Early origins of infant lung function

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1. Preface

1.1 Acknowledgements

First, I want to thank the PreventADALL study participants, the children and their parents, contributing to knowledge by giving of their time and energy during the busy infant and toddler years. Without you, there would be no study.

My journey towards this thesis started in early 2014, by meeting Karin Cecilie Lødrup Carlsen in the university basement at Ullevål. I had been a paediatric resident for four years, currently working at NICU Ullevål, my goal department when I, three years earlier, moved from Iceland to Norway to continue my specialist training. My main interests in paediatrics were, and still are, lung function and lung diseases, neonatology, and chronic diseases complicated with respiratory symptoms. In addition, physical activity is for me an essential part of life, and I believe in its power to improve both physical and mental health. I feel lucky to combine these interests in research, and I am deeply indebted to all my supervisors on the way, Professors Karin Cecilie Lødrup Carlsen, Kai-Håkon Carlsen and Guttorm Haugen, and Eva Maria Rehbinder, who became a co-supervisor when Kai-Håkon retired.

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And last, but definitely not the least, my friends and family.

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1.2 Summary of thesis

Background

Impaired lung function shortly after birth tracks through childhood and adolescence and is associated with lower lung function values and obstructive lung diseases in children and adults. Lung development starts in early fetal life and while the formation of airways completes in-utero, alveoli keep growing postnatally and lung function peaks in early adulthood. Infant lung function can be measured with tidal flow-volume (TFV) loops from birth and the ratio of time to peak tidal expiratory flow to expiratory time (t_{PTEF}/t_E) reflects the rate of expiratory airflow.

Maternal lifestyle during pregnancy may affect fetal lung development, with maternal smoking being associated with lower infant t_{PTEF}/t_E, wheeze and asthma. Maternal asthma, prematurity and low birthweight increase the risk of lower infant t_{PTEF}/t_E. Physical activity (PA) during pregnancy is safe for the fetus and beneficial for maternal and possibly offspring health, however, if maternal PA is associated with lung function in infancy is unknown.

Fetal development, including general and organ-specific growth, may impact later health. Larger fetal size has been positively associated with lung function in childhood and inversely associated with asthma. Fetal thoracic circumference (TC) indicates fetal lung size, and TC measured in children and adults is associated with lung function. However, it is not clear if fetal TC is associated with postnatal lung function.

Objective and aims

The objective of this thesis is to explore maternal and fetal factors that may be associated with lung function in infancy, with four specific aims:

1. To explore the role of pre-pregnancy factors on PA in pregnancy, and to explore if maternal PA is associated with pregnancy outcomes, focusing on infant size.
2. To determine if maternal PA in pregnancy is associated with early infant lung function.
3. To determine if fetal TC at mid-pregnancy is associated with early infant lung function.
4. To explore potential sex differences in the associations of maternal PA or fetal TC with early infant lung function.

Methods

The thesis is based upon the Scandinavian, general population-based Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL) birth cohort of 2394 mother-child pairs. In 2014-2016, 2697 pregnant women were recruited in Norway and Sweden at approximately 18 (16-22) gestational weeks (GW). Their healthy singletons or twins, born after at least 35.0 GWs, were included at birth. Information on mid-pregnancy fetal size, including (TC), head circumference (HC), abdominal circumference (AC) and femur length (FL) was collected at the routine 18-week ultrasound examination. The women reported socioeconomic factors, general health, family history of allergic diseases and lifestyle factors including PA, in electronic questionnaires at 18 and 34 GWs. Based on self-reported intensity and amount of PA in the first half of pregnancy, the general physical activity (GPA) level was estimated, and women were classified as inactive or active. Active women were further defined as fairly or highly active. To account for variation in gestational age (GA) at the time of ultrasound, fetal

TC relative to general fetal size, as TC/HC, TC/AC and TC/FL, was explored for the association with infant lung function. Tidal flow-volume loops were measured at three months of age and analysed according to pre-defined criteria.

The main outcomes are the GPA level in the first half of pregnancy (aim 1), GA at birth, birth type, placenta size and infant size at birth and three months of age (aim 1), low lung function by t_{PTEF}/t_E <0.25 (aims 2-4), t_{PTEF}/t_E, continuous and dichotomized at the 10^{th}, 25^{th} and 50^{th} percentiles to explore associations with lung function in the lower range (aims 3 and 4) and tidal volume (V_T) and V_T/kg (aims 2-4).

Associations between pre-pregnancy factors and the GPA level were assessed using univariable logistic regression. Pregnancy outcomes and infant size were explored according to maternal GPA level using the independent sample t-test, one-way ANOVA and the Chi-squared test (χ^2). To explore the associations of maternal PA and fetal TC with infant lung function, linear and logistic regression models were used, adjusted for relevant covariates. To assess if the associations between early life factors and infant lung function differed among girls and boys, interaction terms were added to the regression models, in addition to an adjustment for sex (PA and lung function) and stratification for sex (TC and lung function). The results of the regression analyses are reported as regression coefficients (β estimate ($\hat{\beta}$)) and odds ratios (OR), for linear and logistic regression respectively, with 95% confidence intervals (CI) and p-values.

Results

Aim 1: Of 2348 women, 919 women (39.1%) were defined as *inactive* in the first half of pregnancy, while 648 (27.6%) had been *fairly active* and 781 (33.3%) *highly active*. Regular pre-pregnancy PA (OR 4.82, 95% CI [3.83, 6.09], $p<0.001$) and higher education (OR 1.38, 95% CI [1.03, 1.86], $p=0.033$) were positively associated with being active compared to inactive in pregnancy, while the opposite was observed for parity ≥1 (OR 0.62, 95% CI [0.52, 0.75], $p<0.001$), not living with a partner (OR 0.48, 95% CI [0.28, 0.82], $p=0.007$), currently being on sick leave and being Swedish or of non-Nordic origin compared to Norwegian. Among the 812 mother-child pairs included in aim 2, no significant differences in GA at birth, birth mode, placenta weight nor infant size at birth or three months of age were observed according to maternal GPA level.

Aim 2: Among the 812 infants (48.8% girls) with available information on maternal PA and infant lung function, infants of inactive mothers had twice the odds of having t_{PTEF}/t_E <0.25 (OR 2.07, 95% CI [1.13, 3.82], $p=0.019$). While no significant difference in V_T/kg was observed between infants of inactive compared to all active mothers, high maternal activity was inversely associated with V_T/kg (OR -0.48, 95% CI [-0.84, -0.13], $p=0.008$).

Aim 3: Among the 851 infants (47.8% girls) with available information on fetal size and infant lung function, no significant association between fetal TC/HC nor TC/AC and t_{PTEF}/t_E was observed, while fetal TC/FL was weakly, inversely associated with t_{PTEF}/t_E ($\hat{\beta}$=-0.03, 95% CI [-0.05, -0.007], $p=0.01$). Fetal TC/HC and TC/FL were positively associated with infant V_T, but not V_T/kg.

Aim 4: The interaction terms of infant sex and maternal GPA level or the TC ratios were not significantly associated with infant lung function. The association between maternal GPA level and infant lung function was similar among girls and boys. When stratified for sex, the association between fetal TC/FL and t_{PTEF}/t_E was significant among girls only, and adjusting for sex increased the strength of the associations of fetal TC/HC and TC/FL with infant V_T.

Conclusions

Regular pre-pregnancy PA, higher education, nulliparity and living with a partner were positively associated with the maternal GPA level, while current sick leave and a Swedish or non-Nordic origin were associated with lower GPA level. Maternal GPA level was not associated with GA at birth, birth mode, placenta weight, nor infant size at birth or three months of age. Maternal inactivity was associated with increased odds of low lung function while V_T/kg was lowest among infants of highly active mothers. Neither fetal TC/HC nor TC/AC were associated with infant t_{PTEF}/t_E while a weak inverse association of TC/FL with t_{PTEF}/t_E was observed. Fetal TC/HC and TC/FL were positively associated with infant V_T. The associations of maternal GPA level and fetal thoracic size with infant t_{PTEF}/t_E were similar in girls and boys.

1.3 Norsk sammendrag

Bakgrunn

Nedsatt lungefunksjon i tidlig spedbarnsalder kan spores gjennom barne- og ungdomsårene og er assosiert med lavere lungefunksjonsverdier og obstruktive lungesykdommer hos barn og voksne. Lungeutviklingen starter tidlig i fosterlivet. Mens dannelsen av luftveier fullføres i fosterlivet utvikles alveolene videre også etter fødselen, og lungefunksjonen er på sitt høyeste nivå i starten av tyveårene. Lungefunksjonen hos spedbarn kan måles med tide flow-volum (TFV) kurver fra fødselen av. Forholdet mellom tid til maksimal ekspiratorisk flow og total ekspirasjonstid (t_{PTEF}/t_E) reflekterer hastigheten på luftstrømmen på utpust.

Mors livstil i svangerskapet kan påvirke lungeutvikling, og eksponering i fosterlivet for mors røyking er assosiert med lavere t_{PTEF}/t_E i spedbarnsalder samt piping i brystet og astma. Astma hos mor, prematur fødsel og lav fødselsvekt øker også risikoen for lavere t_{PTEF}/t_E hos spedbarn. Fysisk aktivitet (FA) i svangerskapet er trygt for fosteret og fordelaktig for mors og sannsynligvis også barnets helse, mens det er ukjent om mors fysiske aktivitet i svangerskapet er assosiert med lungefunksjon i spedbarnsalder.

Både generell og organspesifikk fostervekst kan påvirke barnets senere helse. Det er beskrevet en positiv assosiasjon mellom fosterstørrelse og lungefunksjon i barnealder og en omvendt assosiasjon mellom fosterstørrelse og astma. Fosterets thorakalomkrets (TO), målt med ultralyd, indikerer føtal lungestørrelse, og TO målt hos barn og voksne er assosiert med lungefunksjon. Det er imidlertid ikke klart om føtal TO er assosiert med postnatal lungefunksjon.

Målsetting

Hovedformålet med denne avhandlingen er å utforske maternelle faktorer og faktorer i fosterlivet som kan ha betydning for lungefunksjon hos spedbarn, med fire spesifikke formål:

1. Å utforske hvordan maternelle faktorer er assosiert med FA i svangerskapet, og om mors FA er assosiert med svangerskapsutfall, med fokus på barnets størrelse.
2. Å undersøke om mors FA i svangerskapet er assosiert med lungefunksjon i tidlig spedbarnsalder.
3. Å undersøke om føtal TO i midtre del av svangerskapet er assosiert med lungefunksjon i tidlig spedbarnsalder.
4. Å utforske potensielle kjønnsforskjeller i assosiasjonene mellom mors FA eller føtal TO og lungefunksjon i tidlig spedbarnsalder.

Metode

Denne avhandlingen bygger på data fra den skandinaviske fødselskohortstudien Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL) med 2394 deltagende mor-barn par fra den generelle befolkningen. Gravide kvinner (n=2697) i Norge og Sverige ble i 2014-2016 rekruttert rundt svangerskapsuke 18 (16-22). Deres friske barn, enkelfødte eller tvillinger, født med gestasjonsalder (GA) 35.0 uker eller mer, ble inkludert ved fødselen. Informasjon om fosterstørrelse midt i svangerskapet, inkludert TO, hodeomkrets (HO), abdominalomkrets (AO) og femurlengde (FL) ble samlet inn fra rutineundersøkelsen med ultralyd i svangerskapsuke 18. Kvinnene rapporterte blant annet generell bakgrunn og helse, samt livsstilsfaktorer inkludert FA, i elektroniske spørreskjemaer i svangerskapsuke 18 og 34. Basert på selvrapportert intensitet og mengde av FA i første halvdel av svangerskapet, ble det generelle fysiske aktivitetsnivået (GFA) estimert og kvinnene klassifisert som inaktive eller aktive. Aktive kvinner ble videre definert som nokså eller meget aktive. For å ta hensyn til variasjonen i GA på tidspunktet for ultralydundersøkelsen, ble føtal TO relatert til generelle størrelsesmål. De føtale størrelsesmålene TO/HO, TO/AO og TO/FL ble undersøkt for mulig assosiasjon med lungefunksjon i spedbarnsalder. Tide flow-volum kurver ble målt ved tre måneders alder og analysert i henhold til forhåndsdefinerte kriterier.

Hovedutfallene er GFA-nivå i første halvdel av svangerskapet (formål 1), GA ved fødsel, fødselsmåte, placentavekt ved fødsel og barnets størrelse ved fødselen og tre måneders alder (formål 1), lav lungefunksjon definert som t_{PTEF}/t_E <0.25 (formål 2-4), t_{PTEF}/t_E både som kontinuerlig variabel samt dikotomisert ved 10, 25 og 50 persentilen for å utforske assosiasjoner med lungefunksjon i nedre del av skalaen (formål 3 og 4), og tidevolum (V_T) og V_T/kg (formål 2-4).

Assosiasjoner mellom maternelle faktorer og GFA-nivået ble analysert med univariabel logistisk regresjon. Svangerskapsutfall og barnets størrelse ble utforsket i henhold til mors GFA-nivå ved bruk av t-tester, enveis ANOVA og Chi-kvadrattester (χ^2). Mulige assosiasjoner mellom mors FA i svangerskapet eller føtal TO og lungefunksjon i spedbarnsalder ble analysert med lineære og logistiske regresjonsmodeller, justert for relevante kovariater. For å vurdere om assosiasjonene mellom faktorer i fosterlivet og lungefunksjon i spedbarnsalder varierte mellom jenter og gutter, ble interaksjonsledd lagt til regresjonsmodellene, i tillegg til justering for kjønn (FA og lungefunksjon) og stratifisering for kjønn (TO og lungefunksjon). Resultatene rapporteres som regresjonskoeffisienter (β-estimat ($\hat{\beta}$)) og odds ratio (OR), for henholdsvis lineær og logistisk regresjon, med 95% konfidensintervall (KI) og p-verdier.

Resultater

Formål 1: Av 2348 kvinner ble 919 kvinner (39,1%) definert som *inaktive* i første halvdel av svangerskapet, mens 648 (27,6%) hadde vært *nokså aktive* og 781 (33,3%) *meget aktive*. Regelmessig FA før svangerskapet (OR 4.82, 95% KI [3.83, 6.09], p<0.001) og høyere utdanning (OR 1.38, 95% KI [1.03, 186], p=0.033) var positivt assosiert med å være aktiv sammenlignet med inaktiv i svangerskapet. Paritet ≥1 (OR 0.62, 95% KI [0.52, 0.75], p<0.001), å ikke bo sammen med partner (OR 0.48, 95% KI [0.28, 0.82], p=0.007), være sykemeldt samt å ha svensk eller ikke-nordisk opprinnelse sammenlignet med norske kvinner var negativt assosiert med å være fysisk aktiv i svangerskapet. Blant de 812 mor-barn par der barnet også hadde tilgjengelig lungefunksjonsmåling ble det ikke observert signifikante forskjeller i GA ved fødsel, fødselsmåte, placentavekt eller barnets størrelse ved fødselen eller tre måneders alder, i henhold til mors GFA-nivå.

Formål 2: Blant 812 spedbarn (48.8% jenter) med tilgjengelig informasjon om mors FA og lungefunksjon i spedbarnsalder, hadde barn av inaktive mødre høyere odds for å ha t_{PTEF}/t_E <0.25 (OR 2.07, 95% KI [1.13, 3.82], p=0.019). Til tross for at ingen signifikant forskjell ble observert i V_T/kg mellom spedbarn av inaktive sammenlignet med alle aktive mødre, var høy GFA-nivå hos mor omvendt assosiert med V_T/kg (OR -0.48, 95% KI [-0.84, -0.13], p= 0.008).

Formål 3: Blant 851 spedbarn (47.8% jenter) med tilgjengelig informasjon om fosterstørrelse midt i svangerskapet og lungefunksjon i spedbarnsalder ble det ikke observert signifikant sammenheng mellom fosterets TO/HO eller TO/AO og t_{PTEF}/t_E, mens føtal TO/FL var svakt, omvendt assosiert med t_{PTEF}/t_E ($\hat{\beta}$=-0.03, 95% KI [-0.05, -0.007], p=0.01). Føtal TO/HO og TO/FL var positivt assosiert med V_T i spedbarnsalder men ikke med V_T/kg.

Formål 4: Det ble ikke observert signifikant interaksjon mellom barnets kjønn, mors GFA-nivå eller TO ratioene i forhold til lungefunksjon. Assosiasjonen mellom mors GFA-nivå og lungefunksjon var lik blant jenter og gutter. Ved stratifisering for kjønn, var assosiasjonen mellom føtal TO/FL og t_{PTEF}/t_E signifikant kun blant jenter, og ved justering for kjønn økte styrken av assosiasjonene mellom føtal TO/HO, TO/FL og $V_{T.}$

Konklusjon

Regelmessig FA før svangerskapet, høyere utdanning, å ikke ha barn fra før og å bo sammen med partner var positivt assosiert med mors GFA-nivå i første halvdel av svangerskapet, mens det motsatte ble funnet for å være sykemeldt og for svensk eller ikke-nordisk opprinnelse. Mors GFA-nivå var ikke assosiert med GA ved fødsel, fødselsmåte, placentavekt eller barnets størrelse ved fødselen eller tre måneders alder. Maternell inaktivitet var assosiert med lavere lungefunksjon i spedbarnsalder, mens V_T/kg var lavest blant spedbarn av meget aktive mødre. Hverken føtal TO/HO eller TO/AO var assosiert med t_{PTEF}/t_E i spedbarnsalder, mens en svak omvendt assosiasjon mellom TO/FL og t_{PTEF}/t_E ble observert. Føtal TO/HO og TO/FL var positivt assosiert med V_T. Assosiasjonene mellom mors GFA-nivå og føtal TO og t_{PTEF}/t_E i spedbarnsalder ble ikke påvirket av kjønn.

1.4 Abbreviations

AC	abdominal circumference
BMI	body mass index
BW/PW ratio	birth weight to placenta weight ratio
CI	confidence interval
FL	femur length
GA	gestational age
GPA level	general physical activity level
GW	gestational week
HC	head circumference
OR	odds ratio
PA	physical activity
PreventADALL	Preventing Atopic Dermatitis and ALLergies in Children
R^2	percentage of variation explained by the respective exposure(s)
SD	standard deviation
TC	thoracic circumference
TFV	tidal flow-volume
t_{PTEF}/t_E	ratio of time to peak tidal expiratory flow to expiratory time
V_T	tidal volume
V_T/kg	tidal volume per kg body weight
$\hat{\beta}$	β estimate, regression coefficient

1.5 List of papers

Paper I

Physical activity in pregnancy: a Norwegian-Swedish mother-child birth cohort study.

AJOG Global Reports. 2021; DOI: https://doi.org/10.1016/j.xagr.2020.100002

Oda C. L. Carlsen, Hrefna K. Gudmundsdóttir, Karen Eline S. Bains, Randi Bertelsen, Karin C. L. Carlsen, Kai-Håkon Carlsen, Kim M. A. Endre, Berit Granum, Guttorm Haugen, Gunilla Hedlin, Christine M. Jonassen, Ina Kreyberg, Linn Landrø, Caroline-Aleksi Olsson Mägi, Björn Nordlund, Live S. Nordhagen, Kristian Pehrson, Carina M. Saunders, Katrine Sjøborg, Håvard O. Skjerven, Anne Cathrine Staff, Cecilie Svanes, Cilla Söderhäll, Riyas Vettukattil, Magdalena Værnesbranden, Johanna Wiik, Eva Maria Rehbinder.

Paper II

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

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Hrefna Katrín Gudmundsdóttir, Oda C. L. Carlsen, Karen Eline Stensby Bains, Martin Färdig, Guttorm Haugen, Christine M. Jonassen, Marissa LeBlanc, Björn Nordlund, Eva Maria Rehbinder, Håvard O. Skjerven, Anne Cathrine Staff, Riyas Vettukattil, Karin C. Lødrup Carlsen.

Paper III

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

Pediatric Pulmonology. 2023; DOI: https://doi.org/10.1002/ppul.26153

Hrefna Katrín Gudmundsdóttir, Katarina Hilde, Karen Eline Stensby Bains, Martin Färdig, Guttorm Haugen, Marissa LeBlanc, Live Solveig Nordhagen, Björn Nordlund, Eva Maria Rehbinder, Håvard O. Skjerven, Anne Cathrine Staff, Riyas Vettukattil, Karin C. Lødrup Carlsen.

2. General introduction

2.1 Early origins of lung function

Impaired lung function at birth or in early infancy, is associated with and precedes clinical symptoms of obstructive airways disease such as wheeze and asthma, both in children [1-7] and adults [5, 6]. Tracking through childhood and adolescence to adult life, lower lung function values at birth are associated with a lower peak lung function in early adulthood, before the natural age-related decline in older adults [6, 8-12]. Having a lower baseline lung function from early life may contribute to accelerating the progress of lung function reduction leading to chronic obstructive pulmonary disease (COPD) [10-12], a disease constituting the third leading cause of death worldwide [13].

Lower lung function measured shortly after birth, by tidal breathing and maximal expiratory flow at functional residual capacity ($V_{max}FRC$), was associated with an increased risk of wheezing during infancy and the pre-school years in the Tucson Children's Respiratory Study, a birth cohort study including infants born in 1980-1984 [14, 15]. Further follow-up of the study participants showed tracking of low lung function values until adulthood, and those with lowest lung function in infancy had a significantly increased risk of developing asthma by 36 years of age [5, 9].

A low ratio of time to peak tidal expiratory flow to expiratory time (t_{PTEF}/t_E) significantly increased the risk of bronchial obstruction before two years of age in the Norwegian Environment and Childhood Asthma study, measuring lung function by tidal flow-volume (TFV) loops in 802 newborn infants born in 1992-1993 [1]. At 10 years, an increased risk of asthma was observed in children with infant t_{PTEF}/t_E values at or below median [3]. At 16 years, those with lower t_{PTEF}/t_E in infancy as well as reduced spirometric z-scores at 10 and 16 years of age, had the highest risk of developing asthma with both atopic dermatitis and allergic rhinitis as comorbidities [16].

Long-term associations of impaired lung function early in life with later wheeze and asthma have been shown also in other birth-cohort studies [6, 7, 17], suggesting in-utero origins of a deviating development of lung function and respiratory diseases.

The long-lasting influence of early-life lung function on respiratory health decades later, are in line with the concept of developmental origins of health and diseases (DOHaD). The DOHaD concept was established in the 1990s, originally around the discovery of a link between reduced birth weight and an increased risk of non-communicable diseases later in life, such as cardiovascular diseases and insulin resistance [18-21]. Whether the origins of asthma and COPD are established even earlier than in infancy, via fetal life origins of infant lung function, remains to be fully explored.

