



# Fetal thoracic circumference in mid-pregnancy and infant lung function

Hrefna K. Gudmundsdóttir MD<sup>1,2</sup>  | Katarina Hilde MD<sup>1,3</sup> |  
 Karen E. S. Bains MD<sup>1,2</sup> | Martin Färdig MSc<sup>4,5</sup> | Guttorm Haugen MD, PhD<sup>1,3</sup> |  
 Marissa LeBlanc PhD<sup>6</sup> | Live S. Nordhagen MSc<sup>2,7</sup> | Björn Nordlund RN, PhD<sup>4,5</sup>  |  
 Eva M. Rehbinder MD, PhD<sup>1,8</sup> | Håvard O. Skjerven MD, PhD<sup>1,2</sup> |  
 Anne C. Staff MD, PhD<sup>1,3</sup> | Riyas Vettukattil MBBS, PhD<sup>1,2</sup> |  
 Karin C. L. Carlsen MD, PhD<sup>1,2</sup>

<sup>1</sup>Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

<sup>2</sup>Division of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway

<sup>3</sup>Division of Obstetrics and Gynaecology, Oslo University Hospital, Oslo, Norway

<sup>4</sup>Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

<sup>5</sup>Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

<sup>6</sup>Oslo Centre of Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway

<sup>7</sup>Faculty of Health, VID Specialized University, Oslo, Norway

<sup>8</sup>Department of Dermatology and Venereology, Oslo University Hospital, Oslo, Norway

## Correspondence

Hrefna K. Gudmundsdóttir, MD, Division of Paediatric and Adolescent Medicine, Oslo University Hospital, Ullevål, Postboks 4956 Nydalen, 0424 Oslo, Norway.  
 Email: [h.k.gudmundsdottir@medisin.uio.no](mailto:h.k.gudmundsdottir@medisin.uio.no)

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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

**Abbreviations:** AC, abdominal circumference; BMI, body mass index; CI, confidence interval; FL, femur length; GA, gestational age; HC, head circumference; SD, standard deviation; TC, thoracic circumference; TFV, tidal flow-volume;  $t_{PTEF}/t_E$ , the ratio of time to peak tidal expiratory flow to expiratory time;  $V_T$ , tidal volume.

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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 weak 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<sup>1–4</sup> and is associated with an increased risk of wheeze and asthma,<sup>3,5–7</sup> indicating in utero origins of aberrant lung function development.

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

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,<sup>7,11,12</sup> making TFV loops a suitable measure of infant lung function. Exposure to maternal smoking in utero<sup>13,14</sup> and a family history of asthma<sup>13,15</sup> 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.<sup>1,7,16</sup> Infant boys tend to have lower  $t_{PTEF}/t_E$  than girls,<sup>9,17</sup> 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<sup>18</sup> and with more severe outcome in infants with lung hypoplasia.<sup>19</sup> While infant  $t_{PTEF}/t_E$  values decrease during the first weeks of life, tidal volume ( $V_T$ ) increases with age.<sup>20</sup>

Fetal size and growth trajectories have been associated with respiratory health.<sup>21</sup> 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.<sup>22,23</sup>

Fetal thoracic circumference (TC) measured by ultrasound indicates fetal lung size.<sup>24</sup> 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.<sup>25–27</sup> In older children and adults, TC has been positively related to lung function.<sup>28,29</sup>

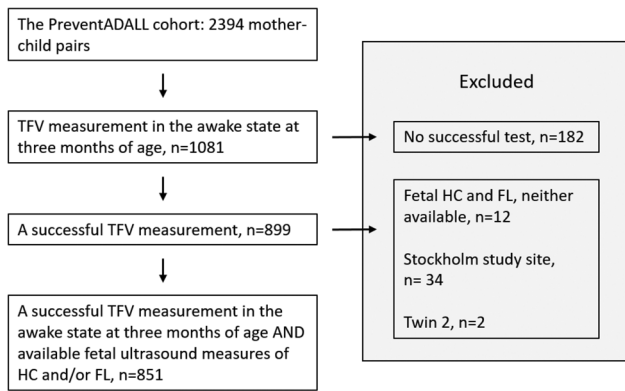
We hypothesize that fetal TC may be positively associated with infant lung function and we are not aware of previous studies relating fetal TC and future lung function in healthy infants.

