Infant lung function and maternal physical activity in the first half of pregnancy

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There is an association between self-reported maternal physical activity in the first half of pregnancy and lung function in healthy 3-month-old infants, with higher odds of low lung function among infants of inactive compared to active mothers https://bit.ly/3BVVv39

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Abstract

Background and aim Physical activity (PA) in pregnancy is important for maternal and possibly offspring health. To study the early origins of lung function we aimed to determine whether PA in the first half of pregnancy is associated with lung function in healthy 3-month-old infants.

Methods From the general population-based Preventing Atopic Dermatitis and Allergies in Children birth cohort recruiting infants antenatally in Norway and Sweden, all 812 infants (48.8% girls) with available tidal flow–volume measures in the awake state at 3 months of age and mid-pregnancy data on PA were included. PA was self-reported by the mothers and, based on intensity, we categorised them as active or inactive during pregnancy. Furthermore, we defined active mothers as fairly or highly active. The main outcome was a ratio of time to peak tidal expiratory flow to expiratory time (t_{PTEF}/t_E) <0.25. Associations were analysed by logistic regression, adjusting for maternal age, education, parity, pre-pregnancy body mass index, *in utero* nicotine exposure and parental atopy.

Results The mean±SD t_{PTEF}/t_E was 0.391±0.08 and did not differ significantly according to maternal PA level in pregnancy. The 290 infants of inactive mothers had higher odds of having t_{PTEF}/t_E <0.25 compared to infants of all active mothers (OR 2.07, 95% CI 1.13–3.82; p=0.019) and compared to infants (n=224) of fairly active (OR 2.83, 95% CI 1.26–7.24; p=0.018) but not highly active mothers (n=298).

Conclusion Based on self-reported maternal PA in the first half of pregnancy, 3-month-old infants of inactive compared to active mothers had higher odds of a low t_{PTEF}/t_E.

Introduction

Impaired infant lung function precedes wheezing and asthma both in childhood [1–3] and adulthood [4] as well as persistently lower lung function values [5, 6], suggesting that asthma likely originates in early life. Development of the respiratory system starts in the first weeks of fetal life [6, 7], and both genetics and the intrauterine environment impact lung function at birth [8].

Regular physical activity (PA) is an important contributor to a healthy lifestyle and is recommended during pregnancy in many countries [9, 10]. Staying physically active during pregnancy is safe for the fetus [11, 12], beneficial for maternal wellbeing, and reduces the risk of pregnancy complications [13–17] and the risk of caesarean deliveries in nonobese women [13, 14, 18]. For healthy women, PA in pregnancy is not associated with preterm delivery [10, 12–14] or abnormal birth weight [12, 13]. Accordingly, Norwegian guidelines recommend ⩾150 min moderate or high intensity PA per week [19] although many women do not meet these recommendations [20]. However, the potential impact of maternal PA on early fetal airways and lung development is not clear.

Tidal flow–volume (TFV) loops in awake or naturally sleeping infants is a feasible method to measure lung function from the first day of life. The TFV ratio of time to peak tidal expiratory flow to expiratory time (t_{PTEF}/t_E) is a measure of expiratory airflow that correlates with maximal flow at functional residual capacity, using the rapid thoracoabdominal compression technique in sedated infants [5, 21]. Maternal asthma [22, 23], maternal hypertension in pregnancy [22] and smoking in pregnancy [22, 24] are among risk factors that have been associated with impaired lung function observed as lower t_{PTEF}/t_E values in offspring. A t_{PTEF}/t_E ⩽0.25 is associated with obstructive lung disease, while values ⩾0.30 are usually considered normal [1, 3, 7, 21, 25, 26] and higher ratios are unlikely to represent improved health. Previous studies have shown lung function differences between girls and boys, with infant t_{PTEF}/t_E values tending to be higher in girls [6, 23, 27].

Tidal volume (V_T) increases after birth [28, 29], with lower volumes in early infancy observed with prematurity [30] and lung hypoplasia [31]. While most studies exploring lung function in infancy have been performed in sleeping or sedated infants, both t_{PTEF}/t_E and V_T seem to be higher in the awake compared to the sleeping state [32].

In the quest to identify modifiable factors during pregnancy that may impact infant lung health, here, we hypothesise that PA positively influences infant lung function and that lack of PA may be associated with lower lung function. The aim of the present study was therefore to determine, in a large cohort of infants from a general population, whether self-reported maternal PA in the first half of pregnancy is associated with infant lung function at 3 months of age primarily as lower lung function by t_{PTEF}/t_E <0.25 and, secondarily, by V_T corrected for body weight (in kilograms).

Subjects and methods

Study design and setting

3-month-old infants with available lung function measurements and information on maternal PA in the first half of pregnancy from the Preventing Atopic Dermatitis and Allergies in Children (PreventADALL) cohort were included in this prospective observational study (figure 1). The PreventADALL study, described in detail elsewhere [33], is a Scandinavian general population-based mother–child birth cohort study including 2394 antenatally recruited mother–child pairs. Pregnant women planning to give birth at Oslo University Hospital or Østfold Hospital Trust, Norway, or in the region of Stockholm, Sweden, were eligible for participation. From December 2014 to October 2016, 2697 women at approximately 18 weeks of pregnancy (range 15.7–22.7 weeks) were recruited. Their healthy singletons or twins, born at ⩾35.0 gestational weeks, were included at birth.