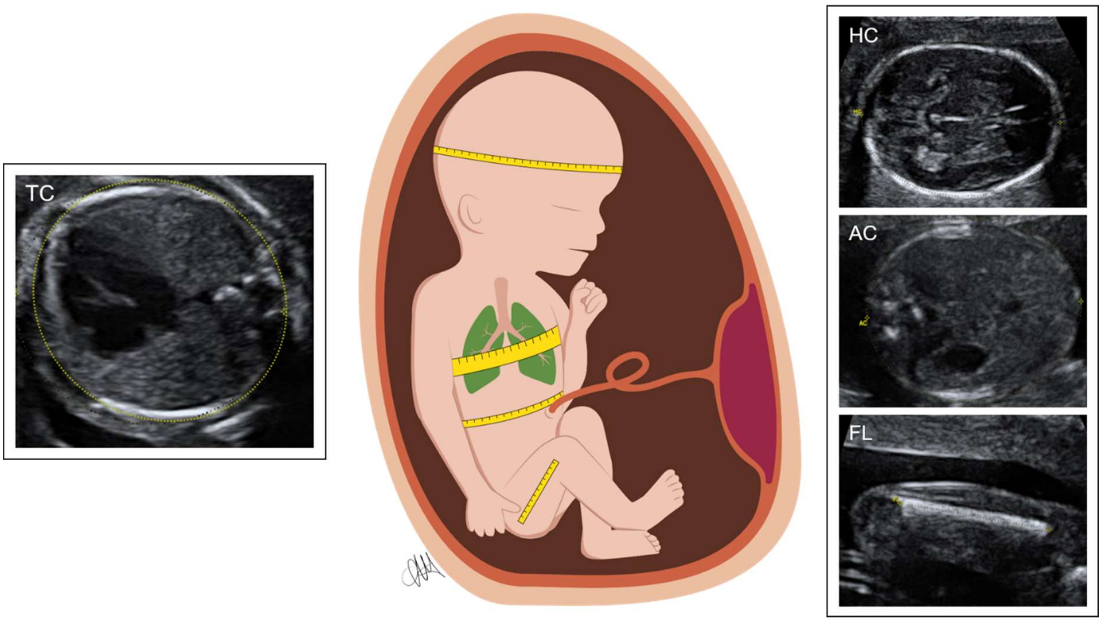
2.2 The fetus

The normal duration of pregnancy is 40 weeks, divided into three trimesters of almost equal duration [22]. The first eight weeks of fetal life, the embryonic period, encompass organogenesis. At the beginning of the 9th week, when the fetal period begins, all fetal organs have been established [23]. The fetal period, lasting until birth, is characterized by fetal maturation and growth, with approximately half of the fetal weight at term gained during the last 10 weeks of intrauterine life [23-25]. Throughout pregnancy, fetal weight is estimated to be higher in boys compared to girls [25, 26].

2.2.1 Fetal size and ultrasound measurements

Fetal growth and well-being during pregnancy can be assessed and followed with ultrasound examinations, including two- and three-dimensional biometric and volume measures in addition to Doppler velocimetry. Ultrasound examinations are an essential part of standard antenatal care and aim to detect fetal anomalies, date the pregnancy and assess fetal well-being including growth abnormalities. Measuring first-trimester crown-rump length (CRL) is assumed to be the most reliable method to estimate the date of delivery [27], but after 14 gestational weeks (GWs), head circumference (HC) and/or femur length (FL) should be used [27-29]. Fetal biparietal diameter, HC, abdominal circumference (AC) and FL are biometric measurements of general fetal size, measurable from the second trimester onward, and a combination of these is used to estimate fetal weight [25, 30]. Fetal growth is out of the scope of this thesis, but is indirectly assessed by repeated measurements of fetal biometry. While biparietal diameter and FL mostly reflect skeletal development, HC reflects the size of the brain and AC measures the size of the liver, subcutaneous fat and the surrounding skin, indirectly reflecting fetal nutritional status [24, 27]. Ultrasound measurements of fetal thoracic circumference (TC), assessing thoracic size, can be used as a proxy for fetal lung size [31]. Ultrasound measurements of fetal HC, TC, AC and FL are illustrated in Figure 2.1.

Figure 2.1 Biometric fetal size measured by ultrasound at mid-pregnancy. Head circumference (HC), thoracic circumference (TC), abdominal circumference (AC) and femur length (FL). The estimated fetal weight at 20 weeks GA is approximately 300-400 g [25].
Illustration of fetus: Øystein Horgmo, University of Oslo. Photos of ultrasound measures from PreventADALL study participants: Katarina Hilde.



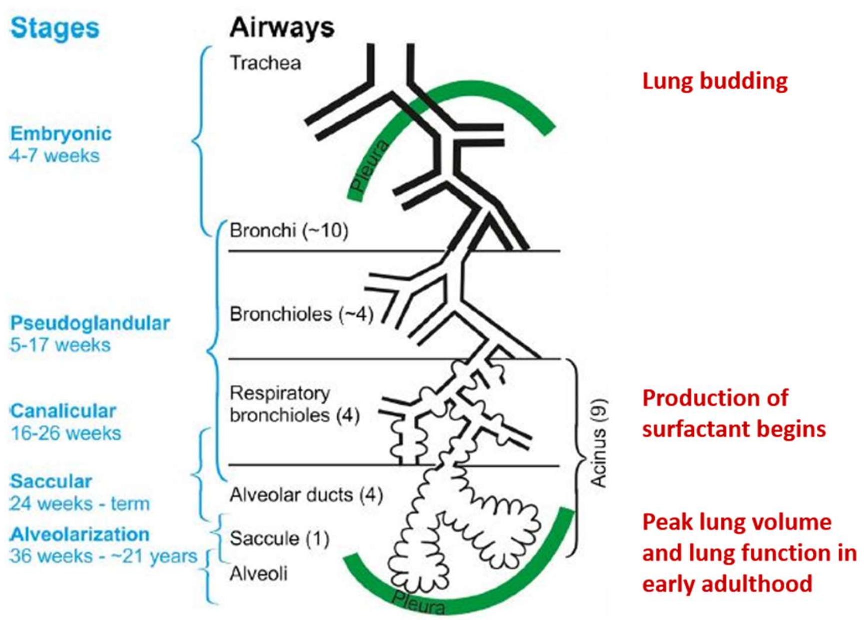
A recent study in the Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL) cohort [32] showed a correlation (r=0.74) between fetal TC and lung volume at 30 GWs [33]. Previously, a correlation (r^2=0.61) between fetal TC in the second half of pregnancy and lung weight among 24 fetuses, whereof 21 had lethal lung hypoplasia, born within a week of the ultrasound measurement has been observed [34].

Doppler velocimetry of flow in the uterine and umbilical arteries indicates placental health while measurements in the umbilical and middle cerebral arteries as well as the ductus venosus reflect fetal well-being. Changes in flow or resistance in these vessels may suggest centralization of blood flow to vital organs due to placental deficiency and fetal stress [24, 35, 36].

2.2.2 Lung development

The development of the respiratory system starts with lung budding in the fourth week of fetal life [11, 37, 38]. These buds become the main bronchi of the left and right lung, and with continuous branching, an average of 23 airway generations are formed, distally ending in the alveoli [38]. At 22-24 GWs type II epithelial cells in the alveolar ducts start producing small amounts of surfactant to reduce alveolar surface tension, enabling gas exchange in preterm infants born at this stage [37, 38]. Branching of the airways completes during the second trimester [11, 38], while alveolarization starts at approximately 36 GWs. The alveoli keep growing in both size and number after birth, resulting in the lung volume and function increasing until a peak has been reached in early adulthood [11, 37] (Figure 2.2).

Figure 2.2 Development of the airways.
Reproduced with Creative Commons Attribution 4.0 International License, CC BY 4.0 (http://creativecommons.org/licenses/by/4.0/). Schittny JC. Development of the lung. Cell Tissue Res. 2017 Mar;367(3):427-444. doi: 10.1007/s00441-016-2545-0.



The lungs seem to mature more rapidly, with surfactant production starting earlier, in girls compared to boys, while boys have larger lungs at term compared to same-sized girls [37].

Both genetics and the intrauterine environment affect the development of the lungs and airways, leading to future lung function in postnatal life [10, 11].

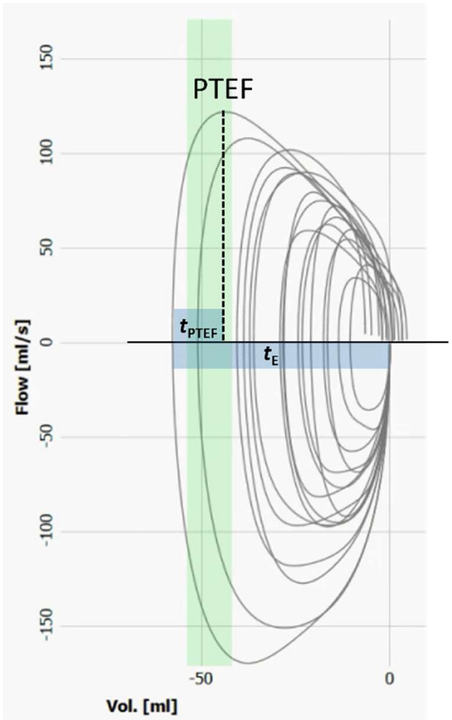
2.3 Lung function in infancy

Several methods to measure lung function in infants are available. Forced expiratory outcomes such as the V_{max}FRC or forced expiratory volume in the first 0.4 seconds of expiratory flow ($FEV_{0.4}$) measured by the chest-compression technique, functional residual capacity and airway resistance by plethysmography, and respiratory system compliance by the occlusion technique are well known [39, 40]. These methods are partly comparable with voluntarily measured spirometry outcomes from older children and adults [5]. Due to the need of cooperation during measurement, forced expiratory methods usually demand sedation in infants and small children. Therefore, measurements of TFV loops, which can be performed in both awake and naturally sleeping infants from birth, are more readily applicable in this age group Figure 2.3.

Figure 2.3 Tidal flow-volume loops measured in a three-month-old infant.
Printed with parental consent.
Photo: Karen Eline Stensby Bains.

The main TFV parameter is the ratio of time to peak tidal expiratory flow to expiratory time, t_{PTEF}/t_E (Figure 2.4), which in previous studies has been shown to correlate with $V_{max}FRC$ (r=0.28 and r=0.61) [5, 41] and FEV_1 predicted (r=0.72) [42].

Figure 2.4 Tidal flow-volume loops from a three-month-old infant in the PreventADALL study.
The time to peak tidal expiratory flow (t_{PTEF}) and expiratory time (t_E) are marked, demonstrating the t_{PTEF}/t_E ratio.



Associations of in-utero exposure to maternal smoking [43-45] and a family history of asthma [43, 46] with lower infant lung function measured by t_{PTEF}/t_E have also been detected in studies using forced expiratory outcomes [2, 6, 15, 47]. In-utero exposure to maternal hypertension [43] and to household air pollution [48, 49] have also been identified as risk factors associated with lower infant t_{PTEF}/t_E. Having a t_{PTEF}/t_E in the lower range in infancy is associated with an increased risk of airway hyper-responsiveness and asthma in both children [3-5, 14] and adults [5]. Cut-off values to define impaired lung function by t_{PTEF}/t_E have yet to be defined. Nevertheless, infants with t_{PTEF}/t_E values ≤0.20 and up to 0.25 have been described at a higher risk of developing obstructive lung disease later in life [1, 3, 41, 42] while those with higher values, from 0.30 and onward, were not [1, 3-5, 14, 41, 50]. Other studies have compared the prevalence of respiratory illnesses among children with infant t_{PTEF}/t_E in the lower percentiles to those with higher values [3, 5]. The t_{PTEF}/t_E ratio has been reported higher in girls compared to boys [37, 46, 48], but known advantages of having a

t_{PTEF}/t_E in the highest compared to the middle range in regard to later clinical outcomes have not been described.

Compared to t_{PTEF}/t_E, little is known about tidal volume (V_T) in healthy infancy and its associations with later respiratory health. Lower infant V_T is associated with prematurity [51], and has been a predictor of poor outcome in infants with lung hypoplasia [52]. The V_T increases with age [53, 54], while t_{PTEF}/t_E has been shown to decrease during the first weeks of life [5]. When tidal breathing indices have been compared according to arousal state, t_{PTEF}/t_E [55, 56] and V_T [56] were shown to be higher in awake compared to sleeping infants, but in most previous lung function studies, the infants were sleeping or sedated during the measurements.

2.4 Early-life factors associated with lung function

Fetal size and growth trajectories before and after birth are associated with later respiratory health [57-61]. A British cohort study from the general population showed that children with a larger fetal crown-rump length in the first trimester had higher lung function values at five and 10 years of age, and a lower risk of wheeze and asthma [59, 60]. A larger second-trimester biparietal diameter of the head was associated with a higher forced expiratory volume at five years of age and higher flow rates at 10 years, as well as a reduced risk of wheezing and asthma [59, 60]. Lower, compared to higher, fetal growth rate was associated with lower lung function at 10 years of age [60], and an increased risk of childhood wheeze and asthma, being more pronounced in girls compared to boys [59]. In a population-based birth cohort from the Netherlands, lower fetal growth from mid-pregnancy to birth was associated with higher airway resistance at six years of age [58] and higher lung function by spirometry at 10 years of age [61].

In addition, preterm birth [11, 62, 63], lower birth weight [60-62, 64], being born small for gestational age (SGA) [65, 66] and higher weight gain in infancy [58, 61, 62, 64, 67] are associated with lower lung function [11, 60-62, 64], and an increased risk of wheezing and childhood asthma [11, 58, 62, 63, 67].

Overall, fetal growth restriction measured as lower general fetal size as early as in the first trimester, and lower fetal growth rates, appears to be associated with lung function and respiratory symptoms in childhood. However, it is not known if fetal thoracic size, measured as the fetal TC, is associated with postnatal lung function.

2.5 Thoracic circumference and lung function

Thoracic circumference reflects lung size [33, 34, 68], and a positive association between TC and lung function has been observed among school-aged children and young adults [69, 70]. While fetal thoracic size is not routinely measured in normal pregnancies, an ultrasound measure of fetal TC can provide supportive information when fetal lung development may have been disturbed. Fetal TC, particularly adjusted for AC as the TC/AC ratio, has a role in prenatal diagnosis of neonatal lung hypoplasia and is among biometric variables used to predict postnatal outcome in fetuses at risk for this disease, such as those with prolonged oligohydramnios [34, 71-73].

To the best of my knowledge, no previous studies have explored the association between fetal TC and postnatal lung function in healthy infants.

2.6 Physical activity in pregnancy

Regular physical activity (PA) is a principal element of a healthy lifestyle in all phases of life, including the pregnancy [74, 75]. Maternal PA is safe for the fetus [76-78] and neither associated with abnormal birth weight [77, 79], nor preterm birth [74, 75, 77, 79, 80] in infants of healthy mothers. Staying physically active during pregnancy is beneficial for maternal and fetal health and well-being, by reducing pregnancy complications (Table 2.1), and among non-obese women, reducing the risk of a caesarean delivery [79-82].

Table 2.1 Benefits of physical activity in pregnancy; associations with complications of pregnancy

Reduced risk of pregnancy complications	References
Excessive weight gain	[75, 82, 83]
Hypertensive disorders of pregnancy	[79, 84]
Gestational diabetes mellitus	[75, 79, 84]
Depressive disorders during pregnancy and postpartum	[85, 86]
Lumbopelvic pain	[86]

In line with recommendations from other countries [74, 87], the Norwegian Directorate of Health recommends that pregnant women complete at least 150 minutes of moderate or high intensity PA per week [88]. Additionally, recent guidelines from the World Health Organization state that sessions of any duration may add up to the recommended weekly minutes [75]. Previous studies have repeatedly shown that large groups of pregnant women do not meet these recommendations [86, 89-91]. Regular PA prior to pregnancy [90, 92], younger age [91, 93], higher education [91-93], and nulliparity [86, 90, 92] have been associated with higher levels of PA during pregnancy, while smoking [90, 91], overweight [86, 90, 91] and cultural barriers [90, 92] increase the risk of not meeting national PA recommendations for pregnant women.

Pregnancy complications that may be improved or partly prevented by PA, such as hypertensive disorders of pregnancy and gestational diabetes mellitus, have been associated with adverse respiratory outcomes in offspring, including wheezing and asthma [43, 94-97]. If maternal PA during pregnancy affects early development of airways and postnatal lung function is not clear.

Although many prenatal and perinatal factors that may impact the development of early life lung function have been discovered, significant knowledge gaps remain. In this thesis, associations of maternal PA in the first half of pregnancy, during an important phase in fetal lung development, and fetal thoracic size in mid-pregnancy, with lung function in healthy three-month-old infants are explored.

3. Objective and specific aims of the thesis

In order to shed light on early origins of infant lung function, the objective of this thesis is to explore maternal and fetal factors that may be associated with lung function in infancy.

The specific aims are:

1. To explore the role of pre-pregnancy factors on physical activity in pregnancy, and to explore if maternal physical activity is associated with pregnancy outcomes, focusing on infant size.
2. To determine if maternal physical activity in pregnancy is associated with early infant lung function.
3. To determine if fetal thoracic circumference at mid-pregnancy is associated with early infant lung function.
4. To explore potential sex differences in the associations of maternal physical activity and fetal thoracic circumference with early infant lung function.

4. Methods and participants

4.1 Study design and recruitment

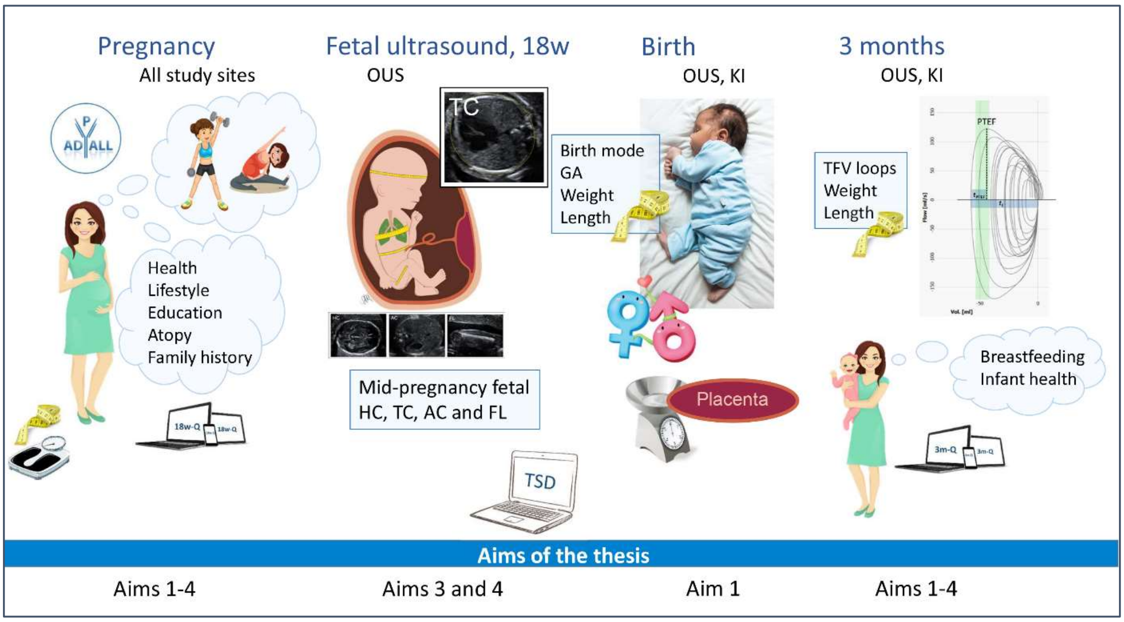
The three papers building this thesis use data from pregnant women and three-month-old infants from the Scandinavian general population-based mother-child birth cohort study Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL) initiated in 2014 [32]. The PreventADALL study is an ongoing prospective observational study with two main objectives; the first with focus on primary prevention of allergic diseases by simple and low-cost strategies and the second on assessing early life factors and exposures, including the intrauterine environment, involved in the development of asthma, allergic diseases and other non-communicable diseases. The first objective comprises a 2x2 factorially designed randomized clinical trial of two primary interventions in infancy, skin care with oil baths and use of facial cream from two weeks to nine months of age, and tasting of four common allergenic foods; peanut, cows' milk, eggs and wheat, from three to six months of age. The second objective incorporates this thesis, exploring early origins of infant lung function.

From December 2014 to October 2016, 2697 pregnant women were enrolled in the PreventADALL study, with 2701 pregnancies, as four women participated with two pregnancies. The women were recruited in relation to the routine fetal ultrasound examination at approximately 18 (15.7-22.7) GWs performed at Oslo University Hospital or Østfold Hospital Trust, Norway, or at maternity clinics in collaboration with the Karolinska University Hospital, Stockholm, Sweden. Their healthy infants, singletons or twins born after at least 35.0 GWs, were included in the study at birth, from April 2015 to April 2017. Exclusion criteria at recruitment were more than two fetuses, severe fetal diseases or malformations, insufficient Norwegian/Swedish language skills and plans of moving away from the area within the infant's first year of life. Otherwise, all pregnant women planning to give birth at one of the participating hospitals or clinics were eligible for participation.

4.1.1 Setting

An overview of the aims and methods of this thesis is shown in Figure 4.1.

Figure 4.1 Aims and methods.
Illustration of fetus: Øystein Horgmo, University of Oslo. Photos of ultrasound measures from PreventADALL study participants: Katarina Hilde. Photo of infant: Hessam Nabavi on Unsplash. TFV loops from a PreventADALL study participant. Other figures from 123rf.com and cleanpng.com.

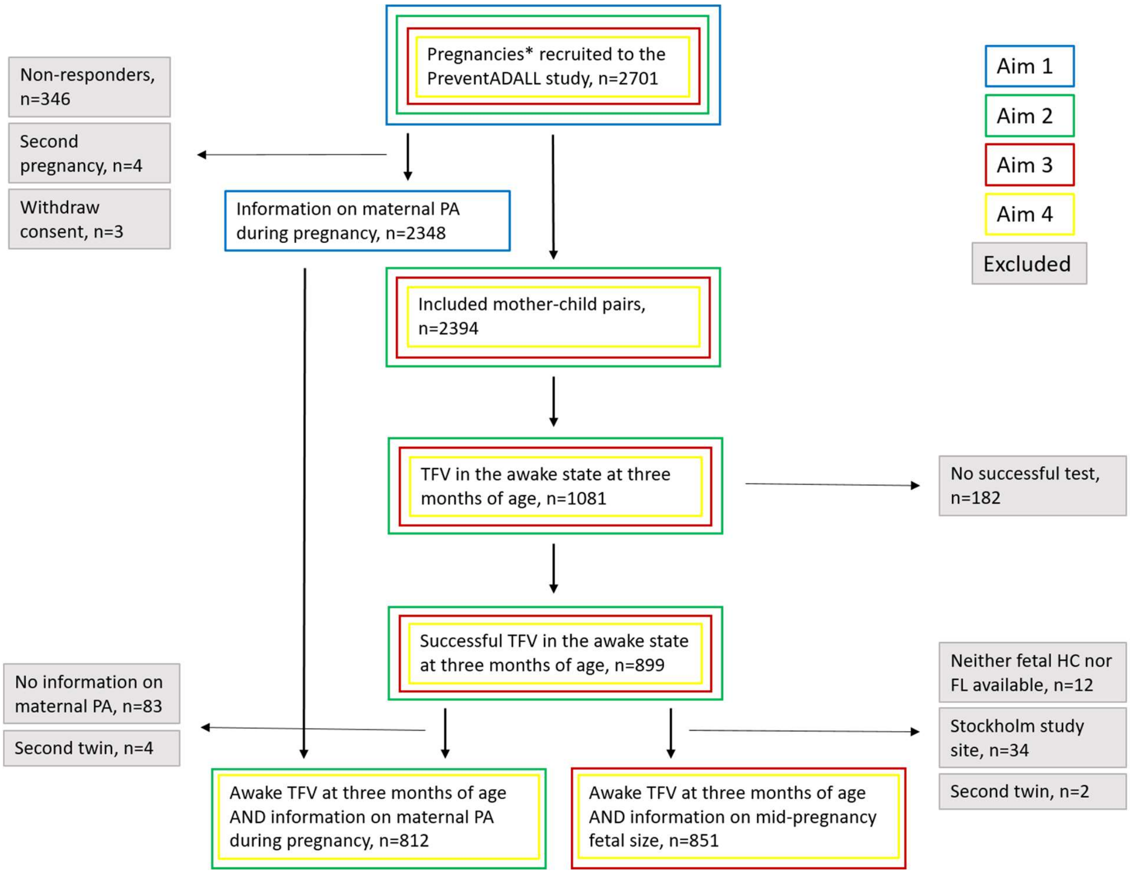


Abbreviations: 18w-Q; electronic questionnaire at 18 gestational weeks, OUS; Oslo University Hospital, HC; head circumference, TC; thoracic circumference, AC; abdominal circumference, FL; femur length, TSD; services for sensitive data (University of Oslo), KI; Karolinska Institutet, GA; gestational age, TFV; tidal flow-volume; tPTEF; time to peak tidal expiratory flow, tE; expiratory time.