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),<sup>30</sup> 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 [clinicaltrials.gov](https://clinicaltrials.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.<sup>30</sup>

## 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.<sup>31</sup> 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<sub>2</sub> 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)<sup>32</sup> 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<sup>33,34</sup> 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.<sup>35</sup> 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 ( $\beta$  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	Included infants (n = 851)	
	n	Count (%) or mean (SD)
<i>Infant characteristics</i>		
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 <sup>a</sup>	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)
<i>Fetal measures (mid-pregnancy)</i>		
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)
<i>Maternal characteristics</i>		
Age in years	851	33.0 (3.9)
Parity (previous deliveries)	851	
Nullipara		542 (63.7)
Pre-gestational BMI (kg/m <sup>2</sup> )	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)
<i>Family history of asthma,<sup>b</sup> no. (%)</i>		
Maternal asthma	770	132 (17.1)
Paternal asthma	775	104 (13.4)

TABLE 1 (Continued)

Background characteristics	Included infants (n = 851)	
	n	Count (%) or mean (SD)
<i>Sociodemographic factors, no. (%)</i>		
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.

<sup>a</sup>Partly or exclusively breastfed at 3 months of age.

<sup>b</sup>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<sup>29</sup> and in young adults.<sup>28</sup> 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<sup>36,37</sup> and postnatally, body length predicts lung function.<sup>3,17,28,29</sup> 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.<sup>22,23</sup> 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.<sup>38</sup>

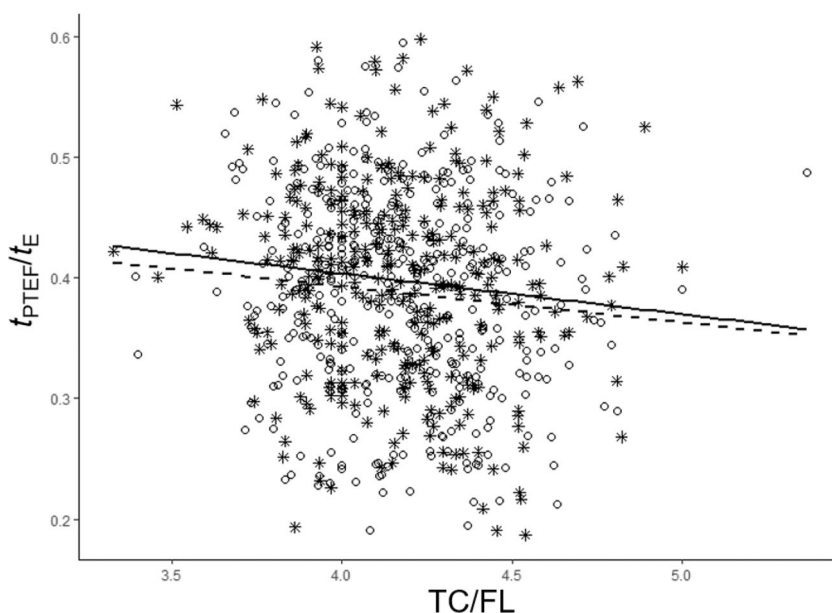
Although the observed association between fetal TC/FL and infant  $t_{PTEF}/t_E$  was statistically significant, the  $R^2$  was low, indicating that fetal TC/FL alone only explains 1.0% of the total variation in infant  $t_{PTEF}/t_E$ , and 2.3% when adjusted for relevant covariates. It is therefore 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
$t_{PTEF}/t_E < 10\text{th percentile}$		-4.05	-10.32 to 2.36	0.212		-4.38	-10.76 to 2.10	0.181
$t_{PTEF}/t_E < 25\text{th percentile}$		-3.30	-7.78 to 1.18	0.148		-3.71	-8.28 to 0.86	0.111
$t_{PTEF}/t_E < 50\text{th percentile}$		-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
$t_{PTEF}/t_E < 10\text{th percentile}$		-3.30	-8.53 to 2.03	0.221		-3.23	-8.53 to 2.15	0.235
$t_{PTEF}/t_E < 25\text{th percentile}$		-2.02	-5.76 to 1.72	0.288		-1.94	-5.73 to 1.87	0.317
$t_{PTEF}/t_E < 50\text{th percentile}$		-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	<b>0.006</b>	0.023	-0.03	-0.05 to -0.01	<b>0.010</b>
$t_{PTEF}/t_E < 0.25$		-0.75	-1.90 to 0.43	0.210		-0.65	-1.84 to 0.57	0.289
$t_{PTEF}/t_E < 10\text{th percentile}$		-0.99	-1.88 to -0.10	<b>0.030</b>		-0.94	-1.84 to -0.03	<b>0.041</b>
$t_{PTEF}/t_E < 25\text{th percentile}$		-0.78	-1.41 to -0.15	<b>0.016</b>		-0.74	-1.39 to -0.10	<b>0.024</b>
$t_{PTEF}/t_E < 50\text{th percentile}$		-0.84	-1.41 to -0.28	<b>0.004</b>		-0.81	-1.38 to -0.25	<b>0.005</b>

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 ( $\beta$  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,<sup>8,39</sup> while the more rapid growth of

respiratory bronchioles and alveoli during the third trimester<sup>9</sup> along with increased fetal general growth may provide greater variation also in fetal thoracic size.<sup>33</sup> 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.

