusively breastfed at 3 months of age.

[b]Doctor diagnosed asthma.

Fetal TC/HC and TC/FL were positively associated with infant V_T, while no association was observed between TC/AC and V_T (Table 3). The association between TC/HC and V_T was only significant when adjusted for relevant covariates, while TC/FL was significantly associated with V_T in both univariable and adjusted regression analyses. No significant associations were observed between the fetal TC ratios and V_T/kg.

As shown in Supporting Information: Table 4, the positive association between both fetal TC/HC and TC/FL and infant V_T became stronger when preterm infants (i.e., GA at birth 35.0–36.9 weeks) were excluded, while the weak inverse association between TC/FL and t_{PTEF}/t_E remained similar (results not shown).

Fetal TC/HC and infant t_{PTEF}/t_E were significantly higher in girls than boys, while TC/AC and TC/FL were similar in both sexes (Supporting Information: Table 5). Infant sex was weakly ($R^2 = 0.007$) but significantly associated with continuous t_{PTEF}/t_E in univariable regression ($\hat{\beta} = 0.014$, 95% CI [0.003, 0.03], $p = 0.016$), while no significant effect of infant sex was observed on the associations between the fetal TC ratios and t_{PTEF}/t_E (results not shown). When stratified for sex, the weak inverse association observed between TC/FL and t_{PTEF}/t_E remained significant among girls, although only in the univariable model, with R^2 for the adjusted model being higher in girls than in boys (Table 4).

The mean V_T at 3 months of age was higher in boys, while girls had significantly higher V_T/kg (Supporting Information: Table 5). Adjusting for infant sex had a significant impact on the association between TC/HC and V_T, and the significant association between TC/FL and V_T became somewhat stronger when infant sex was included in the model (Table 3). No significant association was observed between the fetal TC ratios and V_T or V_T/kg when stratified for sex (not shown).

4 | DISCUSSION

In healthy 3-month-old infants, no significant association was observed between mid-pregnancy fetal TC relative to head and abdominal circumferences and the t_{PTEF}/t_E ratio, while a weak inverse association between fetal TC relative to femur length and t_{PTEF}/t_E was observed. The associations between the fetal TC ratios and t_{PTEF}/t_E were similar in girls and boys. Fetal TC relative to head circumference and femur length, but not relative to abdominal circumference, were weakly associated with tidal volume at 3 months of age, while no association between the fetal TC ratios and V_T/kg was observed.

The lack of association between the mid-pregnancy fetal ratios of thoracic relative to head and abdominal circumferences and infant t_{PTEF}/t_E at 3 months of age, as well as the weak inverse association between fetal TC relative to FL and infant t_{PTEF}/t_E, are to the best of our knowledge novel findings. However, a positive correlation between TC and lung function, measured simultaneously, has been reported both in preschool children[29] and in young adults.[28] The observed inverse association between fetal TC/FL and infant t_{PTEF}/t_E implies that fetuses with smaller TC in relation to FL had higher t_{PTEF}/t_E in infancy. Fetal FL is regarded as a proxy for fetal length[36,37] and postnatally, body length predicts lung function.[3,17,28,29] However, we cannot rule out that a smaller TC contributes to the observed association, as TC/FL and t_{PTEF}/t_E appeared to be closer associated than was the case for AC/FL and t_{PTEF}/t_E (Supporting Information: Table 6). Our results are partly in line with those of Turner et al. who found no association between second trimester FL and lung function at 5 or 10 years of age, but a positive association between first-trimester crown-rump length and childhood lung function.[22,23] Similarly, in the Dutch Generation R study, higher estimated fetal weight in the second and third trimesters was associated with higher lung function at 10 years of age, while femur length, used as a proxy for fetal length, was not.[38]

Although the observed association between fetal TC/FL and infant t_{PTEF}/t_E was statistically significant, the R^2 was low, indicating that fetal TC/FL alone only explains 1.0% of the total variation in infant t_{PTEF}/t_E, and 2.3% when adjusted for relevant covariates. It is therefore uncertain if the association observed between fetal TC/FL and infant t_{PTEF}/t_E is of any clinical relevance.