For aim 1, on PA in pregnancy, data were collected retrospectively and women answering the electronic questionnaire in relation to recruitment to the PreventADALL study at approximately 18 GWs were included. Aims 2-4, on infant lung function, were based on prospectively collected data including three-month-old infants with available information on the maternal GPA level (aims 2 and 4), or mid-pregnancy ultrasound information on fetal size (aims 3 and 4), as well as lung function measurements at three months of age. Lung function was measured at the study sites in Oslo, Norway and Stockholm, Sweden. To ensure independence of participants in the studies included in this thesis, the second pregnancy for mothers enrolled with two pregnancies was excluded from analyses regarding maternal PA and the second twin of all twin pairs was excluded in studies regarding lung function.

Study populations in analyses performed to answer the specific aims of this thesis are shown in the flow chart in Figure 4.2.

Figure 4.2 The study population of the thesis.



** A total of 2697 women were recruited with 2701 pregnancies, as four women participated with two pregnancies.*

4.2 Participants

Of all 2697 pregnant women recruited to the PreventADALL study, 2349 (87%) women answered the 18-week questionnaire and were included in the overview study on self-reported *PA in pregnancy* (Paper I). Concerning age, parity and mid-pregnancy body mass index (BMI) there were no significant differences between the included women and those who did not respond to the questionnaire, as reported in Paper I. One woman withdrew her consent later, leaving 2348 women that were included in additional, previously unpublished analyses reported in this thesis. Baseline characteristics for the 2348 women are listed in Table 4.1.

Table 4.1 Baseline characteristics for the included women (n=2348, previously unpublished).

Baseline characteristics	n	Mean (SD) or count (%)
Background characteristics		
Age (years)	2348	32.4 (4.15)
Pre-pregnancy BMI	2125	24.8 (3.64)
Parity (previous deliveries)	2348	
0		1406 (59.9%)
1		750 (31.9%)
2		168 (7.2%)
≥3		24 (1.0%)
Regular physical activity before pregnancy	2348	1885 (80.3%)
Country of origin	2348	
Norway		1562 (66.5%)
Sweden		522 (22.2%)
Other Nordic		31 (1.3%)
Rest of the world		233 (9.9%)
Dog owner	2348	297 (12.6%)
Socioeconomic factors, n (%)		
Education	2337	
High school only or less		257 (11.0%)
Higher education <4 years		757 (32.4%)
Higher education ≥4 years		1256 (53.7%)
PhD		67 (2.9%)
Marital status	2348	
Married/cohabitant		2283 (97.2%)
Other		65 (2.8%)
Living environment	2348	
City - densely populated		915 (39.0%)
City - less densely populated		881 (37.5%)
Suburb		373 (15.9%)
Village		52 (2.2%)
Countryside outside village		127 (5.4%)
Family income	2307	
<300.000 NOK/SEK		30 (1.3%)
300.000-600.000 NOK/SEK		306 (13.3%)
600.000-1.000.000 NOK/SEK		958 (41.5%)
1.000.000-1.400.000 NOK/SEK		743 (32.2%)
>1.400.000 NOK/SEK		270 (11.7%)
Study location	2348	
Oslo, Norway		1488 (63.4%)
Østfold, Norway		329 (14.0%)
Stockholm, Sweden		531 (22.6%)

Table 4.1 continued

Pregnancy factors, n (%)		
IVF pregnancy	2333	187 (8.0%)
Any nicotine use in pregnancy[1]	2348	281 (12.0%)
Any smoking in pregnancy	2348	118 (5.0%)
Current smoking at mid-pregnancy	2348	18 (0.8%)
Any snus in pregnancy	2348	179 (7.6%)
Current snus at mid-pregnancy	2348	13 (0.6%)
Current sick leave at 18 weeks	2348	364 (15.5%)
Atopic diseases, n (%)[2]		
Any atopic disease	2348	980 (41.7%)
Asthma	2348	405 (17.2%)
Atopic dermatitis	2348	461 (19.6%)
Allergic rhinitis	2242	477 (21.3%)

[1] Any nicotine use, smoking or snus. Snus is a smokeless, ground tobacco, placed between the gum and the lip, increasingly used among Scandinavian women [98]. Another term for snus is moist snuff.
[2] Doctor-diagnosed atopic diseases, self-reported in questionnaires. "Any atopic disease" includes asthma, atopic dermatitis, allergic rhinitis and food allergies combined into one category.
Abbreviations: n; number, SD; standard deviation, BMI; body mass index, NOK; Norwegian krone, SEK; Swedish krona, IVF; in-vitro fertilization.

To explore the association between *maternal PA and infant lung function* (aims 2 and 4, Paper II) we included all 812 three-month-old infants with a successful TFV measure of lung function in the awake state, as well as available information on maternal general physical activity (GPA) level in the first half of pregnancy. The GPA level is in Papers I and II referred to as the maternal general activity level. The baseline characteristics of the included infants are reported in Table 4.2.

Table 4.2 Baseline characteristics for the included infants, n=812 in aims 2 and 4, and n=851 in aims 3 and 4.

Baseline characteristics	Aims 2 and 4 Included infants (n=812)		Aims 3 and 4 Included infants (n=851)	
	n	Mean (SD) or count (%)	n	Mean (SD) or count (%)
Infant factors				
Sex, female	812	396 (48.8%)	851	407 (47.8%)
Age in days (3 months)	812	93 (7.21)	851	92.8 (6.96)
GA at birth (weeks)[1]	810	40.1 (1.32)	838	40.2 (1.29)
GA at birth <37 weeks	812	17 (2.1%)	838	16 (1.9%)
Birth weight (kg)	808	3.6 (0.46)	849	3.6 (0.46)
Birth weight <3rd percentile		-	838	11 (1.3%)
Weight at 3 months (kg)	808	6.3 (0.78)	847	6.3 (0.77)
Length at 3 months (cm)	802	61.9 (2.40)	838	61.9 (2.21)
Weight gain until 3 months (kg)	804	2.70 (0.65)	845	2.70 (0.65)
Birth mode, caesarean	811	129 (15.9%)	851	137 (16.1%)
Placenta weight (g)	754	668 (133.2)	824	668 (130.8)
BW/PW ratio	753	5.46 (0.98)	823	5.5 (0.95)
Breastfeeding at 3 months[2]	721	691 (95.8%)	742	709 (95.6%)
Twins no. (%)[3]	812	4 (0.5%)	851	2 (0.2%)
Fetal factors				
HC (mm)	-	-	848	157.2 (10.12)
TC (mm)	-	-	727	117.5 (9.27)
AC (mm)	-	-	846	135.1 (10.44)
FL (mm)	-	-	846	28.2 (2.55)
GA at ultrasound, based on HC (weeks)	-	-	848	18.7 (0.83)
Maternal factors				
Age (years)	812	33 (3.89)	851	33 (3.87)
Parity, no previous deliveries	812	516 (63.5%)	851	542 (63.7%)
Pre-pregnancy BMI	799	24.4 (3.27)	831	22.8 (3.17)
Regular physical activity before pregnancy	812	667 (82.1%)	-	-
Hypertensive disorders of pregnancy	807	68 (8.4%)	848	71 (8.4%)
Any nicotine use in pregnancy[3]	812	90 (11.1%)	851	87 (10.2%)
Any smoking in pregnancy	812	30 (3.7%)	851	27 (3.2%)
Current smoking at mid-pregnancy	812	1 (0.1%)	851	1 (0.1%)
Any snus in pregnancy	812	63 (7.8%)	851	61 (7.2%)
Current snus at mid-pregnancy	812	0	851	0

Table 4.2, continued

Sociodemographic factors, n (%)				
Country of origin - mother	812		770	
Norway		684 (84.2%)		677 (87.9%)
Sweden		53 (6.5%)		22 (2.9%)
Other Nordic		6 (0.7%)		6 (0.8%)
Rest of the world		69 (8.5%)		65 (8.4%)
Education	809		767	
High school only or less		45 (5.6%)		39 (5.1%)
Higher education <4 years		226 (27.9%)		205 (26.7%)
Higher education ≥4 years		517 (63.9%)		503 (65.6%)
PhD		21 (2.6%)		20 (2.6%)
Family history of atopic diseases, n (%)[4]				
Maternal atopic disease	812	328 (40.4%)	-	-
Asthma	812	140 (17.2%)	770	132 (17.1%)
Parental atopic disease	773	498 (64.4%)	-	-

[1] GA at birth is based on mid-pregnancy fetal femur length in Paper II (aim 2) and mid-pregnancy fetal head circumference in Paper III (aim 3).
[2] Exclusively or partly breastfed at three months of age.
[3] The first twin from four twin pairs was included in the study population while the second twin was consequently excluded.
[4]Any nicotine use, smoking or snus. Snus is a smokeless, ground tobacco, placed between the gum and the lip, increasingly used among Scandinavian women [98]. Another term for snus is moist snuff. In the study on fetal thoracic size and infant lung function, mothers of 12 included infants did not respond to the questionnaires during pregnancy. In the PreventADALL database, best-case imputation has been used to handle missing information of nicotine use during pregnancy, giving them the value of no use, as very few women reported any use of nicotine products after the first few weeks of pregnancy [98]. Best-case imputation for the maternal use of nicotine in 12 infants was not reported in Paper III.
[5] Doctor diagnosed atopic diseases, self-reported in the questionnaires. "Any atopic disease" includes asthma, atopic dermatitis, allergic rhinitis and food allergies combined into one category.
Abbreviations: n; number, SD; standard deviation, GA; gestational age, BW/PW ratio; birth weight to placenta weight ratio, HC; head circumference, TC; thoracic circumference, AC; abdominal circumference, FL; femur length, BMI; body mass index.

The included infants were similar to the remaining PreventADALL infants (n=1582), except for a marginally higher GA at birth, higher breastfeeding rates and fewer infants exposed to maternal use of nicotine beyond the first few weeks of fetal life (see Table 1 in Paper II). As lung function was measured in Oslo and Stockholm only, the baseline characteristics reflected some demographic differences from participants in Østfold, as previously reported [32]. The mothers of included infants were slightly older, of higher education and more were pregnant with their first child, compared to the rest of the PreventADALL cohort.

Studying the associations between *mid-pregnancy fetal thoracic size and infant lung function* (aims 3 and 4, Paper III), all 851 infants with available ultrasound measurements including fetal HC and/or FL, as well as a successful, awake-state TFV measurement at three months of age were included. The infants were recruited in Oslo, the only study site measuring both fetal TC and infant TFV, with baseline characteristics reported in Table 4.2. They were largely similar to the remaining infants of the PreventADALL cohort (n=1543), except that more were breastfed and fewer had been exposed to nicotine in utero for longer than the first few weeks of fetal life (see supplementary E-table 1 in Paper III). Their mothers were somewhat older, had lower pre-pregnancy body mass index (BMI) and higher education, and more were nullipara compared to the mothers of the remaining infants.

4.3 Methods

4.3.1 Enrolment visit and electronic questionnaires

In addition to receiving information and signing an informed consent at the enrolment visit, the women's weight, height and blood pressure were measured according to a standardized procedure. A short interview was performed, including a question on pre-pregnancy weight, used to calculate pre-pregnancy BMI (kg/m^2). Ultrasound data was recorded by study personnel.

Detailed electronic questionnaires were sent by e-mail to the participants in relation to the enrolment visit, at approximately 18 weeks of pregnancy. One remainder was sent, and the answer could only be submitted once. The women reported PA prior to and during the first half of pregnancy in addition to general health, family history of atopic diseases, socioeconomic factors and lifestyle including the use of nicotine. At approximately 34 GWs the women received a second questionnaire for further information. At this point, they were also asked about the father of their unborn child, including questions on his general health and family history of atopic diseases.

Mothers included in the mother-child cohort received electronic weekly diaries at weeks 2-26 after birth, where they were asked to report their infants' feeding and bathing habits. At approximately three months postpartum they answered the third questionnaire, with questions on infant health and development as well as breastfeeding, lifestyle, quality of life and socioeconomic factors.

4.3.2 Information on physical activity

The 18-week questionnaire included one question on pre-pregnancy PA, one question comparing the present to pre-pregnancy activity level and four questions about leisure-time PA usually performed so far during the pregnancy. In addition, the women were asked if they had been physically active for the last two weeks, with PA defined as at least one activity session of a minimum of 20 minutes per week.

The questions on PA are listed in the Online Supplement to Paper II.

The women reported how frequently they had performed different types of activities so far in pregnancy. The activities were strolling, brisk walking, jogging, bicycling, strength training, aerobics, skiing, ballgames, swimming, horse riding, yoga/pilates and other types of PA. Also, they reported the usual intensity (low, moderate, high) and duration (<30 minutes, 30-60 minutes, 1-2 hours, >2 hours) of exercise. 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'. Frequency of the different activities was reported as; rarely or never, 1-3 times monthly, once weekly, 2-3 times weekly, 4-5 times weekly, 5-6 times weekly, every day and more than once daily.

The questions on PA were adapted from questions previously used in the Norwegian Mother and Child Cohort Study (MoBa) where the questions had been validated in a subgroup by comparing the answers with results from a position and motion sensor measuring PA [99].

4.3.3 Fetal ultrasound examination

The mid-pregnancy ultrasound examination was performed by specially trained midwifes at the participating hospitals, at approximately 18 GWs. At the time of recruitment to the PreventADALL study, the 18-week examination was the only routine fetal ultrasound examination in Norway and served therefore as the pregnancy dating scan. Fetal HC, AC and FL are routinely measured biometric indices of general fetal size, and in addition to these, fetal TC was measured in women planning to participate in the PreventADALL study in Oslo and Østfold. Fetal 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 (Figure 2.1). All midwifes measuring fetal TC were trained by the same experienced fetal medicine obstetrician (K. Hilde) who also controlled the quality of random samples of measurements.

Fetal size measurements at mid-pregnancy, not adjusted for GA are reported for girls and boys separately in Table 4.3.

Table 4.3 Ultrasound measurements of fetal size at mid-pregnancy, for the included girls and boys separately, compared with the independent sample t-test.*
Reprinted with Creative Commons Attribution 4.0 International License, CC BY 4.0 (http://creativecommons.org/licenses/by/4.0/). Gudmundsdottir HK et al. Fetal thoracic circumference in mid-pregnancy and infant lung function. Pediatr Pulmonol. 2023 Jan;58(1):35-45. doi: 10.1002/ppul.26153. From the online supplement.

Fetal size measures in mm	Girls			Boys			p-value
	n	Mean	95% CI	n	Mean	95% CI	
HC	407	155.3	154.3, 156.3	441	158.9	158.0, 159.9	**<0.001**
TC	344	116.9	115.9, 117.9	383	118.0	117.1, 118.9	0.100
AC	407	134.0	133.0, 135.0	439	136.2	135.2, 137.2	**0.002**
FL	405	28.1	27.8, 28.3	441	28.4	28.1, 28.6	0.117

**Fetal size measures, not adjusted for gestational age at the time of ultrasound examination. Abbreviations: n; number, CI; confidence interval, HC; head circumference, TC; thoracic circumference, AC; abdominal circumference, FL; femur length.*

In aims 1 and 2, GA is based on mid-pregnancy fetal FL as previously described for the PreventADALL cohort [32]. In aim 3, the GA estimate was based on fetal HC [28, 100], according to the clinical routine at Oslo University Hospital, as all infants included in this sub-study were recruited at the Oslo study site. While GA based on HC may be slightly overestimated in boys due to their larger HC [28], the influence of fetal sex on estimated GA based on FL is smaller, and both methods are considered equally reliable [29].

4.3.4 Newborn inclusion and birth records

Healthy infants, singletons or twins, born at GA of at least 35.0 weeks, were included in the PreventADALL study by trained study personnel within 1-2 days after birth, or as soon as possible within two weeks, if later. A total of 2397 infants were included to the PreventADALL study, but as three mothers withdrew their consent, the cohort consists of 2394 mother-child pairs.

Information about parity, pregnancy complications, the delivery and the newborn infant, such as birth weight and length, birth mode and placenta weight, was registered from electronic hospital records. Hospital personnel at the maternity units measured the infants and placentas according to hospital routines, as soon as appropriate after birth.

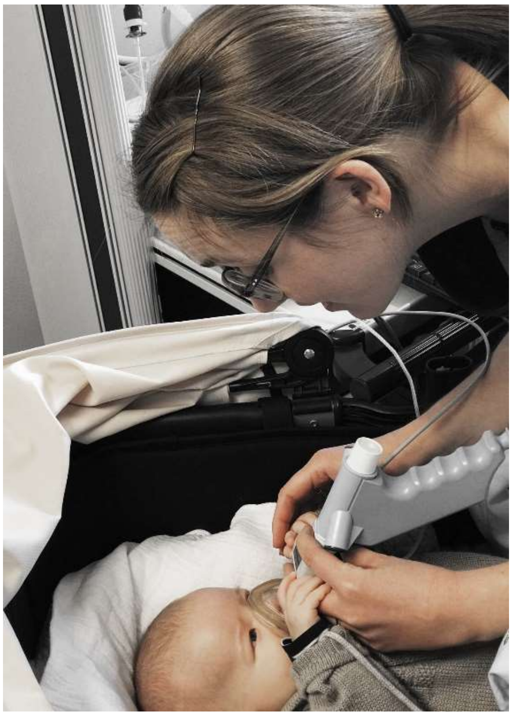
4.3.5 Follow-up at three months of age

The first follow-up of the infant was three months after birth, with measurement of lung function at the study sites in Oslo and Stockholm and anthropometric measurements for all infants. The infants had a clinical examination and a thorough evaluation of the skin. Their blood pressure and transepidermal water loss (TEWL) were measured and infants in the food intervention group had their first taste of peanut butter. In addition, there was biological sampling of skin microbiota, urine and blood, and home-kits for faecal microbiota samples and salivary cortisol were handed out. All procedures were performed by trained study personnel, according to the study protocol.

Lung function was measured by tidal flow-volume (TFV) loops in calm, awake or naturally sleeping infants, using the Eco Medics Exhalyzer® D (Duernten, Switzerland) equipment [101] (Figure 4.3).

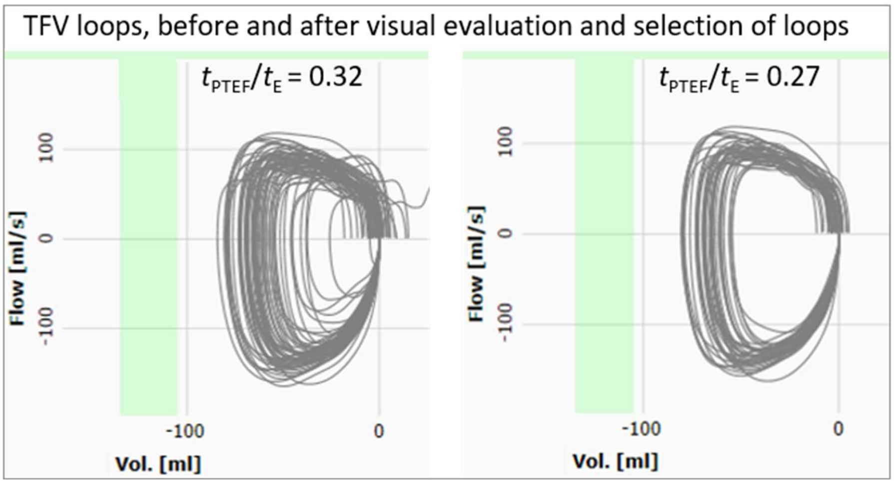
A face mask of the appropriate size (usually the Intersurgical Ltd, Economy anaesthetic face mask, size 2) was connected to an ultrasonic flow head, with a dead space reducer, a filtering spirette and a CO_2 adapter with a capnostat in between. While holding the mask tight over the infant's nose and mouth, adjusting the pressure to minimize leakage of air, as many TFV loops as possible were recorded. All infants included in the studies of this thesis were measured in the awake state, lying in the supine position, with head and neck in midline, on a firm pillow on their caregiver's lap or in a stroller/bed. All sampled loops were saved for later review.

Figure 4.3 Tidal flow-volume loops measured in a 3-month-old infant.
Printed with parental consent.
Photo: Karen Eline Stensby Bains.



After all three-month visits had been completed, three independent raters (H.K. Gudmundsdóttir, M. Färdig and K.E.S. Bains) visually evaluated the TFV loops according to a standardized procedure based on ERS/ATS guidelines [102], using the Spiroware® software, version 3.2.1. The focus was on shape and reproducibility of the loops, as reported in detail elsewhere [101], with an example as shown in Figure 4.4.

Figure 4.4 TFV loops, before and after evaluation and manual selection.
Reproduced with Creative Commons Attribution 4.0 International License, CC BY 4.0 (http://creativecommons.org/licenses/by/4.0/). Bains KES et al. Infant lung function: criteria for selecting tidal flow-volume loops. ERJ Open Res. 2022 Oct 24;8(4):00165-2022. doi: 10.1183/23120541.00165-2022.



Abbreviations: TFV; tidal flow-volume loops, t_{PTEF}/t_E; ratio of time to peak tidal expiratory flow to expiratory time.

After the evaluation of loops, the raters concluded on the quality of the TFV test, and registered the mean values for t_{PTEF}/t_E, V_T, respiratory rate and more. For the 899 infants with a successful test in the awake state, a mean (standard deviation (SD)) of 21 (14) loops were saved for analyses.

Infant weight and length were measured using a digital scale and a measuring board. The infants were weighed naked and the measures registered with an accuracy of 0.01 kg and 0.1 cm. Other anthropometries measured were the circumferences of the head, thorax, abdomen and the left upper arm, measured with a measuring tape.