Informed consent was signed by the mothers at recruitment and by both parents at birth. The study was approved by the regional committees for medical and health research ethics in Norway (2014/518) and Sweden (2014/2242–31/4), and registered at www.clinicaltrials.gov (identifier number NCT02449850).

Participants

In this substudy, we included all 812 3-month-old infants with a successful TFV measure of lung function in the awake state and available information on self-reported maternal PA in the first half of pregnancy. Lung function was measured at the Oslo and Stockholm study sites. Except for somewhat higher gestational age (GA) at birth, a higher rate of breastfeeding and less exposure to maternal use of nicotine after the first few weeks of pregnancy, the included infants were similar to the remaining infants (n=1582) from the PreventADALL cohort (table 1). The mothers of the included, compared to the remaining, infants were slightly older, had lower pre-pregnancy body mass index (BMI) and weight gain in the first half of pregnancy, and more were nullipara and highly educated, in line with previously described differences between the PreventADALL study sites [33]. Lung function measurements missing, unsuccessful or performed in the sleeping state were the main reasons for exclusion from the present study.

Methods

Maternal PA in the first half of pregnancy was self-reported using electronic questionnaires sent to the mothers in relation to study recruitment. They answered how frequently they had performed different types of activities (strolling, brisk walking, jogging, bicycling, strength training, aerobics, skiing, ballgames,

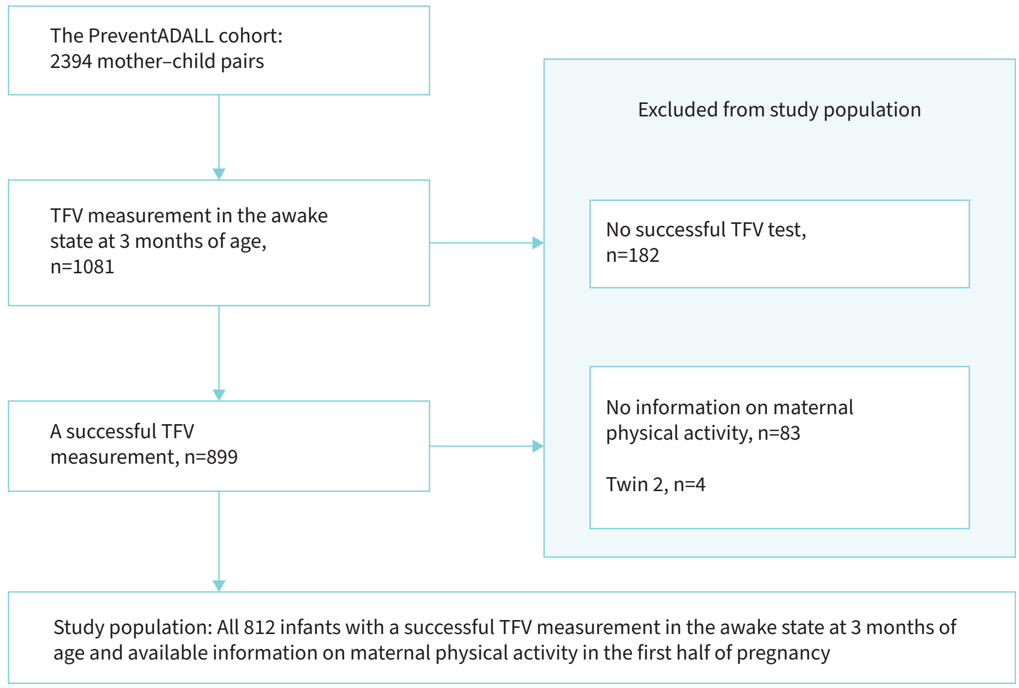

FIGURE 1 Study population. The present study population includes all 812 infants from the Preventing Atopic Dermatitis and Allergies in Children (PreventADALL) cohort with a successful tidal flow–volume (TFV) measurement in the awake state at 3 months of age and available information on maternal physical activity in the first half of pregnancy. To ensure independency of all participants, the second-born twin was consecutively excluded.

swimming, horse riding, yoga/Pilates and other types of PA) so far in their pregnancy. The usual intensity (low, moderate or high) and duration (<30 min, 30–60 min, 1–2 h or >2 h) of exercise was also reported. Low intensity was defined as "no sweating or shortness of breath", moderate as "sweaty and some shortness of breath" and high as "very sweaty and very heavy breathing". Based on all available answers, the general activity level for 2349 women in the PreventADALL cohort was estimated [20]. We defined women reporting PA of moderate or high intensity as "active" and calculated their minimum number of active minutes per week by multiplying the minimum number of sessions per week with their usual duration of exercise. Women with active minutes per week at or above the median of 120 min were further defined as "highly active" and those below the median as "fairly active". Women reporting only low intensity or no exercise at all were defined as "inactive". For further information, see the supplementary material.

Additionally, the questionnaire included questions on socioeconomic factors, health and lifestyle as well as family history of atopic diseases.