The lack of a clear association between the fetal thoracic size in mid-pregnancy and infant t_{PTEF}/t_E may not be surprising. Fetal TC is a structural measure, previously mostly related to lung volume, while infant t_{PTEF}/t_E is a measure of airway function. Including infants who are generally healthy, limits the possibility to assess the potential impact of aberrant development leading to lung disease. One may therefore speculate that the room for normal variation in lung

TABLE 2 Associations between TC, by (a) TC/HC, (b) TC/AC, and (c) TC/FL, and infant t_{PTEF}/t_E assessed in univariable and multivariable regression models

a)

$t_{PTEF}/t_E \sim$ TC/HC	Univariable regression (n = 726)				Multivariable regression (n = 726)			
	R^2	$\hat{\beta}$	95% CI	p value	R^2	$\hat{\beta}$	95% CI	p value
Continuous t_{PTEF}/t_E	0.002	−0.11	−0.27 to 0.05	0.191	0.017	−0.12	−0.29 to 0.04	0.147
$t_{PTEF}/t_E < 0.25$		−3.53	−11.73 to 4.94	0.407		−3.86	−12.26 to 4.75	0.373
$t_{PTEF}/t_E <$ 10th percentile		−4.05	−10.32 to 2.36	0.212		−4.38	−10.76 to 2.10	0.181
$t_{PTEF}/t_E <$ 25th percentile		−3.30	−7.78 to 1.18	0.148		−3.71	−8.28 to 0.86	0.111
$t_{PTEF}/t_E <$ 50th percentile		−2.58	−6.54 to 1.36	0.201		−2.71	−6.73 to 1.28	0.184

b)

$t_{PTEF}/t_E \sim$ TC/AC	Univariable regression (n = 725)				Multivariable regression (n= 725)			
	R^2	$\hat{\beta}$	95% CI	p value	R^2	$\hat{\beta}$	95% CI	p value
Continuous t_{PTEF}/t_E	0.001	−0.05	−0.19 to 0.08	0.449	0.015	−0.05	−0.19 to 0.09	0.478
$t_{PTEF}/t_E < 0.25$		−1.71	−8.60 to 5.39	0.631		−1.49	−8.42 to 5.60	0.676
$t_{PTEF}/t_E <$ 10th percentile		−3.30	−8.53 to 2.03	0.221		−3.23	−8.53 to 2.15	0.235
$t_{PTEF}/t_E <$ 25th percentile		−2.02	−−5.76 to 1.72	0.288		−1.94	−5.73 to 1.87	0.317
$t_{PTEF}/t_E <$ 50th percentile		−0.87	−4.16 to 2.41	0.604		−0.77	−4.08 to 2.54	0.648

c)

$t_{PTEF}/t_E \sim$ TC/FL	Univariable regression (n= 724)				Multivariable regression (n= 724)			
	R^2	$\hat{\beta}$	95% CI	p value	R^2	$\hat{\beta}$	95% CI	p value
Continuous t_{PTEF}/t_E	0.010	−0.03	−0.06 to −0.01	**0.006**	0.023	−0.03	−0.05 to −0.01	**0.010**
$t_{PTEF}/t_E < 0.25$		−0.75	−1.90 to 0.43	0.210		−0.65	−1.84 to 0.57	0.289
$t_{PTEF}/t_E <$ 10th percentile		−0.99	−1.88 to −0.10	**0.030**		−0.94	−1,84 to −0.03	**0.041**
$t_{PTEF}/t_E <$ 25th percentile		−0.78	−1.41 to −0.15	**0.016**		−0.74	−1.39 to −0.10	**0.024**
$t_{PTEF}/t_E <$ 50th percentile		−0.84	−1.41 to −0.28	**0.004**		−0.81	−1.38 to −0.25	**0.005**

Note: All multivariable models were adjusted for maternal age, maternal asthma, pre-pregnancy BMI, parity, infant sex, and in-utero exposure to nicotine.