4.3.6 Storage of data

The PreventADALL database is securely stored in the Service for Sensitive Data (TSD) at the University of Oslo, Norway, in compliance with the Norwegian privacy regulation. All questionnaires and registration forms were developed by the study team in collaboration with the University Centre for Information Technology (USIT) and electronically filled out and submitted directly into the database.

4.4 Definitions, exposures, outcomes and covariates

Table 4.4 Exposures, outcomes and covariates for the four aims of this thesis.

		Exposures	Outcomes	Covariates in multivariable models
Aim 1	**Pre-pregnancy factors and PA in pregnancy**	Maternal factors	*GPA 1st half of pregnancy* Inactive / active Inactive / fairly active / highly active	Parity Country of origin Marital status Pre-pregnancy PA Education Current sick leave
	PA in pregnancy, pregnancy outcomes and infant size	*GPA 1st half of pregnancy* Inactive / active Inactive / fairly active / highly active	GA at birth Birth mode Birth weight Placenta weight BW/PW ratio Infant weight gain, 0m-3m Infant weight at 3m Infant length at 3m	No multivariable models
Aim 2	**Maternal PA and infant lung function**	*GPA 1st half of pregnancy* Inactive / active Inactive / fairly active / highly active	*Infant lung function at three months:* Primary: $t_{PTEF}/t_E < 0.25$ Secondary: V_T/kg	Maternal age Maternal education Pre-pregnancy BMI Parity Parental atopy In-utero exposure to nicotine
Aim 3	**Fetal TC and infant lung function**	*Mid-pregnancy fetal thoracic size ratios:* TC/HC TC/AC TC/FL	*Infant lung function at three months:* Primary: t_{PTEF}/t_E (cont.) $t_{PTEF}/t_E < 0.25$ $t_{PTEF}/t_E < 10^{th}$, 25^{th} and 50^{th} percentile Secondary: V_T and V_T/kg	Maternal age Maternal asthma Pre-pregnancy BMI Parity Infant sex In-utero exposure to nicotine
Aim 4	**Sex differences in associations of maternal PA and fetal TC with infant lung function**	*GPA 1st half of pregnancy* Inactive / active Inactive / fairly active / highly active	*Infant lung function at three months:* Primary: $t_{PTEF}/t_E < 0.25$ Secondary: V_T/kg	Maternal age Maternal education Pre-pregnancy BMI Parity Parental atopy In-utero exposure to nicotine
		Mid-pregnancy fetal thoracic size ratios: TC/HC TC/AC TC/FL	*Infant lung function at three months:* Primary: t_{PTEF}/t_E (cont.) Secondary: V_T and V_T/kg	Maternal age Maternal asthma Pre-pregnancy BMI Parity Infant sex In-utero exposure to nicotine

Abbreviations: PA; physical activity, GPA level; general physical activity level, GA; gestational age, BW/PW ratio; birth weight to placenta weight ratio, t_{PTEF}/t_E; the ratio of time to peak tidal expiratory flow to expiratory time, V_T; tidal volume, BMI; body mass index, TC; thoracic circumference, HC; head circumference, AC; abdominal circumference, FL; femur length.

Definitions:

The *general physical activity (GPA) level* in the first half of pregnancy was estimated based on self-reported PA at mid-pregnancy (aim 1, Paper I). Women reporting moderate or high usual intensity of exercise were defined as *active* and active minutes per week estimated based on reported usual duration of exercise and the frequency of performed activities. All types of activities, with the exception of strolling (a low-intensity activity per definition), were added together, and all durations and frequencies apart from rarely/never, were included in the calculations. To report the duration and frequency of PA, the women had to choose between possible answers including both exact values and closed or open ranges. Hence, as the women were not asked to report the total number of exercise sessions per week, it was not possible to calculate the exact number of active minutes per week. The minimum number of active minutes per week was estimated by multiplying the minimum number of PA sessions per week with the usual exercise duration, using the numerical assumptions shown in Table 4.5.

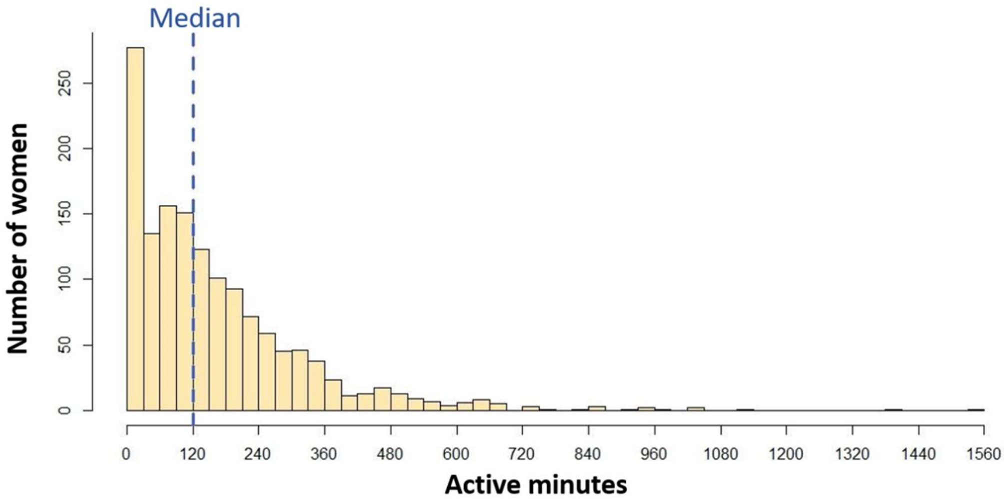
Table 4.5 Numerical assumptions used to calculate the minimum number of active minutes per week, based on self-reported information at mid-pregnancy.
Reproduced with Creative Commons Attribution 4.0 International License, CC BY 4.0 (http://creativecommons.org/licenses/by/4.0/). Carlsen OCL, Gudmundsdottir HK et al. Physical activity in pregnancy: a Norwegian-Swedish mother-child birth cohort study. AJOG Glob Rep. 2021 Jan 27;1(1):100002. doi: 10.1016/j.xagr.2020.100002. From the online supplement.

Duration		**Frequency**	
Categories in Q-18w	Minutes	Categories in Q-18w	Sessions per week
Less than 30 min	1	Rarely or never	0
30-60 min	30	1-3 monthly	0.25
1-2 hours	61	1 weekly	1
More than 2 hours	121	2-3 weekly	2
		4-5 weekly	4
		5-6 weekly	5
		Every day	7
		More than once daily	8

Abbreviations: Q-18w; questionnaire answered at approximately 18 gestational weeks.

Based on the estimated minimum number of active minutes per week, the women had a median of 120 minutes of PA per week, with a distribution as shown in Figure 4.5.

Figure 4.5 A histogram showing the distribution of the minimum number of active minutes per week, estimated based on self-reported information, for all active women.



Active women were further classified into *fairly active* women with less than 120 active minutes per week and *highly active* women with 120 or more active minutes per week.

Women reporting only low-intensity activities or no activities at all were defined as *inactive* in the first half of pregnancy.

Fetal thoracic size was measured by ultrasound at mid-pregnancy. All fetal size measurements reported in Paper III and used in aims 3 and 4 were measured at the same ultrasound examination, at approximately 18 GWs. The different biometric measurements of fetal size, measured at the same time-point, are strongly correlated (Table 4.6). Regression models with TC as the main exposure and fetal GA at the time of ultrasound, based on either HC or FL, as a covariate, would therefore have strong collinearity between variables.

Table 4.6 Fetal size proportions in mid-pregnancy and Pearson's correlation (R^2) between the biometric measures in each ratio.
Reprinted with Creative Commons Attribution 4.0 International License, CC BY 4.0 (http://creativecommons.org/licenses/by/4.0/). Gudmundsdottir HK et al. Fetal thoracic circumference in mid-pregnancy and infant lung function. Pediatr Pulmonol. 2023 Jan;58(1):35-45. doi: 10.1002/ppul.26153. From the online supplement.

Fetal proportions	n	Mean	SD	R^2
TC/HC	726	0.75	0.04	0.598
TC/AC	725	0.87	0.04	0.612
TC/FL	724	4.17	0.26	0.534
AC/FL	843	4.80	0.26	0.651

R^2 is the percentage of variation in the numerator explained by the denominator – e.g. for TC/HC; HC explains 59.8% of the variation in TC.
Abbreviations: n; number, SD; standard deviation, R^2; the percentage of variation explained by the exposure, TC; thoracic circumference, HC; head circumference, AC; abdominal circumference, FL; femur length.

Based on available literature, *low lung function* is defined as a t_{PTEF}/t_E <0.25. *Lung function in the lower range* is defined using three different cut-off values; the 10th (<0.28), 25th (<0.34), and 50th (<0.39) percentiles for all infants in the PreventADALL cohort with a successful awake-state TFV measurement at three months of age (n=899).

Exposures:

Aims 2 and 4: The maternal GPA level in the first half of pregnancy reported in aim 1 was explored for the association with infant lung function. The mothers were primarily categorized as inactive or active and secondarily as inactive, fairly active or highly active.

Aims 3 and 4: Thoracic circumference in relation to general measurements of fetal size, as the thoracic size ratios TC/HC, TC/AC and TC/FL, was explored for associations with infant lung function. The TC/HC and TC/FL ratios may be regarded as a proxy for TC adjusted for GA and the TC/AC ratio has previously been described as independent of GA [34].

Outcomes:

The outcome of aim 1 is the GPA level in the first half of pregnancy.

Infant t_{PTEF}/t_E is the primary outcome for aims 2-4 of this thesis (Table 4.4). There is no clear definition of cut-off values to define low or marginal lung function by t_{PTEF}/t_E and reference values in infants have not been published. The t_{PTEF}/t_E outcome used in this thesis is either continuous or partitioned at cut-off values reflecting low lung function (t_{PTEF}/t_E <0.25) or lung function in the lower range (the 10^{th}, 25^{th} and 50^{th} percentiles).

Infant V_T and/or V_T adjusted for infant weigh at three months of age (V_T/kg) are the secondary outcomes in aims 2-4 of this thesis, both as continuous variables (Table 4.4).

Covariates:

To identify potential confounding variables (that may affect both exposure and outcome) relevant for the associations between fetal life factors and infant lung function we constructed directed acyclic graphs (DAGs) [103] prior to statistical analyses. The DAG for maternal PA and infant lung function is shown in Figure 4.6 and for fetal thoracic size and infant lung function in Figure 4.7.

Figure 4.6 A directed acyclic graph (DAG) for the association between maternal physical activity in the first half of pregnancy and infant lung function.
Reprinted with Creative Commons Attribution 4.0 International License, CC BY 4.0 (http://creativecommons.org/licenses/by/4.0/). Gudmundsdottir HK et al. Infant lung function and maternal physical activity in the first half of pregnancy. ERJ Open Res. 2022 Oct 31;8(4):00172-2022. doi: 10.1183/23120541.00172-2022. From the online supplement.

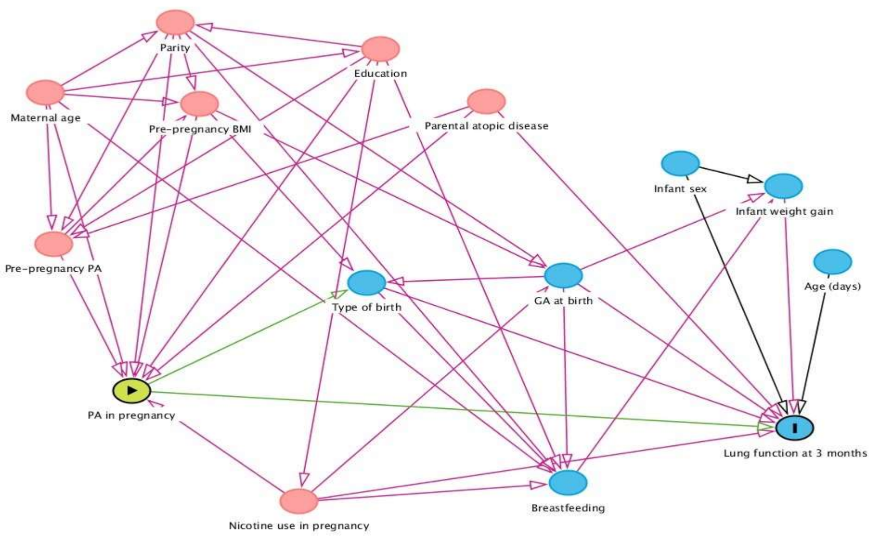
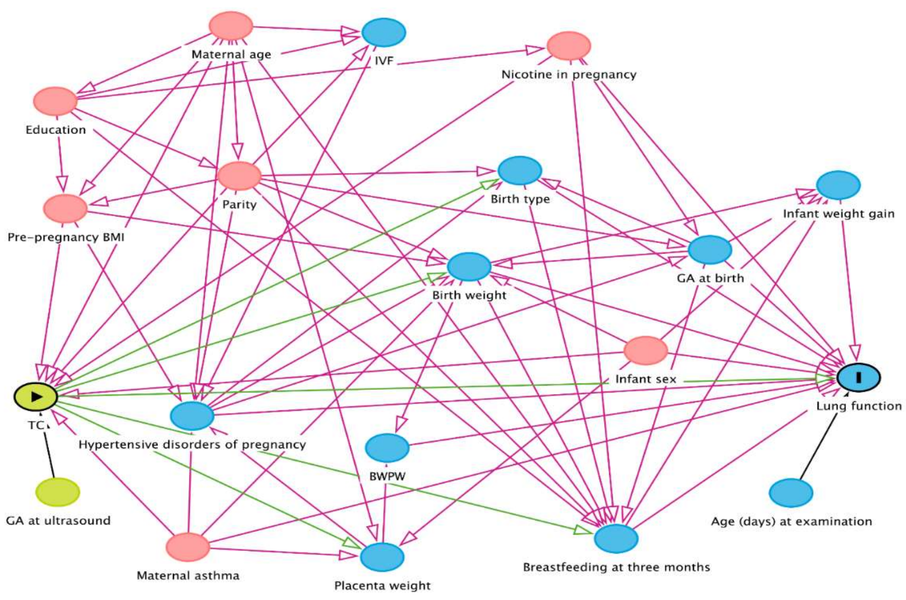


Figure 4.7 A directed acyclic graph (DAG) for the association between fetal thoracic size in mid-pregnancy and infant lung function.
Reprinted with Creative Commons Attribution 4.0 International License, CC BY 4.0 (http://creativecommons.org/licenses/by/4.0/). Gudmundsdottir HK et al. Fetal thoracic circumference in mid-pregnancy and infant lung function. Pediatr Pulmonol. 2023 Jan;58(1):35-45. doi: 10.1002/ppul.26153. From the online supplement.



Maternal age, continuous: An association between younger age and higher PA levels in pregnancy has been described [91, 93] and higher maternal age is associated with larger fetal size in mid-pregnancy [25, 26, 28, 29]. While high maternal age is associated with worse perinatal outcome [104], higher adult lung function has been described in relation to advanced maternal age [105].

Maternal education: Higher maternal education has been associated with being physically active during pregnancy [91-93]. Maternal education is often used as an indicator of socioeconomic status. Disadvantaged socioeconomic circumstances are associated with lower lung function in children, adolescents and adults [106].

Parity, para 0 versus para ≥1: Parity is inversely associated with maternal PA in pregnancy [86, 90, 92] and positively associated with fetal size [26, 100]. A positive association between number of siblings and lung function values has been observed in school-aged children [107] while the effect of parity on infant lung function is not clear.

Pre-pregnancy BMI, continuous: An inverse association between maternal BMI and PA levels in pregnancy has been observed [86, 90, 91] while other studies have shown conflicting results [92, 93]. Maternal BMI is positively associated with fetal size [26, 100] and with an increased risk of wheezing and asthma in childhood [108, 109], where the association with early life wheeze can partly be explained by neonatal lung function [110].

Maternal asthma and parental atopy: Maternal asthma increases the risk of impaired lung function in infants [43, 46], and asthma in primary or secondary relatives is associated with lower lung function values in infancy and later wheeze and asthma [2, 4]. Paper I describes an association between maternal atopic dermatitis and higher levels of jogging [111] and while preparing for Paper II, a weak but significant positive association was observed between paternal atopy and maternal PA (univariable model, results not shown). Maternal allergic rhinitis might affect outdoor activities during spring and summer. Maternal asthma has been associated with reduced fetal growth and lower birth weight [112, 113], while studies relating paternal atopy to fetal growth in the first or second trimester are lacking.

In utero exposure to nicotine: Smoking is associated with lower PA levels, both in pregnant and non-pregnant women [91, 114, 115]. In utero exposure to maternal smoking is associated with lower birth weight [2, 43, 44] and reduced growth of both the fetal lungs and the fetal body in general [116, 117]. The harmful effect of maternal smoking and other nicotine use on lung development and infant lung function is well known [43, 44, 118]. Very few women in the PreventADALL cohort reported smoking during pregnancy [98], while an increasing use of snus (also known as moist snuff), a smokeless, ground tobacco placed between the gum and the lip, has been reported among young women in Scandinavia, also during pregnancy [119-121]. Both smoking and use of snus were reported in the 18-week questionnaire and combined into one nicotine exposure variable.

Infant sex: Already at mid-pregnancy, boys are larger than girls [25, 26] and many studies have reported differences in infant lung function between the sexes [8, 37, 122].

4.5 Statistical analyses

Continuous variables are presented as means with minimum-maximum values (min-max), SD or 95% CI, and categorical variables as counts (n) and percentages (%).

To compare the infants included in aims 2-4 to the remaining infants of the PreventADALL cohort the independent sample t-test was used for continuous variables, the Chi-squared test was used for nominal variables and the Mann-Whitney U test was used for ordinal variables.

For aim 1, retrospectively collected data were analysed to explore the association between maternal factors and the GPA level. Additionally, prospectively recorded pregnancy outcomes were investigated according to the maternal GPA level using descriptive analyses. The maternal GPA level is based on the number of minutes per week spent on PAs with moderate or high intensity and the mothers were defined as inactive (those reporting only low-intensity activities or no activities at all), fairly active or highly active. For details, see chapter 4.4.

Maternal factors associated with the GPA level in the first half of pregnancy were identified in univariable regression models. All variables explored in univariable models are listed in Table 6.1. Logistic regression models were performed for the binary outcome of inactive versus active, and ordinal logistic regression models for the categorical outcome of inactive, fairly active and highly active. The outcome of the ordinal logistic regression models for inactive, fairly active and highly active women is a combined odds ratio (OR). The combined OR representing the odds of all active women compared to inactive women (reference group), combined with the odds of highly active women compared to inactive and fairly active women (combined into one reference group). To fit the final multivariable models, variables significantly associated with the outcome (p-value <0.05) were included. The variables with collinearity to other explanatory variables or no significant association with the outcome after adjustment were removed. Results are presented as ORs with 95% confidence intervals (CI) and p-values.

The descriptive part of aim 1 included GA at birth, birth mode, birth weight, placenta weight, the ratio of birth weight to placenta weight, infant weight gain from 0-3 months of age as well as infant weight and length at three months of age. Differences between groups were tested using the independent sample t-test and the one-way ANOVA test for continuous outcomes and the Chi-squared test (χ^2) for binary outcomes.

For aim 2, the association between the maternal GPA level and infant lung function was determined using regression models, including prospectively collected data on TFV loops measured at three months of age. Logistic regression models were performed to assess the association between maternal GPA level and the dichotomous outcome of low infant lung function defined as t_{PTEF}/t_E <0.25. Results are presented as ORs with 95% CI and p-values. For the continuous V_T/kg outcome, linear regression models were used, and the results presented as regression coefficients (β estimate ($\hat{\beta}$)), R^2, 95% CI and p-values. Supporting analyses to assess the robustness of the association between maternal GPA level and infant lung function were performed, with t_{PTEF}/t_E <0.26, <0.27 and <0.28 as outcomes.

Exploring the association between maternal PA and infant lung function, all multivariable models were adjusted for maternal age, maternal education, parity, pre-pregnancy BMI, in-utero nicotine exposure and parental atopy. The parental atopy variable includes doctor diagnosed asthma, atopic dermatitis, allergic rhinitis and food allergies in either parent combined in one variable. As fetal sex could not affect maternal PA level in the first half of pregnancy, the multivariable models of aim 2 were not adjusted for sex.

For aim 3, the association between mid-pregnancy fetal TC and infant lung function was determined in regression models, using prospectively collected data. Potential associations between the fetal thoracic size ratios and continuous lung function variables, the t_{PTEF}/t_E, V_T and V_T/kg, were analysed using linear regression models and the results are presented as regression coefficients (β estimate ($\hat{\beta}$)), 95% CI and p-values. Logistic regression models were used for dichotomous t_{PTEF}/t_E outcomes, presented as ORs, 95% CI and p-values. Relation between continuous variables was evaluated using Pearson correlation, with R^2 describing the percentage of variability explained by the particular exposure. Sensitivity analyses were performed to explore whether associations between the fetal thoracic size ratios and continuous lung function outcomes differed when preterm infants (with GA of 35.0-36.9 weeks at birth) were excluded.

Exploring the association between fetal TC and infant lung function, all multivariable models were adjusted for maternal age, maternal asthma, pre-pregnancy BMI and parity, as well as infant sex and in-utero exposure to nicotine.

In aim 4, the independent sample t-test was used to test for differences between girls and boys included in the analyses of aims 2 and 3.

To assess if the association between maternal GPA level and infant lung function depended on the sex of the infant, the interaction term "maternal PA * infant sex" was included in the regression models described for aim 2, in addition to adjusting the models for infant sex.

To assess the potential effect of infant sex on the association between the fetal TC ratios and infant t_{PTEF}/t_E, the interaction terms 'TC/HC * infant sex', 'TC/AC * infant sex' and 'TC/FL * infant sex' were included in the regression models described for aim 3.

Additionally, as both fetal size and lung function differs between girls and boys, the analyses in aim 3 were stratified for sex.

Handling of missing data:

Regarding *different types of PAs*, empty fields in the questionnaire were interpreted as not having performed the particular activity and "missing" was coded as "zero" both in univariable and multivariable models.

Data on *Parental atopy* was missing in 39/812 (4.8%) infants in aim 2 and *maternal asthma* in 81/851 (9.5%) infants in aim 3. To include these infants in the multivariable models in aims 2-4, "missing" was coded as a "not-ordered category".

Maternal *pre-pregnancy BMI* was missing in 13/812 (1.6%) infants in aim 2 and 20/851 (2.4%) infants in aim 3. These infants were kept in the multivariable models in aims 2-4, using mean imputation. Mothers with missing BMI were given the mean value of maternal pre-pregnancy BMI for all infants included in the respective studies; a BMI of 24.42 in aim 2 and a BMI of 22.85 in aim 3.

Information on *maternal use of nicotine during pregnancy* was missing in 12/851 (1.4%) infants included in aim 3. The majority of infants in the PreventADALL cohort was not exposed to nicotine in utero [98], and best-case imputation (no use of nicotine during pregnancy) was used to include these infants in multivariable models.

In addition, a few infants were excluded from the multivariable models due to missing information on *maternal education*, and from all models assessing associations with infant V_T/kg due to missing *infant weight* at three months of age.

In this thesis, and all three papers, p-values <0.05 are regarded as significant.

Statistical analyses were performed using IBM SPSS statistics versions 26 and 27, RStudio versions 4.0.3 and 4.1.0, Stata/SE 14.0 for Windows, Texas USA and Microsoft Excel 2016.