TFV loops were measured in calm infants by trained study personnel at the 3-month follow-up visit, using the Exhalyzer D (Eco Medics, Duernten, Switzerland) equipment [35]. An appropriately sized face mask was connected to the ultrasonic flow head with a dead space reducer, a filtering spirette and a carbon dioxide adapter with a Capnostat carbon dioxide sensor in between. The face mask was held tight over the infant's nose and mouth while as many TFV loops as possible were recorded (supplementary table S1). All infants included in the present study were awake, with measurements performed with head and neck on the midline in the supine position on a firm pillow on their caregiver's lap or in a stroller/bed. A procedure for selection of TFV loops in awake infants was tested and validated prior to analyses, with details on visual inspection and loop selection reported elsewhere [35]. Mean values for $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$, V_{T} and respiratory rate were registered for each infant.

Information about the delivery and the newborn was taken from electronic hospital records. At 3 months *post partum*, the mothers answered questions about their infants' health and nutrition. Infant weight and length were measured at the follow-up visit by trained study personnel.

TABLE 1 Baseline characteristics of the 812 infants included in the present study and the 1582 remaining infants from the Preventing Atopic Dermatitis and Allergies in Children (PreventADALL) mother–child birth cohort

	Included infants	Remaining cohort	p-value[#]
Infants	812	1582	
Infant characteristics			
Females	396/812 (48.8%)	743/1582 (47.0%)	0.403
Age at examination[¶], days	93±7.2	93±7.3 (n=549)	0.686
Weight at 3 months, kg	6.3±0.78 (n=808)	6.3±0.78 (n=1318)	0.914
Length at 3 months, cm	61.9±2.40 (n=802)	61.9±2.39 (n=1299)	0.892
Weight gain until 3 months, kg	2.7±0.65 (n=804)	2.7±0.65 (n=1313)	0.493
GA at birth[+], weeks	40.1±1.32 (n=810)	40.0±1.36 (n=1578)	**0.022**
Birth weight, kg	3.6±0.46 (n=808)	3.6±0.49 (n=1576)	0.398
Placenta weight, g	668±133.2 (n=754)	654±136.0 (n=1051)	**0.021**
BW/PW ratio	5.46±0.98 (n=753)	5.61±0.97 (n=1051)	**0.002**
Caesarean birth	129/811 (15.9%)	268/1579 (17.0%)	0.507
Breastfeeding at 3 months[§]	691/721 (95.8%)	1037/1131 (91.7%)	**<0.001**
Examined by a physician for respiratory distress or cough since birth	n=721	n=1130	0.814
No	682 (94.6%)	1066 (94.3%)	
Once	29 (4.0%)	47 (4.2%)	
More than once	10 (1.4%)	17 (1.5%)	
Twins[f]	4/812 (0.5%)	18/1582 (1.1%)	0.117
Maternal characteristics			
Age, years	33±3.9	32±4.3	**<0.001**
Nullipara	516/812 (63.5%)	913/1579 (57.8%)	**0.007**
Pre-pregnancy BMI, kg·m^{-2}	24.4±3.27 (n=799)	25.0±3.86 (n=1554)	**<0.001**
Weight gain until 18 weeks GA, kg	4.4±3.02 (n=791)	4.8±3.29 (n=1543)	**0.006**
Regular physical activity before pregnancy	667/812 (82.1%)	1071/1348 (79.5%)	0.126
IVF pregnancies	68/807 (8.4%)	123/1571 (7.8%)	0.612
Hypertensive disorders of pregnancy	68/807 (8.4%)	157/1569 (10.0%)	0.460
Any nicotine use in pregnancy	90/812 (11.1%)	164/1582 (10.4%)	0.590
Any smoking in pregnancy	30/812 (3.7%)	74/1582 (4.7%)	0.264
Current smoking in mid-pregnancy	1/812 (0.1%)	13/1582 (0.8%)	**0.013**
Any snus[##] in pregnancy	63/812 (7.8%)	102/1582 (6.4%)	0.231
Current snus in mid-pregnancy	0/812 (0%)	7/1582 (0.4%)	**0.036**
Maternal sociodemographic factors			
Country of origin	n=812	n=1359	**<0.001**
Norway	684 (84.2%)	759 (55.8%)	
Sweden	53 (6.5%)	439 (32.3%)	
Other Nordic country	6 (0.7%)	22 (1.6%)	
Rest of the world	69 (8.5%)	139 (10.2%)	
Education	n=809	n=1353	**<0.001**
High school only or less	45 (5.6%)	196 (14.5%)	
Higher education <4 years	226 (27.9%)	464 (34.3%)	
Higher education ⩾4 years	517 (63.9%)	654 (48.3%)	
PhD	21 (2.6%)	39 (2.9%)	
Married/cohabitant	791/812 (97.4%)	1332/1367 (97.4%)	0.971
Living environment	n=812	n=1359	**<0.001**
City			
Densely populated	390 (48.0%)	452 (33.3%)	
Less densely populated	320 (39.4%)	506 (37.2%)	
Suburb	78 (9.6%)	267 (19.6%)	
Village or countryside	24 (3.0%)	134 (9.9%)	
Family history of atopic diseases[¶¶]			
Maternal atopic disease	328/812 (40.4%)	573/1359 (42.2%)	0.418
Asthma	140/812 (17.2%)	231/1359 (17.0%)	0.884
Atopic dermatitis	135/812 (16.6%)	296/1359 (21.8%)	**0.004**
Allergic rhinitis	177/812 (21.8%)	268/1359 (19.7%)	0.240
Paternal atopic disease	284/757 (37.5%)	467/1400 (33.4%)	0.053
Asthma	101/757 (13.3%)	178/1400 (12.7%)	0.784
Atopic dermatitis	73/757 (9.6%)	147/1400 (10.5%)	0.406
Allergic rhinitis	203/757 (26.8%)	307/1400 (21.9%)	**0.026**
Parental atopic disease	498/773 (64.4%)	862/1345 (64.1%)	0.877