Abbreviations: AC, abdominal circumference; CI, confidence interval; FL, femur length; HC, head circumference; R^2, the percentage of variation explained by the exposure(s); TC, thoracic circumference; t_{PTEF}/t_E, the ratio of time to peak tidal expiratory flow to expiratory time; $\hat{\beta}$, the regression coefficient (β estimate).
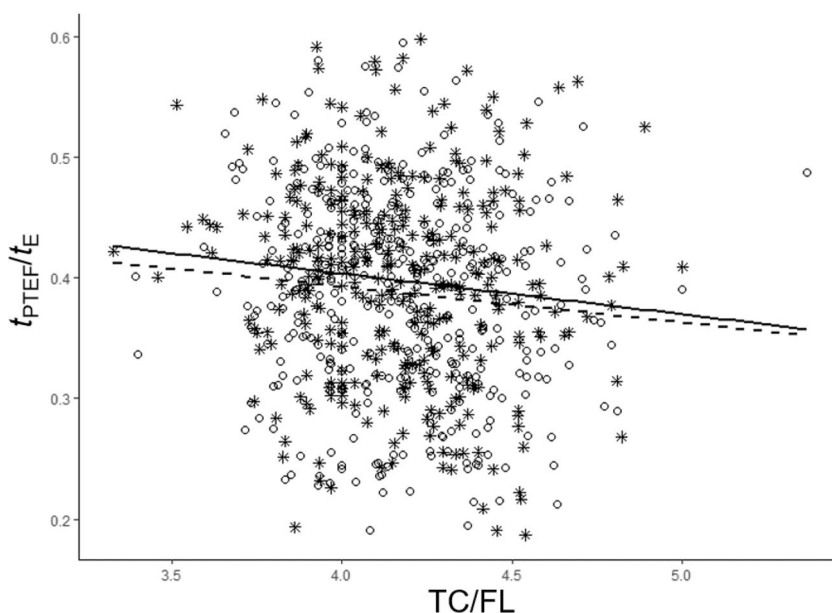
FIGURE 2 The variation in infant t_{PTEF}/t_E in relation to fetal TC/FL ratio. In the unadjusted model, the TC/FL ratio explained 1.0% of the variation in t_{PTEF}/t_E in all infants ($R^2 = 0.010$). R^2 for girls was 0.011 and R^2 for boys was 0.009. TC/FL, fetal thoracic circumference relative to femur length, a proxy for TC adjusted for gestational age at the time of ultrasound; t_{PTEF}/t_E, the ratio of time to peak tidal expiratory flow to expiratory time; Girls are marked with stars triangles and a whole regression line, boys are marked with dots and a broken regression line.

development at this early stage might be limited. The upper airways, together with fetal breathing movements, ensure expansion of the fluid-filled fetal lungs, which is necessary for normal growth and maturation of the lungs,[8,39] while the more rapid growth of respiratory bronchioles and alveoli during the third trimester[9] along with increased fetal general growth may provide greater variation also in fetal thoracic size.[33] It is not clear if third-trimester fetal TC, or TC measured at birth, might potentially have a more pronounced relation with infant lung function.

The positive association between the fetal TC ratios and infant V_T, in line with fetal TC reflecting fetal lung size,[9,24] is to the best of our knowledge a novel finding in healthy infants. Both TC/HC and TC/FL were weakly positively associated with V_T at 3 months of age, while no association was observed between TC/AC and V_T in our cohort. However, the association between fetal TC/AC and postnatal outcome is well documented in neonates with conditions increasing the risk of lung hypoplasia.[25–27] The fetal TC ratios were not associated with V_T adjusted for infant weight (V_T/kg), suggesting that the effect of fetal thoracic size on V_T may be mediated through the weight of the infant.

In supplementary analyses, excluding infants born before 37.0 gestational weeks revealed a somewhat stronger positive association between both TC/HC and TC/FL and V_T, while the weak inverse association between TC/FL and t_{PTEF}/t_E remained similar to when all infants were included, regardless of GA at birth. Shorter time for in-utero development of alveoli,[8] together with a smaller body size, may cause lower V_T in otherwise healthy preterm compared to term infants. Therefore, including both term and preterm infants in the regression models may reduce the visibility of the association between mid-pregnancy fetal thoracic size and infant V_T.

The different associations between the fetal TC ratios and the t_{PTEF}/t_E versus V_T may not be unexpected. Postnatal airway caliber is positively associated with body length[7,40] and our results show that a larger TC relative to HC and FL predicts larger V_T in infancy. Although the effect sizes are small, smaller fetal TC relative to FL might reflect smaller lung size relative to airway caliber, and subsequently somewhat higher t_{PTEF}/t_E in infancy. To further explore our findings suggesting that a smaller fetal TC relative to femur length may be representing relatively larger airway caliber for lung size, resulting in higher flow rates in infancy, even larger cohort studies are needed. Future studies on the PreventADALL cohort may suggest if fetuses with lower TC/FL ratio in mid-pregnancy will have an increased risk of developing obstructive lung diseases in postnatal life.