5. Ethical considerations

Providing sufficient information to the participants prior to inclusion was a key element of the recruitment process. As participating in the PreventADALL study was demanding and it was essential that the participants understood what study participation entailed, the study team gave written and oral information about the study, and the pregnant women with their partners had the opportunity to discuss and ask questions before the women signed a detailed informed consent for participation. The parents to-be were thoroughly informed about the interventions, the detailed electronic diaries, and questionnaires as well as the three follow-up visits, all in the first year of the infant's life. Within 1-2 days after birth, and prior to the randomization, both parents were informed about the study again and invited to sign the informed consent on behalf of the infant. A possible advantage for the participants was the offer to the parents of direct contact with the study team with concerns regarding eczema or potential allergic reactions in the infants throughout the first three years of participation. Depending on the severity of the concern, the parents were given advice by telephone, or an additional appointment was scheduled for examination, with treatment and follow-up of the infant as indicated.

The PreventADALL study was approved by the Regional Committee for Medical and Health Research Ethics in Norway (2014/518) and in Sweden (2014/2242-31/4), including a wide consent within non-communicable diseases. The study is registered at clinicaltrial.gov (NCT02449850).

Infant lung function measurement by TFV is usually well tolerated in both awake and sleeping infants. A calm infant is a prerequisite for measuring tidal breathing, and thus, TFV loops cannot be recorded in infants not accepting the mask and at signs of infant inconvenience the procedure was stopped.

6. Results

6.1 Physical activity in pregnancy

The GPA level in the first half of pregnancy was estimated based on data for 2349 women, with background characteristics as reported in Table 1 of Paper I. Overall, 29% reported no regular PA at mid-pregnancy (Paper I). Strolling and brisk walking were the most commonly reported PAs, followed by strength training and bicycling, as further described in Paper I. The most common duration of exercise was 30-60 minutes, reported by 1413/2349 (60.2%) of the women. While 876/2349 (37.3%) reported low intensity, 1287/2349 (54.8%) reported moderate intensity and 186/2349 (7.9%) high intensity as their usual PA intensity level.

After publication of Paper I, one woman withdrew her consent, resulting in 2348 women included in the additional, unpublished analyses on associations between maternal factors and the GPA level in pregnancy performed for this thesis and reported below.

Nearly two thirds (59.9%) of the 2348 women were pregnant with their first child, their mean (SD) age at inclusion was 32.4 (4.15) years and mean (SD) pre-pregnancy BMI was 24.8 (3.64). They were highly educated and 80.3% were regularly physically active before they became pregnant (Table 4.1).

At mid-pregnancy, 919 women (39.1%) reported no PAs of moderate or high intensity in the first half of pregnancy and were defined as *inactive,* while 648 (27.6%) had been *fairly active* and 781 (33.3%) *highly active*.

6.1.1 Pre-pregnancy factors for PA in pregnancy (additional analyses)

For 2348 pregnant women with information on PA in pregnancy, associations between pre-pregnancy factors and the GPA level in the first half of pregnancy, explored using univariable regression models, are reported in Table 6.1.

Table 6.1 Univariable associations between maternal pre-pregnancy factors and the GPA level in the first half of pregnancy. Only significant associations, with p-values <0.05 are reported in the table, with associations indicating increased PA in pregnancy marked in yellow, associations indicating reduced PA in pregnancy marked in blue. For inactive versus active women, the reference group is 'inactive' while for inactive versus fairly or highly active, the results are combined for all active compared to inactive (reference group) and for highly active compared to both inactive and fairly active (combined into one reference group) women.

Maternal factors	Inactive versus active	Inactive, fairly or highly active
Maternal age, increasing	**0.007**	**0.018**
Maternal age (ref. <25 years)		
25-29 years		**0.029**
30-34 years		**0.037**
35-39 years		
≥40 years		
Pre-pregnancy BMI, increasing		**<0.001**
Pre-pregnancy BMI (ref. 20-24.9)		
<20		
25-29.9		
30-34.9	**0.015**	**<0.001**
≥35		
Parity, para ≥1 versus para 0	**<0.001**	**<0.001**
Pre-pregnancy PA (yes/no)	**<0.001**	**<0.001**
IVF (yes/no)		
Nicotine use in pregnancy (yes/no)		
Sick leave at 18 weeks (yes/no)	**<0.001**	**<0.001**
Maternal country (ref. Norway)		
Sweden	**<0.001**	**<0.001**
Other Nordic	**0.040**	
Rest of the world	**<0.001**	**<0.001**
Marital status (ref. married/cohabitant)		
Other	**0.029**	**0.017**
Maternal education (ref. high school only or less)		
Higher education <4 years	**0.021**	**0.003**
Higher education ≥4 years	**<0.001**	**<0.001**
Living environment (ref. city, densely populated)		
City, less densely populated		

Table 6.1, continued

Suburb	**<0.001**	**<0.001**
Village		**0.042**
Countryside, outside village	**0.005**	**<0.001**
Family income (ref. <300.000 NOK/SEK)		
300.000-600.000 NOK/SEK	**0.035**	**0.047**
600.000-1.000.000 NOK/SEK	**0.007**	**0.013**
1.000.000-1.400.000 NOK/SEK	**0.001**	**0.002**
>1.400.000 NOK/SEK	**<0.001**	**<0.001**
Dog owner (yes/no)		
Study location (ref. Oslo, Norway))		
Østfold, Norway	**<0.001**	**<0.001**
Stockholm, Sweden	**<0.001**	**<0.001**
Maternal asthma (yes/no)		
Maternal atopic dermatitis (yes/no)		
Maternal atopy (yes/no)		

Associations with the binary outcome inactive versus active were analysed using logistic regression models and associations with the outcome of inactive, fairly active and highly active using ordinal logistic regression models.
Abbreviations: ref; reference group, BMI; body mass index, IVF; in-vitro fertilization, NOK; Norwegian krone, SEK; Swedish krona.

The final multivariable models for both the binary outcome of inactive and active women and the outcome of inactive, fairly active and highly active women included parity, maternal country of origin, marital status, pre-pregnancy PA, maternal education and current sick leave as reported in Table 6.2.

Table 6.2 Multivariable associations between maternal factors and the GPA level in the first half of pregnancy. For inactive versus active women, the reference group is 'inactive' while for inactive versus fairly or highly active, the results are combined for all active compared to inactive (reference group) and for highly active compared to both inactive and fairly active (combined into one reference group) women.

a)

Inactive/active ~	n	OR	95% CI	p-value
Parity, para ≥1 (ref. nullipara)		0.62	0.52, 0.75	**<0.001**
Country of origin (ref. Norway)				
Sweden		0.64	0.51, 0.80	**<0.001**
Other Nordic		2.71	1.06, 8.47	0.056
Rest of the world		0.42	0.31, 0.57	**<0.001**
Marital status, other (ref. married/cohabitant)	2337	0.48	0.28, 0.82	**0.007**
Pre-pregnancy PA (ref. no regular pre-pregnancy PA)		4.82	3.83, 6.09	**<0.001**
Education (ref. high school only or less)				
Higher education <4 years		1.15	0.85, 1.57	0.366
Higher education ≥4 years		1.38	1.03, 1.86	**0.033**
Current sick leave at 18 weeks		0.56	0.44, 0.71	**<0.001**

b)

Inactive/fairly active/highly active ~	n	OR	95% CI	p-value
Parity, para ≥1 (ref. nullipara)		0.64	0.54, 0.75	**<0.001**
Country of origin (ref. Norway)				
Sweden		0.69	0.57, 0.84	**<0.001**
Other Nordic		1.50	0.78, 2.93	0.229
Rest of the world		0.45	0.34, 0.60	**<0.001**
Marital status, other (ref. married/cohabitant)	2337	0.48	0.29, 0.78	**0.004**
Pre-pregnancy PA (ref. no regular pre-pregnancy PA)		5.17	4.14, 6.49	**<0.001**
Education (ref. high school only or less)				
Higher education <4 years		1.27	0.96, 1.68	0.100
Higher education ≥4 years		1.53	1.17, 2.00	**0.002**
Current sick leave at 18 weeks		0.56	0.45, 0.71	**<0.001**

Associations with the binary outcome of inactive and active were analysed using logistic regression models and associations with the outcome of inactive, fairly active and highly active using ordinal logistic regression models.
Abbreviations: GPA; general physical activity level, n; number, OR; odds ratio, CI; confidence interval, ref.; reference group, PA; physical activity.

6.1.2 Physical activity in association with pregnancy outcomes and infant size

Among 812 infants with available information on maternal GPA level and lung function at three months of age, no significant differences in neither pregnancy outcomes nor infant size were observed between infants of inactive versus all active mothers (Figure 6.1a). Mean (SD) values for birth weight, placenta weight and infant weight gain according to maternal GPA level for infants of inactive, fairly active and highly active mothers are given in Table 6.3 and means with 95% CI showed in Figure 6.1b.

Figure 6.1 Pregnancy outcomes and infant size according to maternal GPA level. Shown for infants of a) inactive and active mothers, and b) inactive, fairly active and highly active mothers.
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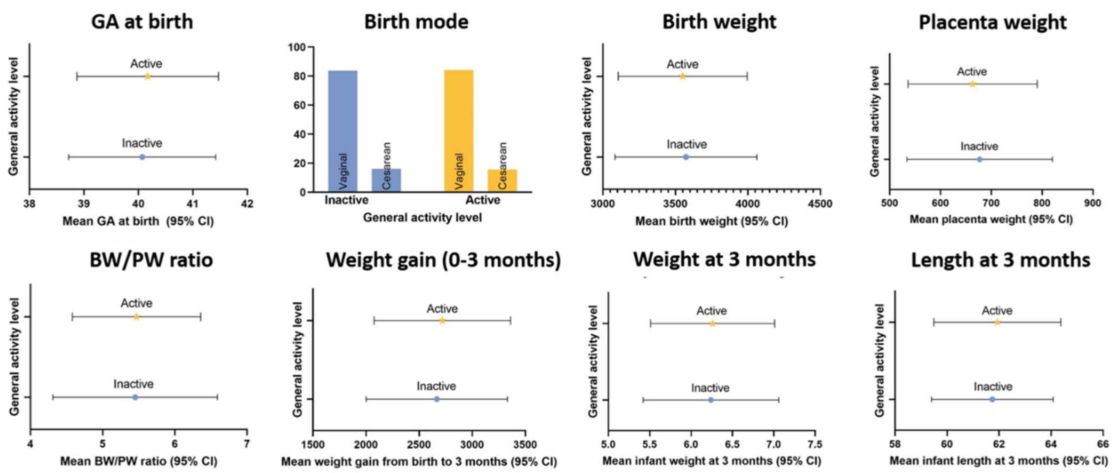
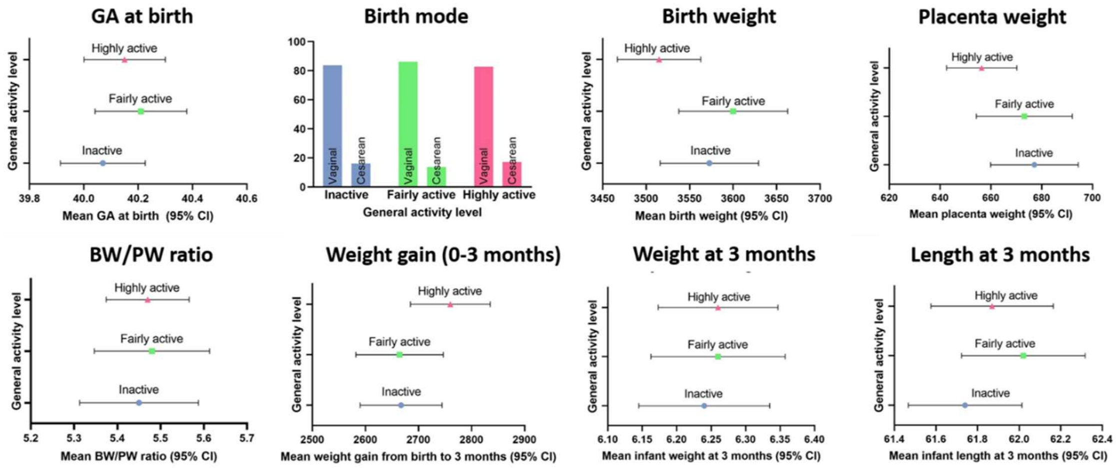
a)



b)



a) Means were compared between infants of inactive and active mothers with the independent sample t-test for continuous outcomes; GA at birth (p=0.305), birth weight (p=0.529), placenta weight (p=0.199), BW/PW ratio (p=0.771), infant weight gain (p=0.281), weight (p=0.676) and length (p=0.272) at three months of age, and with the Chi-squared test (χ^2) for the binary outcome of birth mode (p=0.861).
b) Means were compared between infants of inactive, fairly active and highly active mothers with one-way ANOVA for continuous outcomes; GA at birth (p=0.516), birth weight (p=0.094), placenta weight (p=0.160), BW/PW ratio (p=0.950), infant weight gain (p=0.142), weight (p=0.915) and length (p=0.421) at three months of age, and with the Chi-squared test (χ^2) for the binary outcome of birth mode (p=0.580).
Abbreviations: GA; gestational age, BW/PW ratio; birth weight to placenta weight ratio, CI; confidence interval.

Table 6.3 Birth weight, placenta weight and infant weight gain for inactive, fairly active and highly active women.

		Inactive		Fairly active		Highly active		
	n	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p-value**
Birth weight (kg)	808	3.57	0.49	3.60	0.47	3.51	0.42	0.094
Placenta weight (g)	754	677	143	673	139	656	117	0.160
Infant weight gain (kg)	804	2.67	0.67	2.66	0.62	2.76	0.66	0.142

Means compared between groups with the one-way ANOVA test.
Abbreviation: SD; standard deviation.

6.2 Maternal PA and infant lung function

The 812 infants (48.8% girls) with available information on maternal general activity level and lung function in the awake state at three months of age had a mean (min-max) GA at birth of 40.1 (35.3-42.3) weeks. At the time of lung function testing their mean (min-max) age was 93 (57-137) days and their weight 6.3 (4.4-8.9) kg Table 4.2.

Of the 812 infants, 290 (35.7%) infants had mothers that were inactive in the first half of pregnancy and the mothers of 522 (64.3%) infants were active, with 224 (27.6%) being fairly active and 298 (36.7%) highly active.

The mean (SD, min-max) t_{PTEF}/t_E of all infants was 0.39 (0.08, 0.19-0.63), with the distribution shown in Figure 6.2. Of 812 infants, 47 (5.8%) had a t_{PTEF}/t_E <0.25 and five (0.6%) <0.20. The mean (SD) number of TFV loops per infant was 21 (14).

Figure 6.2 Histograms showing the distribution of infant t_{PTEF}/t_E. In a) all included infants (n=812) and b) infants of inactive (dark grey, n=290) compared to all active (light grey, n=522) mothers, with two histograms on top of each other with partly overlapping transparent bars (middle grey).
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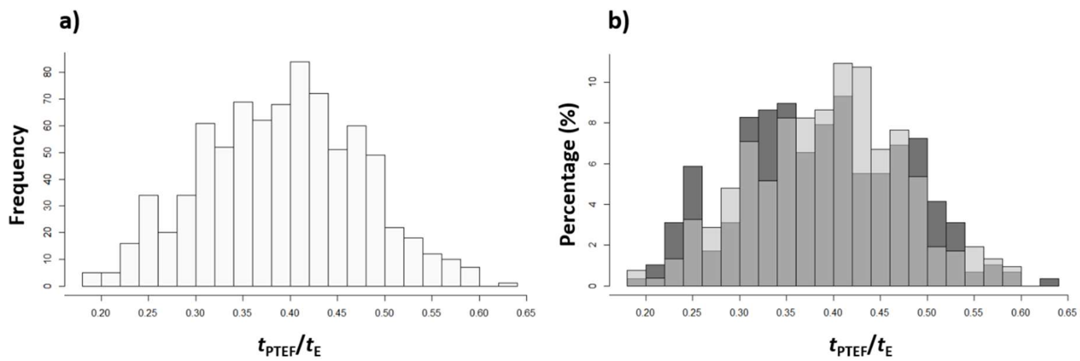

The overlapping histograms in part b) show t_{PTEF}/t_E distribution in differently sized subgroups, with the y-axis representing percentage (%) while the y-axis in a) shows frequency.
Abbreviations: t_{PTEF}/t_E; time to peak tidal expiratory flow to expiratory time.

The mean (SD) t_{PTEF}/t_E was similar among infants of inactive (0.387 (0.09)) and active (0.393 (0.08)) mothers, p=0.321. Infants of fairly and highly active mothers had a mean (SD) t_{PTEF}/t_E of 0.393 (0.08) and 0.394 (0.08), respectively (Figure 6.3). However, the t_{PTEF}/t_E distribution in the lower tail in the histogram in Figure 6.2b appears different between the two groups and the t_{PTEF}/t_E variability appears greater among infants of inactive compared to active mothers.

Figure 6.3 Infant t_{PTEF}/t_E according to the maternal GPA level.
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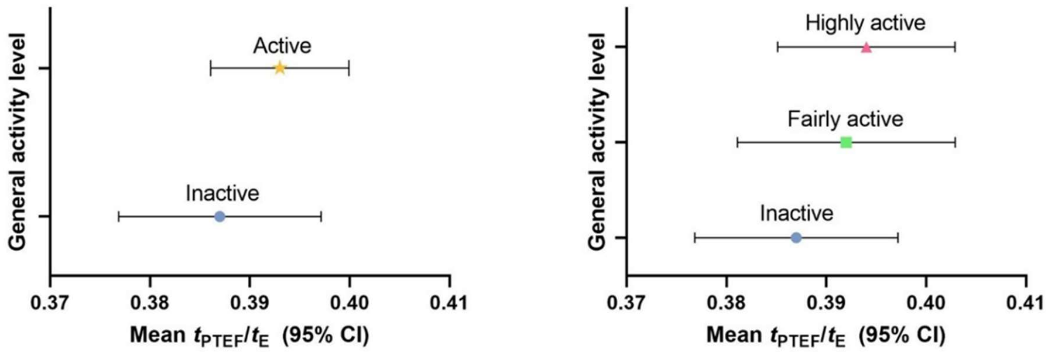

Abbreviations: t_{PTEF}/t_E; time to peak tidal expiratory flow to expiratory time, GPA level; general physical activity level, CI; confidence interval.

The odds of having a t_{PTEF}/t_E <0.25 were significantly higher among infants of inactive mothers compared to those of all active mothers combined, as well as compared to infants of fairly active mothers only, both in univariable and adjusted regression models (Table 6.4).

Table 6.4 The association between maternal GPA level in the first half of pregnancy and infant t_{PTEF}/t_E <0.25, analysed with logistic regression models. In a) infants of inactive mothers were compared to infants of all active mothers. In b) 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 BMI, parental atopy and in-utero exposure to nicotine.
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a)

	n*	**Inactive versus active**		
		OR	95% CI	p-value
t_{PTEF}/t_E <0.25				
Univariable	812	2.14	1.19, 3.90	**0.012**
Multivariable	808	2.07	1.13, 3.82	**0.019**

b)

	n*	**Inactive versus fairly active**			**Inactive versus highly active**		
		OR	95% CI	p-value	OR	95% CI	p-value
t_{PTEF}/t_E <0.25							
Univariable	812	2.92	1.31, 7.45	**0.014**	1.78	0.93, 3.52	0.088
Multivariable	808	2.83	1.26, 7.24	**0.018**	1.67	0.85, 3.41	0.145

** 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.*
Abbreviations: GPA level; general physical activity level, t_{PTEF}/t_E; the ratio of time to peak tidal expiratory flow to expiratory time, BMI; body mass index, n; number, OR; odds ratio, CI; confidence interval.

Supporting analyses of the association between maternal GPA level and t_{PTEF}/t_E <0.26, <0.27 and <0.28 are reported in Table 6.5.

Table 6.5 The association between maternal GPA level in the first half of pregnancy and infant t_{PTEF}/t_E <0.26, <0.27 and <0.28, analysed with logistic regression models. In a) infants of inactive mothers were compared to infants of all active mothers. In b) 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 BMI, parental atopy and in-utero exposure to nicotine.

a)

	n	**Inactive versus active**		
		OR	95% CI	p-value
t_{PTEF}/t_E <0.26				
Univariable	812	1.89	1.11, 3.22	**0.018**
Multivariable	808	1.85	1.07, 3.18	**0.026**
t_{PTEF}/t_E <0.27				
Univariable	812	1.73	1.05, 2.85	**0.030**
Multivariable	808	1.71	1.03, 2.85	**0.038**
t_{PTEF}/t_E <0.28				
Univariable	812	1.45	0.91, 2.32	0.116
Multivariable	808	1.44	0.89, 2.31	0.137

b)

	n	**Inactive versus fairly active**			**Inactive versus highly active**		
		OR	95% CI	p-value	OR	95% CI	p-value
t_{PTEF}/t_E <0.26							
Univariable	812	2.47	1.22, 5.42	**0.016**	1.60	0.89, 2.93	0.117
Multivariable	808	2.38	1.17, 5.24	**0.022**	1.55	0.85, 2.91	0.160
t_{PTEF}/t_E <0.27							
Univariable	812	1.93	1.02, 3.80	**0.049**	1.61	0.92, 2.87	0.099
Multivariable	808	1.86	0.98, 3.69	0.064	1.61	0.90, 2.93	0.113
t_{PTEF}/t_E <0.28							
Univariable	812	1.48	0.83, 2.71	0.191	1.44	0.84, 2.47	0.185
Multivariable	808	1.43	0.80, 2.63	0.238	1.44	0.83, 2.54	0.195

Abbreviations: GPA level; general physical activity level, t_{PTEF}/t_E; the ratio of time to peak tidal expiratory flow to expiratory time, BMI; body mass index, n; number, OR; odds ratio, CI; confidence interval.

Mean (SD) V_T/kg was 7.05 (2.12) ml/kg. V_T/kg was similar among infants of inactive compared to all active mothers, while a significant difference was observed between the groups when active mothers were further classified into fairly or highly active. Infants of highly active mothers had the lowest mean (SD) V_T/kg, 6.79 (2.05) ml/kg, significantly lower than infants of fairly active mothers that had the highest mean (SD) value of 7.25 (2.13) ml/kg), but not significantly different to infants of inactive mothers (7.17 (2.16) ml/kg) (Figure 6.4).

Figure 6.4 Infant V_T/kg according to maternal GPA level.
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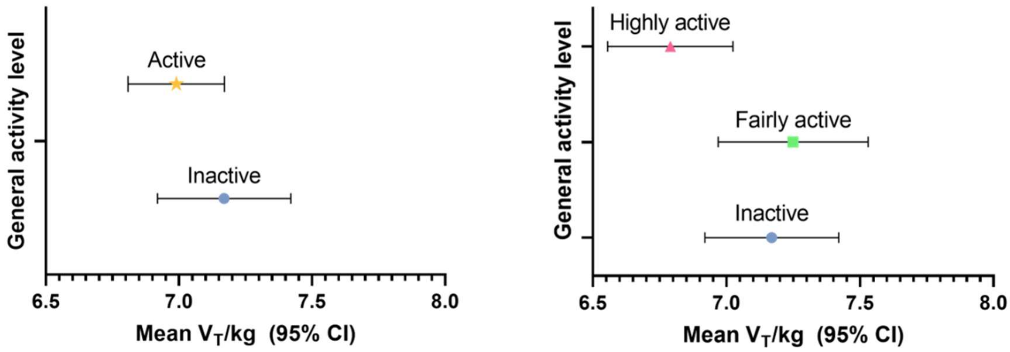

Abbreviations: VT/kg; tidal volume per kg, GPA level; general physical activity level, CI; confidence interval.