Data are presented as mean±SD unless otherwise stated. GA: gestational age; BW/PW: birth weight/placenta weight; BMI: body mass index; IVF: *in vitro* fertilisation. [#]: differences between groups analysed with the independent sample t-test (continuous variables), the Chi-squared test (nominal variables) or the Mann–Whitney U-test (ordinal variables); [¶]: age in days (∼3 months) is based on the date of the lung function measurement and, therefore, is missing when no lung function measurement was registered; [+]: GA is based on fetal femur length at the routine second trimester ultrasound scan, as different methods were used to measure fetal head size at the study sites; [§]: partly or exclusively breastfed at 3 months of age (see supplementary table S5 for further information on nutrition at 3 months of age for the included infants); [f]: the first-born twin from four twin pairs was included while the second twin was consequently excluded; [##]: snus (moist snuff) is a smokeless, ground tobacco, placed between the gum and the lip, increasingly used among Scandinavian women [34]; [¶¶]: doctor-diagnosed atopic diseases included asthma, atopic dermatitis, allergic rhinitis and food allergies. Bold represents statistically significant p-values.

Variables

Primary outcome

The primary outcome, lower lung function, was defined as a t_{PTEF}/t_E ratio <0.25.

Secondary outcome

The secondary outcome, V_T corrected for body weight, was recorded as a continuous variable.

Exposure

The maternal general activity level was based on self-reported intensity of exercise in the first half of pregnancy [20]. Primarily, we compared infants of inactive mothers to those of all active mothers, and secondarily, to infants of active mothers in the subgroups of fairly active and highly active.

Covariates

All multivariable regression models were adjusted for maternal age, education, parity, pre-pregnancy BMI, *in utero* nicotine exposure and parental atopy. These potential confounders of the association between maternal PA in pregnancy and infant lung function were identified using a directed acyclic graph (DAG) [36] prior to statistical analyses (supplementary figure S1). Only conditions arising before the first half of pregnancy and potentially affecting both the exposure and outcome could be considered as confounders and adjusted for in the regression models.

Statistical analysis

Continuous variables are presented as mean (range), mean±SD or mean (95% CI). Categorical variables are presented as n (%).

We used logistic regression models to analyse the association between maternal general activity level and t_{PTEF}/t_E <0.25, presented as odds ratios with 95% confidence intervals and p-values. For the continuous V_T corrected for body weight outcome, linear regression models are presented with regression coefficients ($\hat{\beta}$ estimate), R^2, 95% confidence intervals and p-values.

To assess a potential interaction with infant sex, we added the interaction term "maternal PA×infant sex" to our regression models.

We compared the infants included in the present study to all remaining infants in the PreventADALL cohort with the independent sample t-test (continuous variables), the Chi-squared test (nominal variables) or the Mann–Whitney U-test (ordinal variables). p-values <0.05 were regarded as significant.

IBM SPSS statistics version 27, RStudio version 4.1.0 and Microsoft Excel 2016 were used for statistical analyses.

Results

The 812 infants (48.8% girls) included in the present study were born at mean (range) GA of 40.1 (35.3–42.3) weeks (table 1). Their mean (range) age at the time of lung function testing was 93 (57–137) days and their weight, 6.3 (4.4–8.9) kg.

Approximately one third of the mothers (290 (35.7%) out of 812) were defined as inactive in the first half of pregnancy. Of the 522 (64.3% out of 812) active mothers, 224 (27.6% out of 812) were fairly active and 298 (36.7% out of 812) were highly active.

Mean±SD (range) t_{PTEF}/t_E for the included infants was 0.39±0.08 (0.19–0.63), with the distribution shown in figure 2a. Few had low values; while 47 infants (5.8%) had a t_{PTEF}/t_E <0.25, only five (0.6%) had values <0.20. The mean±SD number of TFV loops was 21±14 per infant (supplementary table S1).

The mean±SD t_{PTEF}/t_E was similar among infants of inactive and active mothers: 0.387±0.09 compared to 0.393±0.08 (figure 3 and supplementary table S2); however, as shown in the histogram in figure 2b, the t_{PTEF}/t_E distribution appears to be different in the lower tail between the two groups and t_{PTEF}/t_E variability greater among infants of inactive mothers.

Infants of inactive mothers had significantly higher odds of having a t_{PTEF}/t_E <0.25 compared to infants of all active mothers as well as when compared to the infants of fairly active mothers only, in both univariable and multivariable regression models (table 2).