**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					
	<i>n</i>	$R^2$	$\hat{\beta}$	95% CI	<i>p</i> value
<b><math>V_T</math></b>					
Univariable	726	0.004	22.57	-2.49 to 47.63	0.077
+ infant sex		0.016	26.41	1.34-51.47	<b>0.039</b>
Multivariable		0.032	26.39	1.34-51.44	<b>0.039</b>
<b><math>V_T/kg</math></b>					
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					
	<i>n</i>	$R^2$	$\hat{\beta}$	95% CI	<i>p</i> value
<b><math>V_T</math></b>					
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
<b><math>V_T/kg</math></b>					
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					
	<i>n</i>	$R^2$	$\hat{\beta}$	95% CI	<i>p</i> value
<b><math>V_T</math></b>					
Univariable	724	0.007	3.95	0.44-7.47	<b>0.028</b>
+ infant sex		0.016	3.87	0.37-7.37	<b>0.030</b>
Multivariable		0.031	3.56	0.06-7.05	<b>0.046</b>
<b><math>V_T/kg</math></b>					
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 ( $\beta$  estimate).

The positive association between the fetal TC ratios and infant  $V_T$ , in line with fetal TC reflecting fetal lung size,<sup>9,24</sup> 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.<sup>25-27</sup> 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,<sup>8</sup> 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<sup>7,40</sup> 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,<sup>34</sup> mid-pregnancy fetal FL is probably unrelated to sex.<sup>33</sup> 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,<sup>3,4,9,17</sup> 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.<sup>5,9,18</sup> While both TC/HC and TC/FL were significantly associated with  $V_T$

**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				
	<i>n</i>	$R^2$	$\hat{\beta}$	95% CI	<i>p</i> value	<i>n</i>	$R^2$	$\hat{\beta}$	95% CI	<i>p</i> value
<b><math>t_{PTEF}/t_E \sim TC/HC</math></b>										
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
<b><math>t_{PTEF}/t_E \sim TC/AC</math></b>										
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
<b><math>t_{PTEF}/t_E \sim TC/FL</math></b>										
Univariable	343	0.011	-0.03	-0.07 to -0.00	<b>0.048</b>	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 ( $\beta$  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.<sup>9</sup> Relatively larger airways for lung size result in higher flow rates in girls compared to boys<sup>6,9,17</sup> 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.<sup>41</sup> 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, visualization. **Karen E. S. Bains:** Investigation, writing—review & editing, data curation. **Martin Färdig:** Investigation, writing—review & editing, data curation. **Guttorm Haugen:**



Conceptualization, methodology, writing—review & editing, supervision, visualization, project administration, funding acquisition. **Marissa LeBlanc:** Writing—review & editing, methodology, supervision, visualization. **Live S. Nordhagen:** Investigation, writing—review & editing. **Björn Nordlund:** Writing—review & editing, project administration, funding acquisition. **Eva M. Rehbinder:** Conceptualization, methodology, visualization, writing—review & editing, project administration, supervision, funding acquisition. **Håvard O. Skjerven:** Writing—review & editing, visualization, project administration. **Anne C. Staff:** Methodology, visualization, writing—review & editing, project administration, funding acquisition, conceptualization. **Riyas Vettukattil:** Software, data curation, writing—review & editing. **Karin C. L. Carlsen:** Conceptualization, funding acquisition, methodology, visualization, writing—review & editing, project administration, supervision.

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### CONFLICTS OF INTEREST

Marissa LeBlanc reports a speaking fee from MSD unrelated to the content of this study, Eva Maria Rehbinder has received honoraria for lectures from Sanofi Genzyme, Leo Pharma, Novartis, Norwegian Psoriasis and Eczema Association, and the Norwegian Asthma and Allergy Association and Karin C. L. Carlsen reports that her institution has received honorarium and travel costs from Thermo Fisher Scientific for international symposium participation. The remaining authors have no conflicts of interest to declare.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are may be available on request from the study PI. The study is still ongoing, and data are not publicly available due to privacy or ethical restrictions.

### ORCID

Hrefna K. Gudmundsdóttir  <https://orcid.org/0000-0002-1248-2874>

Björn Nordlund  <http://orcid.org/0000-0001-9888-1659>

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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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