Linear regression models showed that having a highly active mother was significantly associated with a lower V_T/kg at three months of age, as reported in Table 6.6.

Table 6.6 The association between maternal GPA level in the first half of pregnancy and infant V_T/kg, analysed with linear regression models. Infants of inactive mothers were compared to infants of active mothers further classified into fairly active and highly active. Multivariable models were adjusted for maternal age, education, parity, pre-pregnancy BMI, parental atopy and in-utero exposure to nicotine.
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	n*	**Inactive versus fairly active**			**Inactive versus highly active**			R^2
		$\hat{\beta}$	95% CI	p-value	$\hat{\beta}$	95% CI	p-value	
V_T/kg								
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

** Information on infant weight at three months of age was missing for 4/812 included infants, leaving 808 infants included in models with V_T/kg as outcome (288 with inactive mothers, 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.*
Abbreviations: GPA level; general physical activity level, V_T/kg; tidal volume per kg, BMI; body mass index, n; number, $\hat{\beta}$; β estimate – the regression coefficient, CI; confidence interval, R^2; the amount of variability explained by the particular exposure by Pearson correlation.

6.3 Fetal TC at mid-pregnancy and infant lung function

The 851 infants (47.8% girls) with available ultrasound measures of fetal size at mid-pregnancy and lung function in the awake state at three months of age were born at a mean (min-max) GA of 40.2 (35.0-42.4) weeks. At birth their mean (min-max) weight was 3.6 (1.9-4.9) kg and at the time of lung function measurement their mean (min-max) age was 93 (74-131) days, weight was 6.3 (4.4-8.9) kg and their length 61.9 (55.5-70.9) cm (Table 4.2).

Mean (min-max) GA at mid-pregnancy ultrasound examination was 18.7 (16.3-22.1) weeks. Without being adjusted for GA at the time of measurement, mean fetal HC and fetal AC were significantly smaller in girls compared to boys, whereas TC and FL where similar among both sexes (Table 4.3).

The fetal thoracic size ratios, infant t_{PTEF}/t_E, V_T and V_T/kg, are shown for girls and boys separately in Table 6.7.

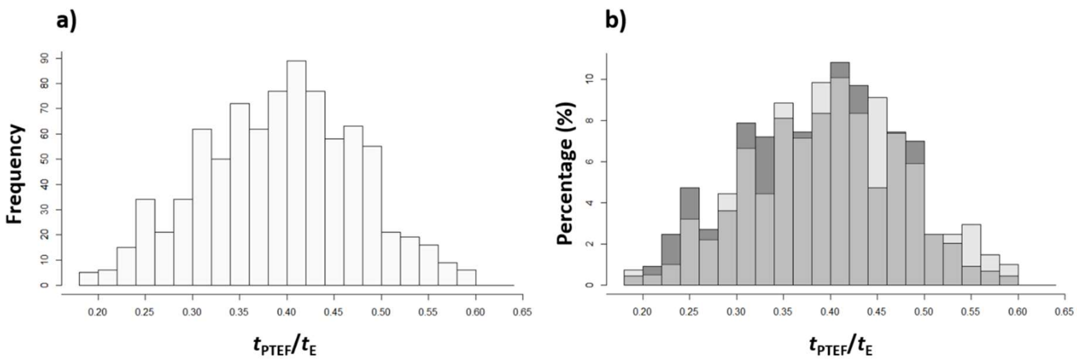
Table 6.7 Mid-pregnancy fetal TC/HC, TC/AC and TC/FL as well as infant t_{PTEF}/t_E, V_T and V_T/kg in girls and boys, compared with the independent sample t-test.
Reprinted with Creative Commons Attribution 4.0 International License, CC BY 4.0 (http://creativecommons.org/licenses/by/4.0/). Gudmundsdottir HK et al. Fetal thoracic circumference in mid-pregnancy and infant lung function. Pediatr Pulmonol. 2023 Jan;58(1):35-45. doi: 10.1002/ppul.26153. From the online supplement.

	n	Girls		Boys		p-value
		Mean	**95% CI**	**Mean**	**95% CI**	
TC/HC	726	0.75	0.75, 0.75	0.74	0.74, 0.75	**0.006**
TC/AC	725	0.87	0.87, 0.87	0.87	0.86, 0.87	0.320
TC/FL	724	4.16	4.13, 4.19	4.17	4.14, 4.20	0.639
t_{PTEF}/t_E	851	0.40	0.39, 0.41	0.39	0.38, 0.39	**0.016**
VT	851	42.84	41.68, 44.00	45.08	43.82, 46.33	**0.010**
VT/kg	847	7.27	7.07, 7.47	6.95	6.75, 7.15	**0.027**

Abbreviations: TC; thoracic circumference, HC; head circumference, AC; abdominal circumference, FL; femur length, t_{PTEF}/t_E; the ratio of time to peak tidal expiratory flow to expiratory time, V_T; tidal volume, n; number, CI; confidence interval.

The mean (SD) t_{PTEF}/t_E of all 851 infants was 0.39 (0.08), significantly higher among girls compared to boys (Table 6.7). A t_{PTEF}/t_E of 0.28 constituted the 10th percentile, while 46/851 infants (5.4%) had t_{PTEF}/t_E <0.25. The t_{PTEF}/t_E distribution was as shown in Figure 6.5, based on a mean (SD) of 22 (14) TFV loops per infant included in the analyses.

Figure 6.5 Histograms showing the distribution of infant t_{PTEF}/t_E. In a) all included infants (n=851) and b) girls (light grey, n=407) compared to boys (dark grey, n=444), with two histograms on top of each other with partly overlapping transparent bars (middle grey).



The overlapping histograms in part b) show t_{PTEF}/t_E distribution in slightly differently sized subgroups, with the y-axis representing percentage (%) while the y-axis in a) shows frequency. Abbreviations: t_{PTEF}/t_E*; the ratio of time to peak tidal expiratory flow to expiratory time.*

No significant association was observed between fetal TC relative to head (TC/HC) or abdominal (TC/AC) circumferences and infant t_{PTEF}/t_E neither in univariable nor multivariable regression models (Table 6.8).

A weak, but significant inverse association was observed between fetal TC relative to femur length (TC/FL) and infant t_{PTEF}/t_E as a continuous outcome, in addition to t_{PTEF}/t_E lower than the 10th, 25th and 50th percentiles, in both univariable and multivariable models, as shown in Table 6.8 and Figure 6.6.

Table 6.8 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.
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a)

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

b)

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

c)

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

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

Figure 6.6 The variation in infant t_{PTEF}/t_E in relation to the 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.
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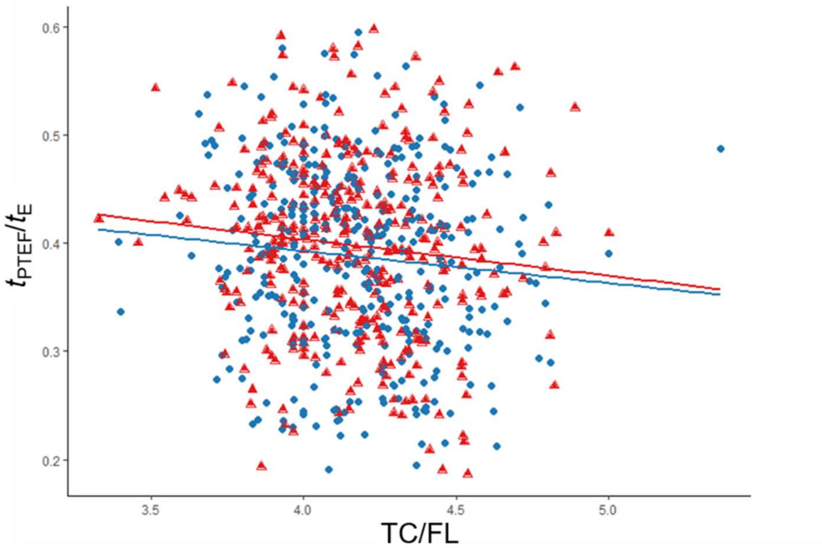

Girls are marked with red triangles and a red regression line, boys are marked with blue dots and a blue regression line.
Abbreviations: t_{PTEF}/t_E: The ratio of time to peak tidal expiratory flow to expiratory time. TC/FL: Fetal thoracic circumference relative to femur length, a proxy for TC adjusted for gestational age at the time of ultrasound.

Excluding preterm infants (GA at birth 35.0-36.9 weeks) from the regression models did not significantly affect the inverse association between TC/FL and t_{PTEF}/t_E (data not shown).

The mean (SD) V_T for the 851 included infants was 44.01 (12.75) ml, and when standardized for body weight, mean (SD) V_T/kg was 7.10 (2.11) ml/kg. While V_T was significantly higher in boys compared to girls, V_T/kg was significantly higher among girls (Table 6.7).

Both fetal TC/HC and TC/FL were positively associated with infant V_T, while TC/AC was not, as shown in Table 6.9. While the association between TC/HC and V_T was only significant when adjusted for relevant covariates, significant associations between TC/FL and V_T were found in both univariable and adjusted models.

Table 6.9 Associations between fetal TC relative to a) head circumference (TC/HC), b) abdominal circumference (TC/AC) and c) femur length (TC/FL), and infant V_T. Reproduced with Creative Commons Attribution 4.0 International License, CC BY 4.0 (http://creativecommons.org/licenses/by/4.0/). Gudmundsdottir HK et al. Fetal thoracic circumference in mid-pregnancy and infant lung function. Pediatr Pulmonol. 2023 Jan;58(1):35-45. doi: 10.1002/ppul.26153.

a)

			TC/HC		
	n	**R^2**	**$\hat{\beta}$**	**95% CI**	**p-value**
V_T					
Univariable		0.004	22.57	-2.49, 47.63	0.077
+ infant sex	726	0.016	26.41	1.34, 51.47	**0.039**
Multivariable		0.032	26.39	1.34, 51.44	**0.039**

b)

			TC/FL		
	n	**R^2**	**$\hat{\beta}$**	**95% CI**	**p-value**
V_T					
Univariable		0.007	3.95	0.44, 7.47	**0.028**
+ infant sex	724	0.016	3.87	0.37, 7.37	**0.030**
Multivariable		0.031	3.56	0.06, 7.05	**0.046**

c)

			TC/AC		
	n	**R^2**	**$\hat{\beta}$**	**95% CI**	**p-value**
V_T					
Univariable		0.001	10.29	10.61, 31.1	0.334
+ infant sex	725	0.011	11.35	-9.48, 32.17	0.285
Multivariable		0.027	10.73	10.07, 31.5	0.311

Potential associations between the fetal TC ratios and infant tidal volume were assessed using univariable models, models adjusted for infant sex only, and multivariable models adjusted for maternal age, maternal asthma, pre-pregnancy body mass index, parity, infant sex and in-utero exposure to nicotine.
Abbreviations: TC; thoracic circumference, HC; head circumference, AC; abdominal circumference, FL; femur length, V_T; tidal volume, n; number, R^2; the percentage of variation explained by the exposure(s), $\hat{\beta}$; the regression coefficient (β estimate), CI; confidence interval.

The fetal TC ratios were not significantly associated with infant V_T/kg (results not shown).

When preterm infants were excluded from the analyses, the strength of the positive association of both fetal TC/HC and TC/FL with infant V_T slightly increased (Table 6.10).

Table 6.10 Associations between fetal TC relative to a) head circumference (TC/HC), b) abdominal circumference (TC/AC) and c) femur length (TC/FL), and infant V_T. For all infants and among term infants only.

	Univariable					Multivariable				
	n	**R^2**	**$\hat{\beta}$**	**95% CI**	**p-value**	**n**	**R^2**	**$\hat{\beta}$**	**95% CI**	**p-value**
V_T ~ TC/HC										
All infants	726	0.004	22.57	-2.49, 47.63	0.077	726	0.032	26.39	1.34, 51.44	**0.039**
Term infants	704	0.008	30.99	4.86, 57.13	**0.020**	704	0.032	33.31	7.20, 59.42	**0.012**
V_T ~ TC/AC										
All infants	725	0.001	10.29	-10.61, 31.19	0.334	725	0.027	10.73	-10.07, 31.53	0.311
Term infants	702	0.002	14.34	-7.26, 35.93	0.193	702	0.025	13.92	-7.60, 35.45	0.204
V_T ~ TC/FL										
All infants	724	0.007	3.95	0.44, 7.47	**0.028**	724	0.031	3.56	0.06, 7.05	**0.046**
Term infants	701	0.010	4.81	1.18, 8.43	**0.010**	701	0.030	4.33	0.71, 7.95	**0.019**

Infants born before 37.0 (35.0-36.9) GWs are defined as 'preterm infants', while 'term infants' are born at 37.0 weeks or later. Multivariable models are adjusted for maternal age, maternal asthma, pre-pregnancy BMI, parity, infant sex and in-utero exposure to nicotine. Abbreviations: TC; thoracic circumference, HC; head circumference, AC; abdominal circumference, FL; femur length, V_T; tidal volume, n; number, R^2; the percentage of variation explained by the exposure(s), $\hat{\beta}$; the regression coefficient (β estimate), CI; confidence interval, BMI; body mass index.

6.4 Infant sex and associations of maternal PA and fetal TC with infant lung function

Among 812 infants with information on *maternal PA in the first half of pregnancy and lung function* in the awake state at three months of age, girls and boys were equally distributed across the groups based on the maternal GPA level (previously unpublished). The mean (SD) t_{PTEF}/t_E was similar in girls (0.40 (0.08)) and boys (0.39 (0.08)) (p=0.071), while mean (SD) V_T/kg was significantly higher among girls, 7.22 (2.09) ml/kg compared to 6.89 (2.14) ml/kg in boys (p=0.024) (previously unpublished).

Including the interaction term 'maternal GPA level * infant sex' in regression models exploring the association between maternal GPA level and infant lung function, no significant interaction of maternal PA in pregnancy and infant sex was observed. Nor was there any significant difference between girls and boys in the associations between maternal GPA level and lung function (Paper II, results not shown).

Among 851 infants with information on *mid-pregnancy fetal size and lung function* in the awake state at three months of age, infant sex was weekly (R^2=0.007), but significantly associated with the continuous t_{PTEF}/t_E in the univariable model ($\hat{\beta}$=0.014, 95% CI [0.003, 0.03], p=0.016). However, the interaction terms 'TC/HC * infant sex', 'TC/AC * infant sex' and 'TC/FL * infant sex' were not significantly associated with infant lung function and neither did an adjustment for only infant sex significantly affect the associations between the fetal thoracic ratios and infant lung function (results not shown).

When stratified for sex, the weak inverse association between TC/FL and t_{PTEF}/t_E remained significant only among girls, and only in the univariable model. Although the significance was lost in the adjusted model, R^2 for the association between TC/FL and t_{PTEF}/t_E was higher among girls than in boys in the adjusted model (Table 6.11).

Table 6.11 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.
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	Girls					Boys				
	n	**R^2**	**$\hat{\beta}$**	**95% CI**	**p-value**	**n**	**R^2**	**$\hat{\beta}$**	**95% CI**	**p-value**
t_{PTEF}/t_E ~ TC/HC										
Univariable	344	0.005	-0.17	-0.41, 0.08	0.178	382	0.002	-0.09	-0.31, 0.13	0.426
Multivariable		0.038	-0.17	-0.42, 0.08	0.185		0.017	-0.09	-0.32, 0.13	0.422
t_{PTEF}/t_E ~ TC/FL										
Univariable	343	0.011	-0.03	-0.07, -0.00	**0.048**	381	0.009	-0.03	-0.06, 0.00	0.063
Multivariable		0.045	-0.03	-0.07, -0.00	0.058		0.023	-0.03	-0.06, 0.01	0.105
t_{PTEF}/t_E ~ TC/AC										
Univariable	344	<0.001	-0.004	-0.20, 0.19	0.965	381	0.003	-0.10	-0.29, 0.08	0.267
Multivariable		0.033	-0.001	-0.20, 0.20	0.989		0.019	-0.10	-0.29, 0.09	0.277

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

An adjustment for infant sex significantly affected the association between TC/HC and V_T, and as was shown in Table 6.9, including infant sex in the model strengthened the significant association between fetal TC/FL and infant V_T. The fetal TC ratios were not associated with infant V_T nor V_T/kg when stratified for sex (not shown).

7. Discussion

7.1 Physical activity in pregnancy

Among women in the PreventADALL cohort reporting PA, 29% reported no regular PA at mid-pregnancy (Paper I). Most of the 2348 pregnant women had been regularly active before pregnancy, were pregnant with their first child, and generally, they were highly educated and of normal pre-pregnancy weight. According to the GPA level, estimated at mid-pregnancy 39.1% of the women were defined as inactive, 27.6% as fairly active and 33.3% as highly active in the first half of pregnancy.

7.1.1 Pre-pregnancy factors for PA in pregnancy

Regular pre-pregnancy PA, higher education and living with a partner were positively associated with a higher GPA level in the first half of pregnancy, while parity was inversely associated with the GPA level. In addition, women currently on sick leave and women from Sweden as well as of non-Nordic origin had significantly reduced odds of being physically active during pregnancy. The associations of pre-pregnancy factors with the maternal GPA level were similar regardless of comparing infants of inactive mothers to those of all active mothers, or when active mothers were further classified as fairly active or highly active.

Women who had been regularly physically active before they became pregnant were more likely to have a higher GPA level during pregnancy, with approximately five-fold odds compared to women that had a more sedentary pre-pregnancy lifestyle, in line with the findings of Broberg et al in a Danish cohort study including around 8000 pregnant women [90].

Highly educated women were more likely to be active during the first half of pregnancy than less well educated women, a finding that is in agreement with the positive association previously described between education and PA level among both pregnant [86, 90, 91] and non-pregnant women [114].

In the PreventADALL study, women having previous children reported reduced PA in the first half of pregnancy in line with previous findings, including cohort studies from Norway [86], Denmark [90] and Sweden [91]. On the other hand, the British Avon longitudinal study of parents and children (ALSPAC) reported higher odds of strenuous PA in parous compared to nulliparous women among almost 10000 pregnant women recruited to the study in the early 1990s [93].

In the present study, not living with a partner was inversely associated with GPA level in the first half of pregnancy, with only half the odds for cohabitant or married women. Previous studies have been inconsistent regarding marital status and PA level among pregnant women [92, 93]. Most of the women included in the PreventADALL study were married or cohabitants at the time of recruitment, which may have affected the results.

Compared to Norwegian women, women of Swedish or non-Nordic origin were less likely to be physically active in the first half of pregnancy. Our findings are in line with lower PA levels reported among women of non-Nordic origin and with language difficulties in previous Scandinavian studies [90, 91], and might be due to cultural barriers. Lower PA among pregnant Swedish compared to Norwegian women is to my knowledge a novel finding and might potentially be explained by a more urban lifestyle among the Swedish women and cultural differences in relation to PA in general between the countries.

The finding that women on sick leave at mid-pregnancy had significantly reduced odds of being physically active in the first half of pregnancy was not unexpected, and supported by a Swedish cross-sectional study on around 4000 pregnant women [91] and the British ALSPAC study [93], finding self-reported general good health positively associated with PA level during pregnancy.

The findings of this thesis, describing associations between pre-pregnancy factors and GPA level in the first half of pregnancy are generally in concordance with previous studies from different countries [92]. As observed in the PreventADALL cohort, in line with other studies, large groups of pregnant women do not meet PA recommendations [86, 89-91]. In view of the importance of PA in pregnancy, encouraging and facilitating PA among pregnant women and women of child-bearing age, especially those in risk groups for low PA levels in pregnancy, is important.

7.1.2 Physical activity in association with pregnancy outcomes and infant size

Maternal GPA level among 812 mother-child pairs was not significantly associated with GA or weight at birth, birth mode, placenta weight, the ratio of birth weight to placenta weight, infant weight gain nor infant weight or length at three months of age.

Gestational age at birth was similar among infants of inactive and active mothers, also when active mothers were further defined as fairly or highly active, in line with studies reporting no increase of preterm birth among physically active compared to inactive women [77, 79, 80, 89, 91, 123].

In our study population, birth mode was similar across groups defined by the GPA level, in contrast to several studies reporting a reduced risk of caesarean deliveries among physically active women [79, 81, 82, 124, 125], while others have not reported significant differences [80, 89]. In a systematic review and meta-analysis from 2018, 'exercise-only interventions' were not significantly associated with birth mode, while 'exercise with co-interventions' reduced the risk of a caesarean section, suggesting an impact of other factors on the association between maternal PA during pregnancy and birth mode [126]. Not finding a different rate of caesarean deliveries according to the GPA level in our study may have several explanations. Firstly, our results are crude estimates, not adjusted for confounding factors that may impact both maternal PA and birth mode. Most of the women in our study population were regularly physically active before pregnancy while randomized studies showing a lower risk of caesarean deliveries among women in the exercise groups, have often included previously sedentary women [79, 82]. Pre-pregnancy PA is a strong predictor of PA levels during pregnancy [90] that may contribute to a reduced risk for caesarean deliveries among physically active women [125]. Also, with the low prevalence of caesarean deliveries in Scandinavia, and especially Norway [127, 128], the study population explored in this thesis might be too small to detect differences in birth mode according to maternal GPA level and comparisons across countries may be challenging.

Birth weight did not differ according to maternal GPA level in the first half of pregnancy, although a trend of lower weight at birth was observed among infants of highly active mothers. Supporting our findings, previous studies have reported that maternal PA reduces the risk of delivering macrosomic infants with birth weight >4000 g [77, 129], without increasing the risk of having infants of low birth weight (<2500 g) or small for GA [77, 79, 123, 129]. In a meta-analysis from eight cohort studies, a trend of slightly lower birth weight has been associated with maternal PA of moderate and high intensity in late pregnancy, [129], while others have not reported a significant difference in birth weight according to maternal PA [79, 82, 123].

Placenta weight at birth was similar among infants of inactive and all active mothers, in line with findings described in a recent systematic review and meta-analysis by Kubler et al. [130]. The slightly smaller placenta weight, although not statistically significant, in infants of highly active compared to inactive and fairly active mothers is similar to the small, but significant association between lower placenta weight and increasing weekly frequency of PA sessions in the Norwegian Mother and Child Cohort study (MoBa) of around 80500 women reported by Hilde et al. [131]. Also, Kubler et al. described different placental composition according to maternal PA, with an increase in villous tissue relative to non-parenchymal tissue among active compared to inactive mothers [130].