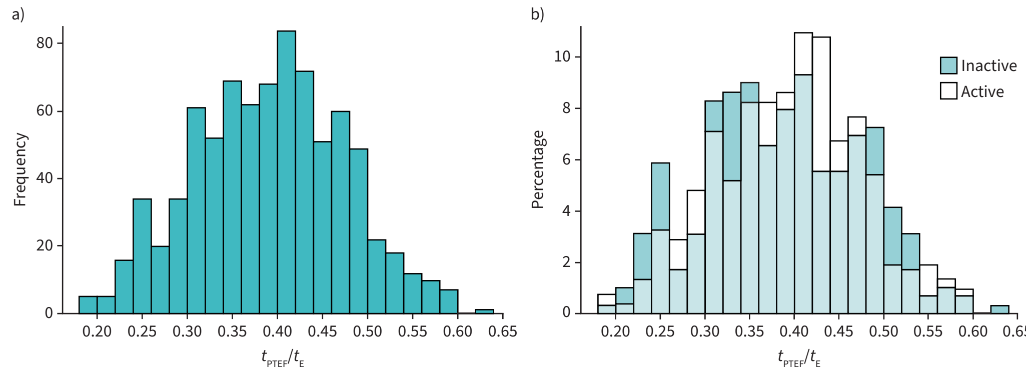

FIGURE 2 Histograms showing the distribution of the infant ratio of time to peak tidal expiratory flow to expiratory time (t_{PTEF}/t_E) in a) all included infants (n=812) and b) infants of inactive (n=290) compared to all active (n=522) mothers, presented with partly overlapping bars. While the *y*-axis in a) shows frequency, the two overlapping histograms in b) have percentage on the *y*-axis to enable comparison of the distribution of infant t_{PTEF}/t_E in subgroups of different size.

The mean±SD V_T corrected for body weight for all included infants was 7.05±2.12 mL·kg^{-1}, with no significant difference between infants of inactive mothers compared to those of all active mothers (results not shown). However, when active mothers were subdivided into fairly and highly active, V_T corrected for body weight differed significantly between the three groups (figure 4a and supplementary table S3a). Infants of highly active mothers had the lowest mean±SD V_T corrected for body weight of 6.79±2.05 mL·kg^{-1}, which was significantly lower than that of the infants of fairly active mothers (7.25±2.13 mL·kg^{-1}, p=0.035), while they did not differ significantly from the infants of inactive mothers (7.17±2.16 mL·kg^{-1}). A significant association was observed between high maternal activity and lower infant V_T corrected for body weight in both univariable and multivariable models (table 3).

There was no significant interaction between maternal PA in the first half of pregnancy and infant sex, and neither did the association between maternal PA and infant lung function change by including infant sex in the regression models (results not shown).

Discussion

Maternal PA in the first half of pregnancy was significantly associated with lung function in 812 healthy awake 3-month-old infants born after ⩾35.0 weeks of pregnancy. Infants of physically inactive mothers

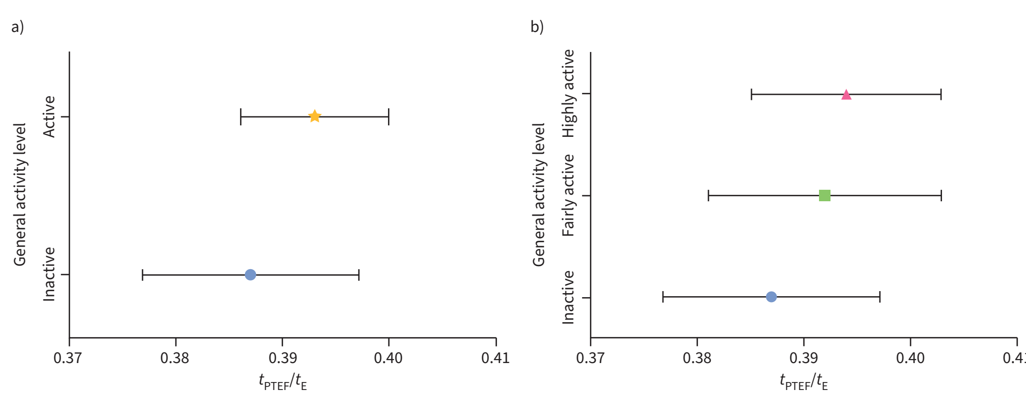

FIGURE 3 Infant ratio of time to peak tidal expiratory flow to expiratory time (t_{PTEF}/t_E) at 3 months of age according to maternal general activity level, shown for infants of a) inactive and active mothers, and b) inactive, fairly active and highly active mothers. Mean t_{PTEF}/t_E for infants of inactive and active mothers was compared with the independent sample t-test (p=0.321), and for infants of inactive, fairly active and highly active mothers, with one-way ANOVA (p=0.594). No statistically significant difference was observed between the groups. Symbols represent means and whiskers represent 95% confidence intervals.

TABLE 2 The association between maternal general activity level in the first half of pregnancy and the infant ratio of time to peak tidal expiratory flow to expiratory time (t_{PTEF}/t_E) <0.25, analysed with logistic regression models

	Infants	Inactive *versus* active		Inactive *versus* fairly active		Inactive *versus* highly active	
		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Univariable	812	2.14 (1.19–3.90)	**0.012**	2.92 (1.31–7.45)	**0.014**	1.78 (0.93–3.52)	0.088
Multivariable	808	2.07 (1.13–3.82)	**0.019**	2.83 (1.26–7.24)	**0.018**	1.67 (0.85–3.41)	0.145

Multivariable models were adjusted for maternal age, education, parity, pre-pregnancy body mass index, parental atopy and *in utero* exposure to nicotine. Of 812 included infants, the mothers of 290 were defined as inactive, 224 as fairly active and 298 as highly active. Information on maternal education was missing for four infants, resulting in 808 infants (290 of inactive mothers, 222 of fairly active mothers and 296 of highly active mothers) in the multivariable models. Bold indicates statistically significant p-values.

were more likely to have low t_{PTEF}/t_E values, with twice the odds of having a t_{PTEF}/t_E <0.25 compared to infants of active mothers. High maternal activity was associated with lower V_T corrected for body weight.