The association between the fetal TC ratios and infant t_{PTEF}/t_E was similar in girls and boys although, when adjusted for covariates, TC/FL explained more of the total variation in t_{PTEF}/t_E in girls. While the higher TC/HC in girls may largely be explained by their smaller HC compared to boys,[34] mid-pregnancy fetal FL is probably unrelated to sex.[33] As TC relative to AC and FL was similar among both sexes our results suggest a minimal impact of sex on fetal TC. Together with a higher t_{PTEF}/t_E in girls, in line with other studies,[3,4,9,17] the sex-related bias introduced in the TC/HC ratio could possibly weaken a potential inverse association between TC/HC and t_{PTEF}/t_E.

The significantly higher V_T and lower V_T/kg in boys compared to girls, reflecting their larger body size, is in line with other studies.[5,9,18] While both TC/HC and TC/FL were significantly associated with V_T

TABLE 3 Associations between fetal TC, by (a) TC/HC, (b) TC/AC, and (c) TC/FL, and tidal volume, by infant V_T and V_T/kg

a) TC/HC

	n	R^2	$\hat{\beta}$	95% CI	p value
V_T					
Univariable	726	0.004	22.57	−2.49 to 47.63	0.077
+ infant sex		0.016	26.41	1.34–51.47	**0.039**
Multivariable		0.032	26.39	1.34–51.44	**0.039**
V_T/kg					
Univariable	722	0.001	1.80	−2.30 to 5.90	0.389
+ infant sex		0.005	1.45	−2.67 to 5.57	0.489
Multivariable		0.018	1.37	−2.75 to 5.50	0.514

b) TC/AC

	n	R^2	$\hat{\beta}$	95% CI	p value
V_T					
Univariable	725	0.001	10.29	−10.61 to 31.19	0.334
+ infant sex		0.011	11.35	−9.48 to 32.17	0.285
Multivariable		0.027	10.73	−10.07 to 31.53	0.311
V_T/kg					
Univariable	721	<0.001	0.68	−2.74 to 4.11	0.696
+ infant sex		0.004	0.56	−2.86 to 3.99	0.746
Multivariable		0.017	0.43	−3.00 to 3.85	0.807

c) TC/FL

	n	R^2	$\hat{\beta}$	95% CI	p value
V_T					
Univariable	724	0.007	3.95	0.44–7.47	**0.028**
+ infant sex		0.016	3.87	0.37–7.37	**0.030**
Multivariable		0.031	3.56	0.06–7.05	**0.046**
V_T/kg					
Univariable	720	0.001	0.24	−0.33 to 0.82	0.407
+ infant sex		0.006	0.25	−0.32 to 0.83	0.389
Multivariable		0.019	0.23	−0.35 to 0.80	0.440

Note: The association between fetal TC and tidal volume was assessed in univariable models, models only adjusted for infant sex, and multivariable models adjusted for maternal age, maternal asthma, pre-pregnancy BMI, parity, infant sex, and in-utero exposure to nicotine.

Abbreviations: AC, abdominal circumference; CI, confidence interval; FL, femur length; HC, head circumference; n, number of infants included in the respective model, R^2, the percentage of variation explained by the exposure(s); TC, thoracic circumference; V_T, tidal volume; $\hat{\beta}$, the regression coefficient (β estimate).