With a slightly smaller birth weight as well as placenta weight among infants of highly active compared to inactive and fairly active mothers, the ratio of birth weight to placenta weight, reflecting placenta efficiency, was similar across different maternal GPA level groups, in agreement with the findings of Kubler et al. [130]. An adequately functioning placenta is essential for normal fetal growth and development. Moderate PA during pregnancy improves maternal and fetal cardiovascular function [132] while high PA level late in pregnancy may reduce the uterine circulation and fetoplacental growth and is associated with smaller placenta size [131] and an increased risk of fetal growth restriction [133]. Smaller placenta size is also independently associated with an increased risk of fetal growth restriction and lower birth weight [134].

Further studies are needed to elucidate potential associations of maternal PA with fetal and infant growth, and how the placenta and potentially alterations in the uteroplacental or placentoumbilical circulations may impact on such associations.

7.2 Maternal PA and infant lung function

Maternal GPA level in the first half of pregnancy was significantly associated with lung function in 812 healthy infants from the general population. At three months of age, infants of inactive mothers had increased odds of low lung function, with twice the odds of having a t_{PTEF}/t_E <0.25 compared to infants of active mothers. The highest maternal activity level was significantly associated with lower V_T/kg.

Our finding of a significant association between maternal inactivity in the first half of pregnancy and lower t_{PTEF}/t_E at three months of age is novel, while previous findings from studies examining fetal responses to maternal exercise may support our results [133, 135]. Fetal breathing movements, observed as early as the first trimester, stimulate maturation of the fluid-filled fetal lungs. Flowing in and out of the lungs, the fluid provides for stretching and expansion of the lung tissue, essential for lung and respiratory system development [11, 38, 136]. How fetal breathing movements relate to postnatal lung function is not clear, but studies have suggested that maternal exercise temporarily affects both fetal breathing and body movements [133, 135, 137]. Fetal heart rate variability may be augmented by fetal breathing movements and has been shown to increase during maternal exercise and [133, 138]. In addition, maternal PA has been associated with improved fetal cardiac function [132] and higher blood flow in the umbilical cord [133]. Taken together, the effects of PA during pregnancy may result in an improved in-utero environment and a lower risk of adverse outcomes in offspring of active women.

The higher odds of low t_{PTEF}/t_E in infants of inactive mothers compared to all active and fairly active mothers are in agreement with studies reporting advantageous associations of moderate maternal PA with fetal development and well-being [132, 133]. However, as the odds for low lung function were not significantly reduced for infants of highly active compared to inactive mothers, our results suggest that the association between maternal GPA level and infant t_{PTEF}/t_E may not be dose-dependent.

To define low lung function in this population-based study of generally healthy participants, we used a t_{PTEF}/t_E <0.25, in line with cut-off values found to be clinically relevant in previous studies [1, 3, 4, 14, 42]. Few of the healthy, awake infants had t_{PTEF}/t_E <0.25 but when the regression models were repeated with t_{PTEF}/t_E <0.26 and t_{PTEF}/t_E <0.27 as the outcome, similar results were obtained, with higher odds of low lung function among infants of inactive mothers. These supportive analyses point to robustness of our results. No significant association of maternal inactivity and infant t_{PTEF}/t_E <0.28, constituting approximately the 10th percentile in the PreventADALL population, was observed.

One could speculate, that the association between maternal inactivity and low infant t_{PTEF}/t_E might reflect higher prevalence of pregnancy complications among physically inactive women. However, maternal PA was reported at mid-pregnancy while complications such as maternal hypertension and gestational diabetes mellitus, associated with lower lung function or asthma in offspring [43, 94, 96] and partly preventable by maternal PA in pregnancy [75, 79, 84], often arise later. Being physically active is associated with appropriate pregnancy weight gain [74, 75, 83] and while the impact of excessive weight gain during pregnancy on infant lung function is not clear, an association with an increased risk for childhood asthma has been described [108, 109]. Our multivariable models were adjusted for maternal pre-pregnancy BMI while information on maternal weight gain throughout pregnancy is not available for the PreventADALL cohort.

The finding that highly active mothers had infants with lower V_T/kg at three months of age is novel, and the reason for the association is not clear. Tidal volume correlates with respiratory rate. Although highest in infants of highly active mothers, respiratory rate unlikely explains the association with lower V_T/kg, as adjusting the model for respiratory rate had little effect on the observed association (Paper II). However, a possible explanation of normal t_{PTEF}/t_E and the lowest V_T/kg in infants of highly active mothers could be that slower fetal growth related to high maternal activity late in pregnancy might lead to imbalance between airway development and lung growth.

Details on maternal PA in the second half of pregnancy are not available for the PreventADALL cohort. One could speculate that higher GPA level in the first half of pregnancy might increase the likelihood of high activity level throughout pregnancy, in line with a positive association between pre-pregnancy PA and PA in pregnancy [90], also observed in the PreventADALL cohort (aim 1). Vigorous, weight bearing or high-volume exercise in the third trimester, as well as weight bearing exercise in the supine position, may be associated with transient fetal bradycardia, reduced uterine blood flow and reduced fetoplacental growth, increasing the risk of fetal growth restriction [133]. As reported for aim 1, birth weight and placenta weight tended to be lowest in infants of highly active mothers, followed by the highest weight gain until three months of age. This trend is in line with previously reported associations of high maternal activity late in pregnancy with lower birth weight and smaller placenta size [129, 131].

Airway branching completes during the second trimester while lung growth and maturation continues throughout pregnancy [11, 37, 38], concomitantly to fetal growth and weight gain in the third trimester. Larger airway calibre relative to lung size results in a higher rate of airflow, and subsequently a higher infant t_{PTEF}/t_E [37]. Body length has been shown to predict airway calibre [139], while low birth weight and high infant weight gain are associated with reduced lung function and asthma in childhood [60, 62, 64, 140]. Our findings may suggest, that even though a “catch-up” body growth is observed, lung growth, with formation of new alveoli as well as alveolar growth, might not catch up as fast, which could be reflected by lower infant V_T/kg at three months of age.

Finding higher odds of low lung function among infants of inactive compared to active mothers adds to the importance of PA in pregnancy. Our results further suggest that in regard to lung function development, high maternal PA may not be superior to more moderate PA levels.

7.3 Fetal TC at mid-pregnancy and infant lung function

The mid-pregnancy measures of fetal TC relative to head or abdominal circumferences were not associated with the t_{PTEF}/t_E ratio in 851 healthy three-month-old infants from the general population, while a weak inverse association was observed between fetal TC relative to femur length and infant t_{PTEF}/t_E. Relative to both HC and FL, but not AC, fetal TC was associated with infant tidal volume, while none of the fetal TC ratios were associated with tidal volume standardized for infant weight.

The lack of association between fetal TC/HC and TC/AC in mid-pregnancy and t_{PTEF}/t_E in three-month-old infants, as well as the weak inverse association between fetal TC/FL and t_{PTEF}/t_E are novel findings. I am not aware of previous studies relating fetal TC to postnatal lung function, whereas TC measured in preschool children [69] and young adults [70] has been positively associated with spirometric lung function.

The inverse association of fetal TC/FL with infant t_{PTEF}/t_E suggests that a smaller TC in relation to FL in mid-pregnancy predicts higher t_{PTEF}/t_E in infancy. The observed association might originate from a positive association between fetal FL, a measure that has been used as a proxy for fetal length [30, 141], and postnatal lung function, as from birth to adulthood height and lung function are strongly correlated [9, 12, 37, 48, 64, 69, 70]. Partly in line with the reported results, Turner et al. showed that first trimester fetal length, measured as the crown-rump-length, was positively associated with childhood lung function at five and 10 years of age, while second trimester fetal FL was not [59, 60]. Exploring associations between fetal growth patterns and lung function at 10 years of age in the Dutch Generation R study, the authors found a positive association between estimated second and third trimester fetal weight and lung function, while no association between second nor third trimester fetal FL, and lung function was observed [61]. In the same cohort, a shorter fetal FL in the third trimester and lower second to third trimester FL growth was related to higher airway resistance, reflecting smaller airway diameters at six years of age [58]. It cannot be ruled out that a smaller fetal TC contributes to the observed inverse association of fetal TC/FL with infant t_{PTEF}/t_E. In addition to the lack of association between fetal FL and childhood lung function described in other studies [59-61], the association between fetal TC/FL and t_{PTEF}/t_E was stronger than that observed for AC/FL and t_{PTEF}/t_E (Paper III, online supplements) although fetal TC and AC are strongly correlated [31], and both being measures of fetal trunk size. Although statistically significant, the observed association between fetal TC/FL and infant t_{PTEF}/t_E was weak and may be of little or no clinical relevance. The low R^2 implies that only 1.0% of the total variation in infant t_{PTEF}/t_E can be explained by fetal TC/FL alone, increasing to 2.3% when adjusted for relevant covariates.

The lack of a clear association between mid-pregnancy fetal thoracic size ratios and infant t_{PTEF}/t_E may not be surprising. While infant t_{PTEF}/t_E is a dynamic measure of airway function, fetal TC is a structural measure of the bony thorax that is related to lung size. When airway branching completes in the second trimester, the development and growth of respiratory bronchioles and alveoli, later constituting the cornerstone of the lung volume, has merely started [37]. Expansion of the fluid-filled fetal lungs, driven by the upper airways and fetal breathing movements, is essential for normal growth and maturation of the lungs [11, 142]. One could speculate that for the generally healthy infants included in our study, variation in thoracic size related to airway and lung growth might be limited so early in fetal life. Fetal growth is greatest during the third trimester, with an increasing variation in general fetal size [100], and possibly also thoracic size, in the second half of pregnancy. Therefore, in Paper III, we speculated that the association between third trimester fetal TC or infant TC measured at birth and infant lung function might be stronger than for mid-pregnancy TC. However, the lack of significant association between third trimester fetal TC or thoracic growth and infant t_{PTEF}/t_E at three months of age in 257 infants from the PreventADALL cohort [33] did not confirm our speculations.

The positive association between fetal TC in relation to general fetal size measures and infant V_T is a novel finding in healthy infants. A weak positive association between fetal TC/HC as well as TC/FL and V_T was observed, while TC/AC was not associated with V_T. Supporting our findings, previous studies have described an association between fetal TC and fetal lung size [31, 34], including the recent PreventADALL sub-study on fetal ultrasound in the third trimester, showing a correlation (r=0.74) between fetal TC and lung volume at 30 GWs [33]. In a study by Ohlsson et al. fetal TC adjusted for FL predicted lethal lung hypoplasia in fetuses with high risk for this disease [73]. In neonates at risk for lung hypoplasia, the association of the fetal TC/AC ratio with clinical outcome is well-established [34, 71-73] while lower sensitivity for this purpose has been described for TC/FL [143]. In our study population, no association was observed between the fetal thoracic ratios and V_T standardized for infant weight (V_T/kg), indicating that the impact of fetal TC on V_T may be mediated through infant size.

Opposite associations between the fetal TC ratios and the lung function outcomes, with an inverse association between fetal TC/FL and infant t_{PTEF}/t_E, versus a positive association of fetal TC/HC and TC/FL with infant V_T, might not be unexpected. The t_{PTEF}/t_E reflects the rate of airflow, and lower t_{PTEF}/t_E values in infancy have been associated with both smaller airways and thinner airway walls in adult life [5]. In postnatal life, there is a positive association between airway calibre and body length [5, 139] and according to our results, a larger fetal TC relative to HC and FL predicts larger V_T in infancy. Although the observed associations are weak, with small effect sizes, a larger fetal TC relative to FL might reflect larger lung size relative to the airway calibre, leading to a somewhat slower rate of the airflow and lower t_{PTEF}/t_E values in infancy.

Smaller HC at birth, potentially a marker of early fetal growth restriction, has been associated with lower lung function both in infants [64] and adults [144]. One might speculate that a potential association between smaller mid-pregnancy HC and lower infant t_{PTEF}/t_E, could possibly affect the association between TC/HC and t_{PTEF}/t_E, and reduce the detectability of a potential association between fetal TC and infant t_{PTEF}/t_E.

When preterm infants, born at 35.0-36.9 GWs, were excluded from the regression models, a somewhat stronger positive association was revealed between both TC/HC and TC/FL and V_T, while the weak inverse association of TC/FL with t_{PTEF}/t_E remained similar. Healthy preterm compared to term infants have had shorter time for alveolar development and growth in-utero [11], which, together with a smaller body size, may lead to lower V_T. Including all infants in the analyses, regardless of GA at birth, might thus diminish the visibility of the association between mid-pregnancy fetal thoracic size and infant V_T.

7.4 Infant sex and associations of maternal PA and fetal TC with infant lung function

For infants from the general population and with available lung function measurement at three months of age, included in aims 2 (n=812) and 3 (n=851), the maternal GPA level was similar in girls and boys. Fetal TC/HC was significantly higher in girls while the TC/AC and TC/FL ratios were similar in both sexes. Infant t_{PTEF}/t_E and V_T/kg were significantly higher in girls, while V_T was significantly higher in boys among the 851 infants with information on fetal size, while the same sex difference in t_{PTEF}/t_E did not reach significance among the 812 infants with information on the maternal GPA level. Infant sex did neither significantly impact the associations between the maternal GPA level and lung function, nor the fetal TC ratios and infant t_{PTEF}/t_E, while an adjustment for sex strengthened the associations observed of TC/HC and TC/FL with infant V_T.

A significantly higher TC/HC ratio in girls compared to boys while TC/AC and TC/FL were similar in both sexes suggest a minimal influence of sex on fetal TC, supported by the findings of Seifnaraghi et al., showing TC as a function of weight, independent of age and sex, in infants and toddlers from 27 weeks GA to 2 years of age [145]. The higher TC/HC ratio in girls is probably related to a smaller HC in girls compared to boys [28], while mid-pregnancy fetal FL is presumably not related to sex [100].

Although the difference was small, infant t_{PTEF}/t_E was significantly higher among girls compared to boys, in line with other studies [37, 46, 48]. Reflecting their smaller body size [26], girls had significantly lower V_T and higher V_T/kg compared to boys, as previously described [2, 37, 51].

The finding that infant sex did not significantly impact the associations observed between maternal PA in the first half of pregnancy and infant lung function is novel, and in contrast to studies describing different effects of maternal asthma [46], in-utero exposure to maternal smoking [37] and household air pollution [49] on lung function in girls and boys.

Finding the associations of fetal TC relative to HC, AC and FL with infant t_{PTEF}/t_E similar in girls and boys, is to my knowledge a novel finding. Nevertheless, when adjusted for relevant covariates, fetal TC relative to FL explained more of the total variation in t_{PTEF}/t_E among girls. A sex-related bias, caused by both a higher TC/HC and a higher t_{PTEF}/t_E among girls, might diminish a potential inverse association between the TC/HC and t_{PTEF}/t_E when both girls and boys are included in the models.

The finding that the association between fetal TC/HC and infant V_T became statistically significant when adjusted for sex is novel, and may be partly explained by the smaller HC in girls. Infant sex did not significantly impact the association between TC/FL and V_T, which is also a novel finding. When the associations between fetal thoracic ratios and infant V_T were analysed in girls and boys separately, no significant association remained, with reduced power as a possible explanation.

Higher t_{PTEF}/t_E in girls and V_T in boys, likely reflects sex differences in fetal lung and airway development. The production of surfactant, a mixture of lipids and proteins necessary to reduce alveolar surface tension, enhancing small airway patency and gas exchange, matures earlier in girls compared to boys [37]. Boys have more respiratory bronchioles and larger lung volumes at birth, preparing for greater thoracic growth during puberty, while their ratio of large compared to small airways at birth may be lower than for the girls [37].

Reflecting larger airways relative to lung size, girls have higher flow rates in infancy compared to boys [14, 37, 48]. Possibly associated with their smaller airway calibre, boys are more prone to neonatal respiratory disease [37, 146] as well as childhood wheezing and asthma compared to girls [15, 63]. However, with increasing age, height and airway growth, boys have a steeper rise in lung function, and as young adults, men have significantly higher lung function than women, even when adjusted for height [8, 37].

The fetal TC/FL ratio explained a higher proportion of the total variation in t_{PTEF}/t_E in girls compared to boys, but to conclude on potentially different associations of fetal TC or fetal thoracic size ratios with lung function in girls and boys separately, a larger study is needed.

7.5 Strengths and limitations

The prospective mother-child design recruiting pregnant women in mid-pregnancy from an unselected general population, routine fetal ultrasound measures expanded with study-specific investigations, detailed data collection as well as a large number of healthy three-month-old infants with available lung function measurements are major strengths of the studies included in this thesis.

Maternal characteristics differ slightly between the study sites [32], which is reflected in the infants included in aims 2-4, as lung function was measured at the Oslo and Stockholm study sites only. Nevertheless, the findings reported in this thesis should be representative for the general Scandinavian population.

Strengths in aims 2-4 were TFV loops measured in awake infants by trained study personnel according to a standard operating procedure. All TFV measurements were analysed by three dedicated researchers using pre-defined and standardized criteria [101].

A methodological strength in aims 2-4 was the generation of DAGs based on available literature, prior to statistical analyses, to identify possible confounders included in the regression models.

A strength of aim 3 is the comprehensive ultrasound examination at mid-pregnancy performed by especially trained midwifes. All midwifes measuring fetal TC received training from one experienced fetal medicine obstetrician, later checking the quality of random samples of measurements.

For aims 1, 2 and 4, certain limitations regarding the estimated GPA level must be acknowledged. Maternal PA in the first half of pregnancy was not measured, but self-reported retrospectively at mid-pregnancy. While the women reported the frequency of different types of activities and their usual duration of exercise, they were not asked for the total number of activity sessions per week and thus, sessions including different PAs may be counted more than once. Possible answers were given as absolute numbers, open or closed ranges. Calculating the number of active minutes per week is therefore challenging and our estimate is not accurate. Nevertheless, I believe that the classification of active women (based on self-reported moderate or high intensity during exercise) into fairly and highly active is likely to be plausible.

Also, the associations of the maternal GPA level with pregnancy outcomes and infant size in aim 1 were not analysed in the whole cohort but among the 812 mother-child pairs included in aim 2. Only crude analyses were performed, while adjusting for confounders would give more informative results.

Excluding severe fetal and/or neonatal disease as well as infants born prior to 35.0 GWs may reduce the possibility of detecting aberrant lung development or airway pathology, and hence could limit the possibility of finding associations between early life factors and infant lung function, for aims 2-4.

Another potential limitation for aims 2-4 may be that while the main focus in the criteria for TFV analysis was on loop shape and the t_{PTEF}/t_E ratio, more differences in loop size were allowed, leading to higher V_T variability.

Determination of GA by second trimester biometric measures, as first trimester ultrasound was not routinely performed in Norway during the years of recruitment to the PreventADALL study, is a limitation for aim 3. It has been suggested, that different ways of determining GA may explain inconsistent results of studies exploring associations between fetal biometric measures and respiratory outcomes [147].

Tidal flow-volume parameters are largely dependent of the measurement settings and no known method can directly compare t_{PTEF}/t_E values measured in different arousal states, making it difficult to compare results between different studies. The chosen cut-offs for low lung function and lung function in the lower range are based on a thorough search in the literature. Not correcting for multiple testing in aim 3, with several exposures representing fetal size and different t_{PTEF}/t_E outcomes included in the regression models is a potential limitation.

8. Clinical implications and future perspectives

Although numerous positive effects of staying physically active during pregnancy are well documented, recognizing factors associated with lower or higher PA levels during pregnancy may be used for individualized advising in maternity care and follow-up.

There is considerable evidence supporting the association between lung function deficits in infancy and low lung function and adverse respiratory outcome later in life. Exploring potential associations between fetal life factors and lung function in infancy provides opportunities to identify strategies to improve lung health and prevent aberrant lung function development from the start of life. The association between maternal inactivity in the first half of pregnancy and low lung function at three months of age adds to the importance of supporting pregnant women and women of child-bearing age to be physically active. Airway development completes during the second trimester and optimal fetal growth, also in the first half of pregnancy, is fundamental for achieving the individual's potential for peak lung function before the natural decline in early adulthood.

Further studies of the PreventADALL cohort may reveal if maternal PA level during pregnancy, or fetal TC/FL or postnatal TC relative to the individual's height, may be associated with later lung function measurements or with clinical symptoms of airway obstruction. At present, clinical follow-up of children at 6-7 years of age is being conducted, including traditional spirometric measures and future studies will potentially reveal if having a t_{PTEF}/t_E in infancy below the chosen cut-off values used in this thesis may predict an increased risk of adverse respiratory outcomes in childhood or later in life.

Exploring the role of the placenta on the associations between maternal PA or fetal size and infant lung function may provide valuable new information about lung function development. Data on placenta size and placenta biomarkers are available for the PreventADALL cohort, and I hope to have the opportunity to continue the search for new information on early life factors associated with lung function in infancy and potential ways of preventing obstructive airway diseases.

9. My role in the PreventADALL study

I have been a part of the PreventADALL study team since the spring 2014 and have worked actively with the data collection for all parts of this thesis. I contributed to the development of questionnaires and organization of clinical follow-ups, recruited pregnant women and newborn infants and examined a large group of infants at birth and at three months of age, including the measurement of lung function at three months of age. In addition, I have participated in collecting, processing and registering biological materials.

Together with Karen Eline Stensby Bains I was responsible for the development of the standard operating procedure for the TFV measurements at three months of age, and the procedure for analysis of lung function data. This work included a pilot study performed to validate the criteria we used to evaluate the tests and manually select TFV loops for analysis, as described in a paper published in the ERJ Open Research in the summer of 2022 [101]. Thereafter I have analysed TFV measurements from approximately 700 infants, while Martin Färdig and Karen Eline Stensby Bains analysed the remaining tests.

In Paper I, I conceptualized, defined and developed the general activity level variable (in this thesis referred to as the GPA level) and wrote about it in the original draft of the manuscript, including Table S1 and Figure S2. I participated in discussions about all other parts of the article, reviewed and edited early and final versions of the manuscript. I performed all additional analyses reported in aim 1 of this thesis.

I performed all statistical analyses reported in Papers II and III (aims 2-4) in addition to writing the original drafts of the manuscripts, editing according to co-authors' comments and suggestions, making all figures and writing the final versions of the manuscripts.

10. Main conclusions

1. *To explore the role of pre-pregnancy factors with physical activity in pregnancy, and to explore if maternal physical activity is associated with pregnancy outcomes, focusing on infant size.*
    - Regular pre-pregnancy PA was the strongest positive predictor of maternal GPA level in the first half of pregnancy. Higher education, nulliparity and living with a partner increased the odds of being active during pregnancy while the opposite was found for current sick leave, being Swedish or of non-Nordic origin.
    - Maternal GPA level by mid-pregnancy was not significantly associated with infant GA at birth, birth mode, placenta weight nor infant size at birth or three months of age.
2. *To determine if maternal physical activity in pregnancy is associated with early infant lung function.*
    - Infants of inactive, compared to active mothers had significantly higher odds of low lung function by t_{PTEF}/t_E at three months of age. High maternal activity reported in mid-pregnancy was inversely associated with infant V_T/kg.
3. *To determine if fetal thoracic circumference at mid-pregnancy is associated with early infant lung function.*
    - Mid-pregnancy fetal TC relative to HC or AC was not associated with t_{PTEF}/t_E in three-month-old infants, while fetal TC/FL was weakly, inversely associated with infant t_{PTEF}/t_E. Fetal TC/HC and TC/FL were positively associated with infant V_T but not V_T/kg.
4. *To explore potential sex differences in the associations of maternal physical activity and fetal thoracic circumference with early infant lung function.*
    - The association between maternal inactivity in the first half of pregnancy and low infant lung function was not affected by infant sex.
    - The associations of fetal TC/HC, TC/AC and TC/FL with infant t_{PTEF}/t_E were similar in girls and boys, although fetal TC/FL explained more of the total variation in t_{PTEF}/t_E among girls.