The significant association between maternal inactivity in the first half of pregnancy and lower t_{PTEF}/t_E at 3 months of age is a novel finding, although studies that have examined the fetus during maternal exercise may support our results [37, 38]. Fetal breathing movements, observed as early as the first trimester, are important for development of the lungs and the respiratory system [8, 39]. While maternal exercise can transiently affect both fetal breathing and body movements [37, 38], little is known about potential associations between breathing movements in the fetus and postnatal lung function. In addition, an increased variability in fetal heart rate during maternal exercise may, together with higher blood flow in the umbilical cord and the placental circulation, indicate an improved *in utero* environment in active women and lower the risk of fetal adverse outcomes [38].

Higher odds of low t_{PTEF}/t_E were observed among infants born to inactive mothers compared to all active and to fairly active mothers. We explored potential associations of PA on lung function values within a normal, healthy infant population, and based upon clinically relevant cut-off values from previous studies, we chose t_{PTEF}/t_E <0.25 to represent low lung function [1, 3, 7, 25, 26]. Future studies of the PreventADALL cohort may reveal whether maternal inactivity in the first half of pregnancy is associated

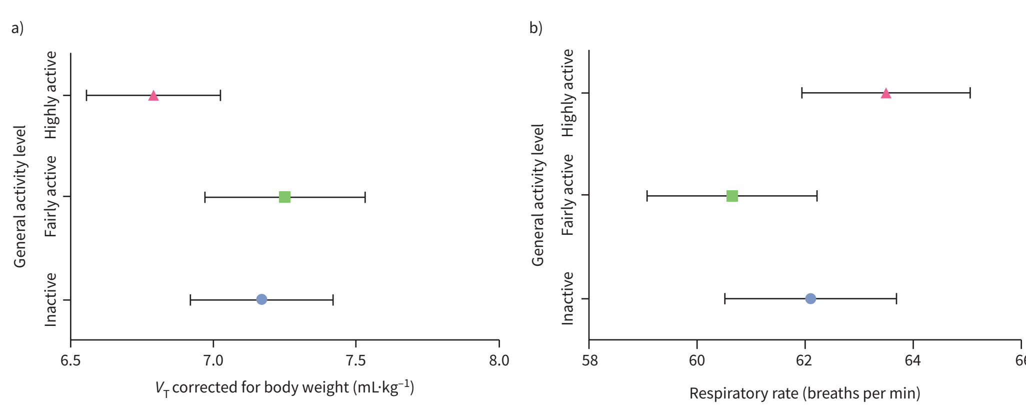

FIGURE 4 Infant a) tidal volume (V_T) corrected for body weight and b) respiratory rate at 3 months of age according to maternal general activity level in three categories. a) Mean V_T corrected for body weight was compared between groups with one-way ANOVA (p=0.023). Mean V_T corrected for body weight differed significantly between infants of fairly active and highly active mothers (mean difference 0.47 mL·kg^{-1}, 95% CI 0.026–0.905 mL·kg^{-1}; p=0.035). b) Mean respiratory rate was compared between groups with one-way ANOVA (p=0.053). Mean respiratory rate differed significantly between infants of highly active and fairly active mothers (mean difference 2.84, 95% CI 0.09–5.59 breaths per min; p=0.041). Symbols represent means and whiskers represent 95% confidence intervals.

TABLE 3 The association between maternal general activity level in the first half of pregnancy and infant tidal volume corrected for body weight, analysed with linear regression models

	Infants#	Inactive *versus* fairly active		Inactive *versus* highly active		R^2
		$\hat{\beta}$ (95% CI)	p-value	$\hat{\beta}$ (95% CI)	p-value	
Univariable	808	0.082 (−0.29–0.45)	0.664	−0.38 (−0.73– −0.04)	**0.029**	0.0093
Multivariable	804	0.041 (−0.33–0.41)	0.829	−0.48 (−0.84– −0.13)	**0.008**	0.0224

Infants of inactive mothers were compared to infants of active mothers subdivided into fairly active and highly active. Multivariable models were adjusted for maternal age, education, parity, pre-pregnancy body mass index, parental atopy and *in utero* exposure to nicotine. $\hat{\beta}$: β estimate. #: information on infant weight at 3 months of age was missing for four out of 812 included infants; therefore, 808 infants could be included in models with tidal volume corrected for body weight as the outcome (288 with inactive, 224 with fairly active and 296 with highly active mothers); additionally, four infants were excluded from the multivariable model due to missing data on maternal education, resulting in 288 infants with inactive mothers, 222 infants with fairly active mothers and 294 infants with highly active mothers. Bold indicates statistically significant p-values.

with an increased risk of obstructive lung diseases in the offspring. Infants of highly active mothers did not have significantly lower odds of having a low t_{PTEF}/t_E, suggesting that the observed association did not depend on the most active mothers.

The present study is based on maternal PA reported around mid-pregnancy, while complications such as excessive gestational weight gain, hypertension and diabetes, improvable and partly preventable [13, 15, 16] by PA, often arise later. One may speculate that the higher prevalence of these pregnancy complications in physically inactive women could partly explain the association with lower infant t_{PTEF}/t_E. To explore the association between maternal PA level in the first half of pregnancy and infant lung function we have only adjusted for variables potentially affecting both the exposure and the outcome. Thus, neither pregnancy complications nor infant factors such as sex, GA, birth weight or breastfeeding [6, 8, 23, 27, 30, 40], previously shown to affect lung function, were regarded as potential confounders.