TABLE 4 The association between mid-pregnancy fetal TC, by TC/HC (n = 726), TC/AC (n = 725), and TC/FL (n = 724), and infant t_{PTEF}/t_E in girls and boys separately

	Girls					Boys				
	n	R^2	$\hat{\beta}$	95% CI	p value	n	R^2	$\hat{\beta}$	95% CI	p value
$t_{PTEF}/t_E \sim$ TC/HC										
Univariable	344	0.005	−0.17	−0.41 to 0.08	0.178	382	0.002	−0.09	−0.31 to 0.13	0.426
Multivariable		0.038	−0.17	−0.42 to 0.08	0.185		0.017	−0.09	−0.32 to 0.13	0.422
$t_{PTEF}/t_E \sim$ TC/AC										
Univariable	344	<0.001	−0.004	−0.20 to 0.19	0.965	381	0.003	−0.10	−0.29 to 0.08	0.267
Multivariable		0.033	−0.001	−0.20 to 0.20	0.989		0.019	−0.10	−0.29 to 0.09	0.277
$t_{PTEF}/t_E \sim$ TC/FL										
Univariable	343	0.011	−0.03	−0.07 to −0.00	**0.048**	381	0.009	−0.03	−0.06 to 0.00	0.063
Multivariable		0.045	−0.03	−0.07 to −0.00	0.058		0.023	−0.03	−0.06 to 0.01	0.105

Note: All multivariable models were adjusted for maternal age, maternal asthma, pre-pregnancy BMI, parity, infant sex, and in-utero exposure to nicotine. Abbreviations: AC, abdominal circumference; CI, confidence interval; FL, femur length; HC, head circumference; n, number; R^2, the percentage of variation explained by the exposure(s); TC, thoracic circumference; t_{PTEF}/t_E, the ratio of time to peak tidal expiratory flow to expiratory time; $\hat{\beta}$, the regression coefficient (β estimate).

when adjusted for sex, no association was observed when analyzed in girls and boys separately, possibly explained by reduced power.

Higher t_{PTEF}/t_E and V_T/kg in girls are likely to reflect sex differences in fetal lung and airway development. Previous studies have shown larger lung volumes and more respiratory bronchioles at birth in boys, preparing for their generally larger thoracic size in adulthood, while surfactant production matures earlier in girls, enhancing small airway patency.[9] Relatively larger airways for lung size result in higher flow rates in girls compared to boys[6,9,17] and although the TC/FL ratio explained more of the total variation in t_{PTEF}/t_E in girls compared to boys, our study population was too small to conclude on potentially different associations between fetal thoracic size and lung function in girls and boys separately.

4.1 | Strengths and limitations

A prospective design and the large group of healthy infants with comprehensive information on mid-pregnancy fetal size and awake-state lung function measurements are among the strengths of our study. Although few participants were of non-Scandinavian origin and some maternal characteristics were related to the study site, we believe that our findings are representative for the general population, possibly limited to Caucasians. One fetal medicine obstetrician trained all midwives in measuring fetal TC and lung function measurements were analyzed according to pre-standardized criteria.

First-trimester ultrasound was not a routine examination in Norway at the time of recruitment and the determination of GA by second-trimester biometric measures only, is a limitation of the study. Differently determined GA has been suggested as an explanation of inconsistent results on associations between fetal biometric measurements and respiratory outcomes.[41] As our participants at large

were healthy very few infants had low t_{PTEF}/t_E values, having excluded severe fetal and/or neonatal disease and preterm birth before 35.0 gestational weeks due to exclusion criteria of the PreventADALL study. This limits the possibility to identify potential associations between fetal size and lung function during aberrant lung development involving early lung or airway pathology. On the other hand, the present study focused on exploring possible associations between lung and airway development among presumably healthy infants. As several exposures representing fetal size and outcomes reflecting infant lung function were included in our regression models, not correcting for multiple testing may also be a limitation.

5 | CONCLUSION

Mid-pregnancy fetal TC adjusted for fetal head or abdominal size was not associated with infant t_{PTEF}/t_E in healthy awake infants at 3 months of age, while a weak inverse association between fetal TC/FL and t_{PTEF}/t_E was observed. Fetal TC relative to HC and FL was positively associated with V_T, probably mediated through infant weight, as the TC ratios were not associated with V_T/kg. The association between fetal thoracic size and lung function was largely similar among girls and boys.

AUTHOR CONTRIBUTIONS
Hrefna K. Gudmundsdóttir: Conceptualization, investigation, writing—original draft, methodology, visualization, writing—review & editing, formal analysis, data curation. **Katarina Hilde**: Writing—review & editing, methodology, vsualization. **Karen E. S. Bains**: Investigation, writing—review & editing, data curation. **Martin Färdig**: Investigation, writing—review & editing, data curation. **Guttorm Haugen:**

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REFERENCES

1. Haland G, Carlsen KC, Sandvik L, et al. Reduced lung function at birth and the risk of asthma at 10 years of age. *N Engl J Med*. 2006;355(16):1682-1689.
2. den Dekker HT, Sonnenschein-van der Voort A, de Jongste JC, et al. Early growth characteristics and the risk of reduced lung function and asthma: a meta-analysis of 25,000 children. *J Allergy Clin Immunol*. 2016;137(4):1026-1035.
3. Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet*. 2007;370(9589):758-764.
4. Turner S, Fielding S, Mullane D, et al. A longitudinal study of lung function from 1 month to 18 years of age. *Thorax*. 2014;69(11):1015-1020.
5. Dezateux C, Stocks J, Dundas I, Fletcher ME. Impaired airway function and wheezing in infancy: the influence of maternal smoking and a genetic predisposition to asthma. *Am J Respir Crit Care Med*. 1999;159(2):403-410.
6. Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig LM. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med*. 1988;319(17):1112-1117.
7. Guerra S, Lombardi E, Stern DA, et al. Fetal origins of asthma: A longitudinal study from birth to age 36 years. *Am J Respir Crit Care Med*. 2020;202(12):1646-1655.
8. Stocks J, Hislop A, Sonnappa S. Early lung development: lifelong effect on respiratory health and disease. *Lancet Respir Med*. 2013;1(9):728-742.
9. Boezen HM, Jansen DF, Postma DS. Sex and gender differences in lung development and their clinical significance. *Clin Chest Med*. 2004;25(2):237-245.
10. Schittny JC. Development of the lung. *Cell Tissue Res*. 2017;367(3):427-444.
11. Morris MJ, Lane DJ. Tidal expiratory flow patterns in airflow obstruction. *Thorax*. 1981;36(2):135-142.
12. Hevroni A, Goldman A, Blank-Brachfeld M, Abu Ahmad W, Ben-Dov L, Springer C. Use of tidal breathing curves for evaluating expiratory airway obstruction in infants. *J Asthma*. 2018;55(12):1331-1337.
13. Stick SM, Burton PR, Gurrin L, Sly PD, LeSouëf PN. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. *Lancet*. 1996;348(9034):1060-1064.
14. Lødrup Carlsen KC, Jaakkola JJ, Nafstad P, Carlsen KH. In utero exposure to cigarette smoking influences lung function at birth. *Eur Respir J*. 1997;10(8):1774-1779.
15. de Gouveia Belinelo P, Collison AM, Murphy VE, et al. Maternal asthma is associated with reduced lung function in male infants in a combined analysis of the BLT and BILD cohorts. *Thorax*. 2021;76(10):996-1001.
16. Young S, Arnott J, Le Souef PN, Landau LI. Flow limitation during tidal expiration in symptom-free infants and the subsequent development of asthma. *J Pediatr*. 1994;124(5 Pt 1):681-688.
17. Gray D, Willemse L, Visagie A, et al. Determinants of early-life lung function in African infants. *Thorax*. 2017;72(5):445-450.
18. Beretta F, Lavizzari A, Pesenti N, et al. Effect of human milk and other neonatal variables on lung function at three months corrected age. *Pediatr Pulmonol*. 2021;56(12):3832-3838.
19. Mank A, Carrasco Carrasco C, Thio M, et al. Tidal volumes at birth as predictor for adverse outcome in congenital diaphragmatic hernia. *Arch Dis Child Fetal Neonatal Ed*. 2020;105(3):248-252.
20. Anık A, Öztürk S, Erge D, Akcan AB, Türkmen MK, Uysal P. Tidal breath in healthy term newborns: an analysis from the 2nd to the 30th days of life. *Pediatr Pulmonol*. 2021;56(1):274-282.
21. Pike KC, Crozier SR, Lucas JSA, et al. Patterns of fetal and infant growth are related to atopy and wheezing disorders at age 3 years. *Thorax*. 2010;65(12):1099-1106.
22. Turner S, Prabhu N, Danielan P, et al. First- and second-trimester fetal size and asthma outcomes at age 10 years. *Am J Respir Crit Care Med*. 2011;184(4):407-413.
23. Turner SW, Campbell D, Smith N, et al. Associations between fetal size, maternal {alpha}-tocopherol and childhood asthma. *Thorax*. 2010;65(5):391-397.
24. Britto IS, Tedesco GD, Herbst SR, et al. New anatomical landmarks to study the relationship between fetal lung area and thoracic circumference by three-dimensional ultrasonography. *J Matern Fetal Neonatal Med*. 2012;25(10):1927-1932.
25. Yoshimura S, Masuzaki H, Gotoh H, Fukuda H, Ishimaru T. Ultrasonographic prediction of lethal pulmonary hypoplasia: comparison of eight different ultrasonographic parameters. *Am J Obstet Gynecol*. 1996;175(2):477-483.
26. Laudy JA, Tibboel D, Robben SG, de Krijger RR, de Ridder MA, Wladimiroff JW. Prenatal prediction of pulmonary hypoplasia: clinical, biometric, and Doppler velocity correlates. *Pediatrics*. 2002;109(2):250-258.
27. Johnson A, Callan NA, Bhutani VK, Colmorgen GH, Weiner S, Bolognese RJ. Ultrasonic ratio of fetal thoracic to abdominal circumference: an association with fetal pulmonary hypoplasia. *Am J Obstet Gynecol*. 1987;157(3):764-769.
28. Carel RS, Greenstein A, Ellender E, Melamed Y, Kerem D. Factors affecting ventilatory lung function in young Navy selectees. *Am Rev Respir Dis*. 1983;128(2):249-252.
29. Zeng X, Xu X, Zhang Y, Li W, Huo X. Chest circumference and birth weight are good predictors of lung function in preschool children