While V_T corrected for body weight was similar among infants of inactive and active mothers overall, a significantly lower V_T corrected for body weight was observed among infants of highly active compared to fairly active mothers. We are unaware of similar findings reported elsewhere. The potential reasons for the association between high-level PA and lower V_T corrected for body weight are not clear and could not be fully explained by the slightly higher respiratory rate observed in infants of highly active mothers (figure 4b and supplementary material). Although weight-bearing exercise in the supine position and late in pregnancy has been associated with transient fetal bradycardia, reduced uterine blood flow and reduced fetoplacental growth, increasing the risk of fetal growth restriction [38], our study cannot elucidate such potential mechanisms. However, although not significant, infants of highly active mothers had the smallest placentas and lowest birthweight, with the subsequent highest weight gain until 3 months of age (supplementary figure S2b), in line with previous findings of lower birthweight in relation to vigorous maternal exercise and exercise during pregnancy in previously inactive women [12, 41]. Low birth weight and high infant weight gain are associated with asthma and lower lung function values in childhood [40]. Important stages of airway development complete during the second trimester [6, 8] while the third trimester of pregnancy is mainly associated with fetal growth and weight gain. It is possible that high activity levels in late pregnancy, causing slower fetal growth, could lead to discrepancy in airway development and lung growth that may partly explain the lowest V_T corrected for body weight and normal t_{PTEF}/t_E in infants of highly active women. A smaller lung size relative to the airway calibre results in higher expiratory flow and t_{PTEF}/t_E [6] and even though a "catch-up" body growth is observed, lung growth might not catch up as fast, reflected by lower V_T corrected for body weight at 3 months of age.

The large group of healthy infants, with lung function measured in the awake state at a relatively similar age, is a strength of this study. The general activity level was slightly higher for the mothers of the infants included in the present study compared with the whole PreventADALL cohort [20] and some maternal differences related to study sites were observed [33]. Nevertheless, we believe our results are representative of the general Scandinavian population. Prior to analyses, we identified confounders by constructing a DAG based on available knowledge. Apart from nonsignificantly lower birthweight and higher weight gain in the first 3 months of life, no differences in infant characteristics according to maternal PA level were observed, supporting our DAG and findings.

Due to the design of the study, all information on maternal PA was self-reported, with certain limitations arising from the questionnaire. Although our analyses are based on an estimate of active minutes per week, as the women were not asked about the total weekly duration or frequency of exercise, we believe that the classification of active women into fairly and highly active is reasonable. In this study, we addressed the role of PA in the first half of pregnancy for early fetal respiratory development, using detailed PA data collected at enrolment. Information on maternal PA in the second half of pregnancy was limited to changes in PA habits from mid-pregnancy until 34 weeks gestation and after this time no information on maternal PA was available. In addition, to account for potential pregnancy complications that may impact on activity levels, more likely to be present in the last part of pregnancy, would necessitate a larger cohort than ours.

Conclusion

Maternal PA in pregnancy was significantly associated with infant lung function, with higher odds of low $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ in infants of inactive compared to active mothers, and an association between high maternal activity and lower V_{T}. The observed association between maternal inactivity and lower infant lung function may have clinical implications, adding to the importance of advising and supporting pregnant women to adhere to guidelines on PA during pregnancy. Nevertheless, there might be confounders for which we have not adjusted and, potentially, maternal PA level could be a proxy for general health or an unknown factor associated with lung function in the offspring.