from an e-waste recycling area. *Environ Sci Pollut Res Int.* 2017;24(28):22613-22621.

30. Lødrup Carlsen KC, Rehbinder EM, Skjerven HO, et al. Preventing Atopic Dermatitis and ALLergies in children—the PreventADALL study. *Allergy.* 2018;73(10):2063-2070.

31. Bains KES, Gudmundsdóttir HK, Färdig M, et al. Infant lung function: criteria for selecting tidal flow-volume loops. *ERJ Open Res.* 2022:00165-2022.

32. Textor J, Hardt J, Knüppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology.* 2011;22(5):745.

33. Johnsen SL, Wilsgaard T, Rasmussen S, Sollien R, Kiserud T. Longitudinal reference charts for growth of the fetal head, abdomen and femur. *Eur J Obstet Gynecol Reprod Biol.* 2006;127(2):172-185.

34. Johnsen SL, Rasmussen S, Sollien R, Kiserud T. Fetal age assessment based on ultrasound head biometry and the effect of maternal and fetal factors. *Acta Obstet Gynecol Scand.* 2004;83(8):716-723.

35. Johnsen SL, Rasmussen S, Sollien R, Kiserud T. Fetal age assessment based on femur length at 10-25 weeks of gestation, and reference ranges for femur length to head circumference ratios. *Acta Obstet Gynecol Scand.* 2005;84(8):725-733.

36. Vintzileos AM, Campbell WA, Neckles S, Pike CL, Nochimson DJ. The ultrasound femur length as a predictor of fetal length. *Obstet Gynecol.* 1984;64(6):779-782.

37. Melamed N, Yogev Y, Linder N, et al. Role of fetal length in the prediction of fetal weight. *J Ultrasound Med.* 2012;31(5):687-694.

38. den Dekker HT, Jaddoe VWV, Reiss IK, de Jongste JC, Duijts L. Fetal and infant growth patterns and risk of lower lung function and asthma. The generation R study. *Am J Respir Crit Care Med.* 2018;197(2):183-192.

39. Wignarajah D, Cock ML, Pinkerton KE, Harding R. Influence of intrauterine growth restriction on airway development in fetal and postnatal sheep. *Pediatr Res.* 2002;51(6):681-688.

40. Rao L, Tiller C, Coates C, et al. Lung growth in infants and toddlers assessed by multi-slice computed tomography. *Acad Radiol.* 2010;17(9):1128-1135.

41. Turner SW, Devereux G. Fetal ultrasound: shedding light or casting shadows on the fetal origins of airway disease. *Am J Respir Crit Care Med.* 2012;185(7):694-695.

SUPPORTING INFORMATION

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