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References

1 Lodrup Carlsen KC, Carlsen KH, Nafstad P, *et al.* Perinatal risk factors for recurrent wheeze in early life. *Pediatr Allergy Immunol* 1999; 10: 89–95.
2 Dezateux C, Stocks J, Dundas I, *et al.* 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: 403–410.
3 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: 1682–1689.
4 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: 1646–1655.
5 Stern DA, Morgan WJ, Wright AL, *et al.* Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet* 2007; 370: 758–764.
6 Boezen HM, Jansen DF, Postma DS. Sex and gender differences in lung development and their clinical significance. *Clin Chest Med* 2004; 25: 237–245.
7 Young S, Arnott J, Le Souef PN, *et al.* Flow limitation during tidal expiration in symptom-free infants and the subsequent development of asthma. *J Pediatr* 1994; 124: 681–688.
8 Stocks J, Hislop A, Sonnappa S. Early lung development: lifelong effect on respiratory health and disease. *Lancet Respir Med* 2013; 1: 728–742.
9 Evenson KR, Barakat R, Brown WJ, *et al.* Guidelines for physical activity during pregnancy: comparisons from around the world. *Am J Lifestyle Med* 2014; 8: 102–121.
10 ACOG Committee. Physical activity and exercise during pregnancy and the postpartum period: ACOG Committee opinion, number 804. *Obstet Gynecol* 2020; 135: e178–e188.
11 Szymanski LM, Satin AJ. Exercise during pregnancy: fetal responses to current public health guidelines. *Obstet Gynecol* 2012; 119: 603–610.
12 Davenport MH, Meah VL, Ruchat SM, *et al.* Impact of prenatal exercise on neonatal and childhood outcomes: a systematic review and meta-analysis. *Br J Sports Med* 2018; 52: 1386–1396.
13 Di Mascio D, Magro-Malosso ER, Saccone G, *et al.* Exercise during pregnancy in normal-weight women and risk of preterm birth: a systematic review and meta-analysis of randomized controlled trials. *Am J Obstet Gynecol* 2016; 215: 561–571.
14 Magro-Malosso ER, Saccone G, Di Mascio D, *et al.* Exercise during pregnancy and risk of preterm birth in overweight and obese women: a systematic review and meta-analysis of randomized controlled trials. *Acta Obstet Gynecol Scand* 2017; 96: 263–273.
15 Davenport MH, Ruchat SM, Poitras VJ, *et al.* Prenatal exercise for the prevention of gestational diabetes mellitus and hypertensive disorders of pregnancy: a systematic review and meta-analysis. *Br J Sports Med* 2018; 52: 1367–1375.
16 Vargas-Terrones M, Nagpal TS, Barakat R. Impact of exercise during pregnancy on gestational weight gain and birth weight: an overview. *Braz J Phys Ther* 2019; 23: 164–169.
17 Davenport MH, McCurdy AP, Mottola MF, *et al.* Impact of prenatal exercise on both prenatal and postnatal anxiety and depressive symptoms: a systematic review and meta-analysis. *Br J Sports Med* 2018; 52: 1376–1385.
18 Owe KM, Nystad W, Stigum H, *et al.* Exercise during pregnancy and risk of cesarean delivery in nulliparous women: a large population-based cohort study. *Am J Obstet Gynecol* 2016; 215: 791.e1–791.e13.
19 Norwegian Directorate of Health. Fysisk aktivitet i forebygging og behandling: 3. Gravide [Physical activity in prevention and treatment: 3. Pregnant women]. www.helsedirektoratet.no/faglige-rad/fysisk-aktivitet-i-forebygging-og-behandling/gravide Date last updated: 9 May 2022. Date last accessed: 23 September 2022.

20 Carlsen OCL, Gudmundsdóttir HK, Bains KES, *et al.* Physical activity in pregnancy: a Norwegian–Swedish mother–child birth cohort study. *AJOG Global Reports* 2021; 1: 100002.

21 Hevroni A, Goldman A, Blank-Brachfeld M, *et al.* Use of tidal breathing curves for evaluating expiratory airway obstruction in infants. *J Asthma* 2018; 55: 1331–1337.

22 Stick SM, Burton PR, Gurrin L, *et al.* Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. *Lancet* 1996; 348: 1060–1064.

23 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: 996–1001.

24 Lødrup Carlsen KC, Jaakkola JJ, Nafstad P, *et al. In utero* exposure to cigarette smoking influences lung function at birth. *Eur Respir J* 1997; 10: 1774–1779.

25 Morris MJ, Lane DJ. Tidal expiratory flow patterns in airflow obstruction. *Thorax* 1981; 36: 135–142.

26 Martinez FD, Morgan WJ, Wright AL, *et al.* Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med* 1988; 319: 1112–1117.

27 Gray D, Willemse L, Visagie A, *et al.* Determinants of early-life lung function in African infants. *Thorax* 2017; 72: 445–450.

28 Anık A, Öztürk S, Erge D, *et al.* Tidal breath in healthy term newborns: an analysis from the 2nd to the 30th days of life. *Pediatr Pulmonol* 2021; 56: 274–282.

29 Kraemer R, Smith HJ, Matthys H. Normative reference equations of airway dynamics assessed by whole-body plethysmography during spontaneous breathing evaluated in infants, children, and adults. *Physiol Rep* 2021; 9: e15027.

30 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: 3832–3838.

31 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: 248–252.

32 Lodrup KC, Mowinckel P, Carlsen KH. Lung function measurements in awake compared to sleeping newborn infants. *Pediatr Pulmonol* 1992; 12: 99–104.

33 Lodrup Carlsen KC, Rehbinder EM, Skjerven HO, *et al.* Preventing Atopic Dermatitis and ALLergies in Children – the PreventADALL study. *Allergy* 2018; 73: 2063–2070.

34 Kreyberg I, Bains KES, Carlsen KH, *et al.* Stopping when knowing: use of snus and nicotine during pregnancy in Scandinavia. *ERJ Open Res* 2019; 5: 00197-2018.

35 Bains KES, Gudmundsdóttir HK, Färdig M, *et al.* Infant lung function: criteria for selecting tidal flow–volume loops. *ERJ Open Res* 2022; 8: 00165-2022.

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

37 Sussman D, Lye SJ, Wells GD. Impact of maternal physical activity on fetal breathing and body movement – a review. *Early Hum Dev* 2016; 94: 53–56.

38 Bauer I, Hartkopf J, Kullmann S, *et al.* Spotlight on the fetus: how physical activity during pregnancy influences fetal health: a narrative review. *BMJ Open Sport Exerc Med* 2020; 6: e000658.

39 Harding R. Fetal pulmonary development: the role of respiratory movements. *Equine Vet J Suppl* 1997; 24: 32–39.

40 den Dekker HT, Sonnenschein-van der Voort AM, 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: 1026–1035.

41 Beetham KS, Giles C, Noetel M, *et al.* The effects of vigorous intensity exercise in the third trimester of pregnancy: a systematic review and meta-analysis. *BMC Pregnancy Childbirth* 2019; 19: 281.