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Paper I

Physical activity in pregnancy: a Norwegian-Swedish mother-child birth cohort study

Physical activity in pregnancy: a Norwegian-Swedish mother-child birth cohort study

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BACKGROUND: Physical activity during pregnancy is important for maternal and offspring health. Optimal conditions during pregnancy may help reduce the burden of noncommunicable diseases. National and international guidelines recommend at least 150 minutes of physical activity of at least moderate intensity per week. To optimize physical activity in pregnant women, it is important to identify factors associated with higher levels of physical activity.

OBJECTIVE: This study aimed to explore types and levels of physical activity in midpregnancy in Norway and Sweden and to identify factors associated with higher levels of physical activity.

MATERIALS AND METHODS: From the population-based mother-child cohort Preventing Atopic Dermatitis and Allergies in Children study recruiting 2697 women in Norway and Sweden from 2014 to 2016, we included 2349 women who answered an electronic questionnaire at enrollment in midpregnancy. Women were asked about regular physical activity in the last 2 weeks of pregnancy and afterward for types and levels of physical activity in pregnancy and before pregnancy and socioeconomic status, lifestyle, and maternal health. Logistic regression analyses were used to identify factors associated with higher levels of physical activity in pregnancy, defined as >30 minutes per session of ≥2 times per week of moderate- or high-intensity brisk walking, strength training, jogging, and bicycling.

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This study was performed within the Oslo Research Group of Asthma and Allergy in Childhood, the Lung and Environment (ORAACLE).

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RESULTS: No regular physical activity during the last 2 weeks before answering the questionnaire at midpregnancy was reported by 689 women (29%). In this study, 1787 women (76%) reported weekly strolling during pregnancy. Regular physical activity at least twice weekly in the first half of pregnancy was reported as brisk walking by 839 women (36%), bicycling by 361 women (15%), strength training by 322 women (14%), and other activities by <10% of women. Among the 1430 women with regular moderate- or high-intensity physical activity, the estimated median duration per week was 120 minutes. Higher physical activity levels were achieved in 553 women (23.5%) by brisk walking, 287 women (12.2%) by strength training, 263 women (11.2%) by bicycling, and 114 women (4.9%) by jogging. Higher physical activity levels were positively associated with regular physical activity before pregnancy, dog ownership, and atopic dermatitis and negatively associated with higher body mass index, study location in Østfold, previous pregnancy or pregnancies, non-Nordic origin, suburban living, and sick leave.

CONCLUSION: At midpregnancy, 29% of women were inactive, and less than 50% of women had at least 2 hours of moderate-intensity physical activity weekly. Awareness of physical activity in pregnancy should be discussed at pregnancy follow-up visits, particularly among women with higher body mass index, sick leave, previous pregnancy or pregnancies, and non-Nordic origin.

Key words: bicycling, brisk walking, maternal exercise, maternal health, mother-child birth cohort, physical activity, pregnancy, risk factors, strength training

Optimal conditions during pregnancy may reduce the burden of noncommunicable diseases in the offspring,[1−3] and modifiable lifestyle factors during pregnancy have been associated with maternal and offspring health. Physical activity (PA) in pregnancy is considered beneficial and safe for the mother and fetus[3−6] and seems to reduce the risk of cesarean delivery,[7,8] hyperemesis gravidarum,[9] gestational diabetes mellitus, hypertensive disorders of pregnancy, excessive gestational weight gain, lumbopelvic pain, and preterm birth.[5,10] Avoiding these adverse pregnancy outcomes seemed to have benefits in women's future health.[11−15]

Patterns of PA among pregnant women have been previously studied[16−19]; however, this knowledge needs to be regularly updated to continually enhance maternity care. Brisk walking and swimming were the most commonly performed exercises in the Avon Longitudinal Study of Parents and Children (ALSPAC)[16]; however, a recent Danish cross-sectional study found that bicycling was the most prevalent activity, followed by brisk walking.[17]

Recommendations for PA during pregnancy are available in many countries.[20] To improve health-related outcomes, pregnant women should perform at least 150 minutes of moderate- to high-intensity exercise per week.[3,5] These recommendations were implemented in Norway in 2019.[21] Nonpregnant adults have similar recommendations, with the addition that ≥150 minutes of moderate-intensity PA may be replaced with ≥75 minutes of high-intensity PA.[22]

To optimize PA in pregnancy, it is important to identify factors associated with lower and higher levels of PA. Primiparity and normal weight have been shown to increase the likelihood of higher PA levels in Scandinavian studies,[17,18] whereas in United Kingdom studies, dog ownership has been associated with more regular PA in pregnancy.[23] Several other factors have previously been explored, such as maternal age, education, regular PA before pregnancy, body mass index (BMI), and smoking, with differing results.[19]

In this study, the primary aim was to explore the types and levels of PA reported in midpregnancy in Norway and Sweden, and the secondary aim was to identify factors associated with higher levels of the most commonly performed physical activities in pregnancy.

AJOG MFM at a Glance

Why was this study conducted?

Physical activity (PA) in pregnancy is important for maternal and offspring health. This study aimed to explore types and levels of midpregnancy PA and factors associated with higher PA levels in women participating in a Scandinavian mother-child birth cohort.

Key findings

Strolling, brisk walking, strength training, and bicycling were most commonly performed at midpregnancy; furthermore, 29% reported no PA in the last 2 weeks before inclusion. Less than 50% reported 120 minutes or more of at least moderate-intensity PA per week. Higher levels of PA were significantly associated (*P*-value <.05) with regular PA before pregnancy and dog ownership and negatively associated with higher body mass index, previous pregnancy or pregnancies, non-Nordic origin, suburban living, and sick leave.

What does this add to what is known?

In this recently established mother-child birth cohort, most women performed less than 2 hours of moderate-intensity PA weekly. Our study points to the need to discuss PA during pregnancy follow-up visits.

Materials and Methods

Study design

Data from the Preventing Atopic Dermatitis and Allergies in Children (PreventADALL) study,[24] a Scandinavian general population-based mother-child birth cohort, enrolling 2697 women from December 2014 to October 2016, were used in this substudy on PA in pregnancy.

Pregnant women were recruited during the routinely offered 18 weeks' gestation ultrasound examination and enrolled in the PreventADALL study at

Oslo University Hospital, Østfold Hospital Trust, Norway, and Karolinska University Hospital, Stockholm, Sweden. All women attending the 18 weeks' gestation routine ultrasound examination at 1 of the participating facilities were invited to participate by letter of invitation attached to the appointment letter and information about the study by the midwife or the study personnel at the maternity clinic. After the ultrasound examination, women were invited to the study facility where they received further information from the study team before enrollment.

The inclusion criteria for the PreventADALL study were gestational age (GA) of 16 to 22 weeks at the time of the routine ultrasound examination, singleton or twin pregnancy, no severe fetal disease, and proficiency in the Scandinavian language.

At the enrollment visit, all women signed informed consent forms, followed by a brief interview; measurements of weight, height, and blood pressure; recording of ultrasound examination data; and information about study participation. The women were asked to complete a detailed electronic questionnaire (e-questionnaire) shortly after enrollment,[24] which provided the basis for this study. The e-questionnaire was sent by email, followed by 1 reminder the following week if there was no response, ensuring 1 response only.

Study population

In this study, we included 2349 women (87%) who returned the e-questionnaire associated with enrollment. The 351 nonresponding women (13%) were similar to those included in the study in age, parity, and BMI (Table 1).

Physical activity

The women were first asked if they had been regularly physically active during the last 2 weeks of pregnancy before answering the questionnaire. All subsequent questions were related to PA typically performed during the pregnancy and the average frequency for each of the following activities: strolling, brisk walking, jogging, bicycling, strength training, aerobics, skiing, ballgames, swimming, horse riding, yoga or pilates, and other types of PA. The frequency alternatives were rarely or never, 1 to 3 times a month, once a week, 2 to 3 times a week, 4 to 5 times a week, 5 to 6 times a week, every day, and more than once per day. Regular PA before pregnancy was defined as 1 or more PAs per week with a duration of at least 20 minutes. The women were asked to compare their current level of PA during the pregnancy with their PA level before pregnancy.

The exercise intensity was recorded with the question, "How intensively do you usually exercise (so far in pregnancy)?" with the following mutually exclusive categories: no sweating or shortness of breath (low intensity), sweaty and some shortness of breath (moderate intensity), or very sweaty and very heavy breathing (high intensity).

The duration of a typical PA session was reported as <30 minutes, 30 to 60 minutes, 1 to 2 hours, or more than 2 hours. The questions on intensity and duration were based on validated questions from the Akershus Birth Cohort study,[18] a Norwegian cohort study by Haakstad et al[25] and the Norwegian Mother and Child Cohort study.[26] The questions were later somewhat modified by our research team during the development of the questionnaire.

Prepregnancy weight was self-reported at the enrollment visit, where current weight was measured and recorded as kilograms with 1 decimal point. Height was measured using a standardized stadiometer. Pregnancy in gestational week was estimated on the basis of fetal femur length, as previously reported.[24]

Outcomes, definitions, and explanatory variables

For the primary aim, the outcomes were frequency, duration, and intensity of the reported types of PA. The general activity level for each woman was estimated among women who reported activity of at least moderate intensity by adding the numbers of reported PA sessions per week and multiplying by exercise duration in minutes. Strolling, being a low-intensity activity, was excluded. Because the frequency and duration of PA was reported with a range, we calculated both the minimum and maximum numbers of minutes of PA per week. The Supplemental Information section provides further details.

Higher PA levels used in the secondary aim required PA at least 2 to 3 times a week, performed with a duration of ≥30 minutes at moderate or high intensity. Women were categorized into higher PA level for each of the 4 activities most commonly reported at least twice a week: brisk walking, bicycling, strength training, and jogging.

For each of the 4 higher level PAs, we included the following possible explanatory variables in the regression model: age, prepregnancy weight, BMI and weight gain at 18 weeks of pregnancy, marital status (cohabitant and married combined into 1 category), previous pregnancy or pregnancies, education, family income, country of origin, living environment, regular PA before pregnancy, current dog and/or cat ownership, current sick leave, smoking and/or snus use in pregnancy, doctor-diagnosed asthma, doctor-diagnosed atopic dermatitis (AD), and/or doctor-diagnosed allergic rhinitis (AR).

Statistical analysis

The descriptive results were given as percentages of women reporting the respective activities; number (n) was listed for each activity. For univariate and multivariate analyses, missing data were set to 0, assuming that missing response reflected lack of performing the relevant activity.

To identify factors associated with higher levels of the 4 most commonly performed PAs in pregnancy, we performed univariate logistic regression analysis for potential covariates, retaining all variables with global P value of ≤.05 and categorical P values of ≤.2 in the final multivariate logistic regression model. The significance level was set to 5%.

We used Stata/SE (version 14.0; StataCorp, College Station, TX) for Windows (Microsoft Corporation, Redmond, Washington, DC) IBM Statistical Product and

TABLE 1
Background characteristics of the 2349 respondents and the 351 nonrespondents of the 18-week electronic questionnaire in the PreventADALL study

Characteristics	Respondents (present study participants) (n=2349)	Nonrespondents (excluded from this study) (n=351)
Age (y)	n=2349 32.4 (4.1)	n=351 31.8 (4.7)
Prepregnancy weight (kg)	n=2296 65.4 (11.3)	n=338 66.0 (12.4)
Weight gain at 18 wk of pregnancy (kg)	n=2293 4.7 (3.2)	n=336 4.3 (3.2)
Weight at 18 wk of pregnancy (kg)	n=2321 70.2 (11.3)	n=341 70.4 (12.6)
BMI at 18 wk of pregnancy (kg/m^2)	n=2311 24.8 (3.7)	n=341 25.0 (4.2)
Marital status		
Married or cohabitant	2280 (97.1)	
Single	44 (1.9)	—
Other	25 (1.1)	
Previous pregnancy or pregnancies		—
Yes	1292 (55.0)	
No	1057 (45.0)	
Previous delivery or deliveries		—
0	1414 (60.2)	
1	741 (31.5)	
≥2	194 (8.3)	
Education,		—
Primary school only[a]	20 (0.9)	
High school only	239 (10.2)	
Higher education of <4 y	757 (32.2)	
Higher education of ≥4 y	1257 (53.5)	
PhD	67 (2.9)	
Missing	9 (0.4)	
Family income		—
<300,000 NOK/SEK	30 (1.3)	
300,000–600,000 NOK/SEK	306 (13.0)	
600,000–1,000,000 NOK/SEK	959 (40.8)	
1,000,000–1,400,000 NOK/SEK	743 (31.6)	
>1,400,000 NOK/SEK	270 (11.5)	
Does not wish to answer	41 (1.7)	
Country of origin		—
Norway	1562 (66.5)	
Sweden	523 (22.3)	
Other Nordic countries	31 (1.3)	

Carlsen. Physical activity in midpregnancy. Am J Obstet Gynecol Glob Rep 2021. *(continued)*

TABLE 1
Background characteristics of the 2349 respondents and the 351 nonrespondents of the 18-week electronic questionnaire in the PreventADALL study *(continued)*

Characteristics	Respondents (present study participants) (n=2349)	Nonrespondents (excluded from this study) (n=351)
Rest of the world	233 (9.9)	
Living environment		—
City, densely populated	915 (39.0)	
City, less densely populated	882 (37.5)	
Suburb	373 (15.9)	
Countryside, outside village	52 (2.2)	
Village	127 (5.4)	
Regular physical activity before pregnancy		—
Yes	1 886 (80.3)	
No	463 (19.7)	
Dog owner		—
Yes	297 (12.6)	
No	2052 (87.4)	
Cat owner		—
Yes	259 (11.0)	
No	2090 (89.0)	
Sick leave at 18 wk		—
Yes	364 (15.5)	
No	1985 (84.5)	
Doctor-diagnosed asthma		—
Yes	405 (17.2)	
No	1944 (82.8)	
Doctor-diagnosed atopic dermatitis		—
Yes	461 (19.6)	
No	1888 (80.4)	
Doctor-diagnosed allergic rhinitis		—
Yes	477 (20.3)	
No	1872 (79.7)	
Smoke in pregnancy		—
Not in pregnancy	2233 (95)	
Quit before 18 wk GA	98 (4.2)	
Smoke at 18 wk GA	18 (0.8)	
Snus in pregnancy		—
Not in pregnancy	2171 (92.4)	
Quit before 18 wk GA	165 (7.0)	
Snus at 18 wk GA	13 (0.6)	

Data are presented as mean (standard deviation) or number (percentage). *BMI*, body mass index; *GA*, gestational age; *NOK*, Norwegian Krone; *PreventADALL*, Preventing Atopic Dermatitis and Allergies in Children study; *SEK*, Swedish Krona.

[a] Two women who answered "other" have been moved to primary school only.

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Service Solutions Statistics, version 26 (International Business Machines Corporation, Armonk, New York), and Microsoft Excel 2016 (Microsoft Corporation, Redmond, Washington, DC) for the statistical analyses.

Ethical approval

The PreventADALL study was approved by the Regional Committee for Medical and Health Research Ethics in Southeast Norway (2014/518) and Stockholm (2014/2242-31/4) and registered on ClinicalTrials.gov (NCT02449850).

Results

Background characteristics

The mean age of the 2349 women included in this study was 32.4 years, the mean BMI at inclusion was 25, most women had higher education, and approximately half of the women were nulliparous (Table 1).

Physical activity levels

At midpregnancy, 689 women (29%) did not report any PA during the last 2 weeks of pregnancy before answering the questionnaire. The most commonly reported regular PA performed at least once per week in the pregnancy was strolling (1787 [76.1%]), followed by brisk walking (1274 [54.2%]), strength training (707 [30.1%]), and bicycling (522 [22.2%]) (Supplemental Figure 1). PA at least twice per week was reported by 1369 women (58.3%) for strolling, 839 women (35.7%) for brisk walking, 361 women (15.4%) for bicycling, 322 women (13.7%) for strength training, and 127 women (5.4%) for jogging (Supplemental Figure 1). Yoga or pilates was reported at least once weekly by 443 women (18.9%) and jogging by 313 women (13.3%), whereas aerobics, skiing, swimming, ballgames, and horse riding were each reported by less than 10% of the women.

In addition, 1413 women (60.2%) reported the duration of a typical PA session to be 30 to 60 minutes, whereas 664 women (28.3%) reported <30 minutes and 271 women (11.5%) 1 to 2 hours. The intensity levels most frequently reported were moderate (1287 [54.8%]), followed by low (876 [37.3%]) and high (186 [7.9%]).

General activity level was estimated for 1430 women (60.9%) reporting moderate- or high-intensity activity. Based on the minimum number of minutes of PA per week (Supplemental Table 1), the median number of active minutes was 120 minutes, with an estimated 386 women (27.0%) performing PA for ≥150 minutes per week (Supplemental Figure 2). Using the maximum estimates (Supplemental Table 1), 711 women (49.7%) were estimated to perform PA of at least 150 minutes per week.

Of the women reporting regular PA before pregancy, 1677 (71.4%) reported less PA during pregnancy, 578 (24.6%) reported similar PA during pregnancy, and 94 (4.0%) reported more PA during pregnancy.

Secondary aim

For each of the 4 activities most commonly performed at least twice weekly, we calculated that higher PA levels were achieved in 553 women (23.5%) by brisk walking, 287 women (12.2%) by strength training, 263 women (11.2%) by bicycling, and 114 women (4.9%) by jogging.

The results of the univariate analyses of factors associated with higher levels of brisk walking, bicycling, strength training, or jogging are shown in Supplemental Table 2. In the multivariate analysis (Table 2; Figure), regular PA before pregnancy was positively associated with higher levels of brisk walking (odds ratio [OR], 5.30; 95% confidence interval [CI], 3.53−7.97), bicycling (OR, 7.35; 95% CI, 3.59−15.05), and strength training (OR, 10.5; 95% CI, 4.93−22.5). Dog owners were more likely to reach higher levels of brisk walking (OR, 2.18; 95% CI, 1.63−2.91), and those with doctor-diagnosed AD were more likely to reach higher levels of jogging (OR, 2.55; 95% CI, 1.07−6.08) (Figure). The odds for higher levels of brisk walking were reduced in women of non-Nordic origin (OR, 0.53; 95% CI, 0.35−0.81), women living in the suburb (OR, 0.64; 95% CI, 0.45−0.92), and women with previous pregnancy or pregnancies (OR, 0.78; 95% CI, 0.63−0.97). For bicycling, the corresponding reduced odds for higher levels were higher BMI (OR, 0.92; 95% CI, 0.85−0.99), living in the suburb (OR, 0.60; 95% CI, 0.37−0.97), living in the greater Østfold (rural) area (OR, 0.49; 95% CI, 0.25−0.93), and sick leave (OR, 0.50; 95% CI, 0.31−0.81). Higher levels of strength training were less likely in women of non-Nordic origin (OR, 0.44; 95% CI, 0.25−0.78) and in women currently on sick leave (OR, 0.59; 95% CI, 0.39−0.89).

Discussion

Principal findings

At midpregnancy, 29% of women reported no regular PA. Furthermore, apart from strolling, the most common PA reported at least twice weekly during pregnancy was brisk walking (36% of women), followed by strength training, bicycling, and jogging. The most commonly performed PAs with higher levels in intensity and duration were brisk walking, bicycling, strength training, and jogging. Women reporting regular prepregnancy PA and dog ownership had higher levels of PA, whereas higher BMI, previous pregnancy or pregnancies, non-Nordic origin, living in Østfold county, and being on sick leave were negatively associated with higher levels of PA in pregnancy.

Results

The frequency of the different activities performed during pregnancy through enrollment in our study is partly in line with other studies. In the Danish National Birth Cohort, including 88,000 pregnancies, approximately one-third of the women reported some type of exercise during early pregnancy or midpregnancy, most often as low-impact activities, such as swimming or bicycling.[27] Geographic, topographic, and cultural differences may partly explain the differences in preferred PA. For example, bicycling may be favored in countries with flat topography, favorable climatic factors, and traffic facilitation.

Our finding that 13% of women reported strength training at least twice per week was higher than the 8% of

TABLE 2
Results of factors in multivariate analyses that were significantly associated with reaching higher levels of physical activity (≥2 times per week, moderate or high intensity, ≥30 minutes) per week for brisk walking, strength training, bicycling, and jogging

Exposure variable	Brisk walking OR (95% CI)	*P* value	Strength training OR (95% CI)	*P* value	Bicycling OR (95% CI)	*P* value	Jogging OR (95% CI)	*P* value
BMI at 18 wk GA					0.92 (0.85–0.99)	.026[a]		
Study location								
Oslo					Ref	Ref		
Østfold					0.49 (0.25–0.93)	.030[a]		
Sweden					1.25 (0.88–1.78)	.217		
Previous pregnancy or pregnancies								
No	Ref	.026[a]						
Yes	0.78 (0.63–0.97)							
Country of origin								
Norway	Ref	Ref	Ref	Ref				
Sweden	0.93 (0.55–1.56)	.777	0.92 (0.67–1.25)	.583				
Other Nordic countries	1.64 (0.73–3.67)	.229	0.66 (0.20–2.24)	.510				
Rest of the world	0.53 (0.35–0.81)	.003[a]	0.44 (0.25–0.78)	.005[a]				
Living environment								
City center	Ref	Ref			Ref	Ref		
City, outside of city center	0.86 (0.68–1.08)	.193			0.88 (0.65–1.18)	.395		
Suburb	0.64 (0.45–0.92)	.015[a]			0.60 (0.37–0.97)	.038[a]		
Countryside, not in a village	1.08 (0.52–2.24)	.841			0.54 (0.12–2.38)	.414		
Village	0.80 (0.46–1.38)	.420			0.43 (0.15–1.24)	.117		
Regular PA before pregnancy								
No	Ref	Ref	Ref	Ref	Ref	Ref		
Yes	5.30 (3.53–7.97)	<.001[a]	10.50 (4.93–22.50)	<.001[a]	7.35 (3.59–15.05)	<.001[a]		
Dog owner								
No	Ref	Ref						
Yes	2.18 (1.63–2.91)	<.001[a]						
Doctor-diagnosed AD								
No							Ref	Ref
Yes							2.55 (1.07–6.08)	.034[a]
Current sick leave at 18 wk GA								
No			Ref	Ref	Ref	Ref		
Yes			0.59 (0.39–0.89)	.012[a]	0.50 (0.31–0.81)	.005[a]		

The following variables that were significant in univariate analyses but not in multivariate analyses are not shown in the data: age, prepregnancy weight, education, and doctor-diagnosed AR.

AD, atopic dermatitis; *BMI*, body mass index; *CI*, confidence interval; *GA*, gestational age; *OR*, odds ratio; *PA*, physical activity; *Ref*, reference.

[a] *P*-values <.05.

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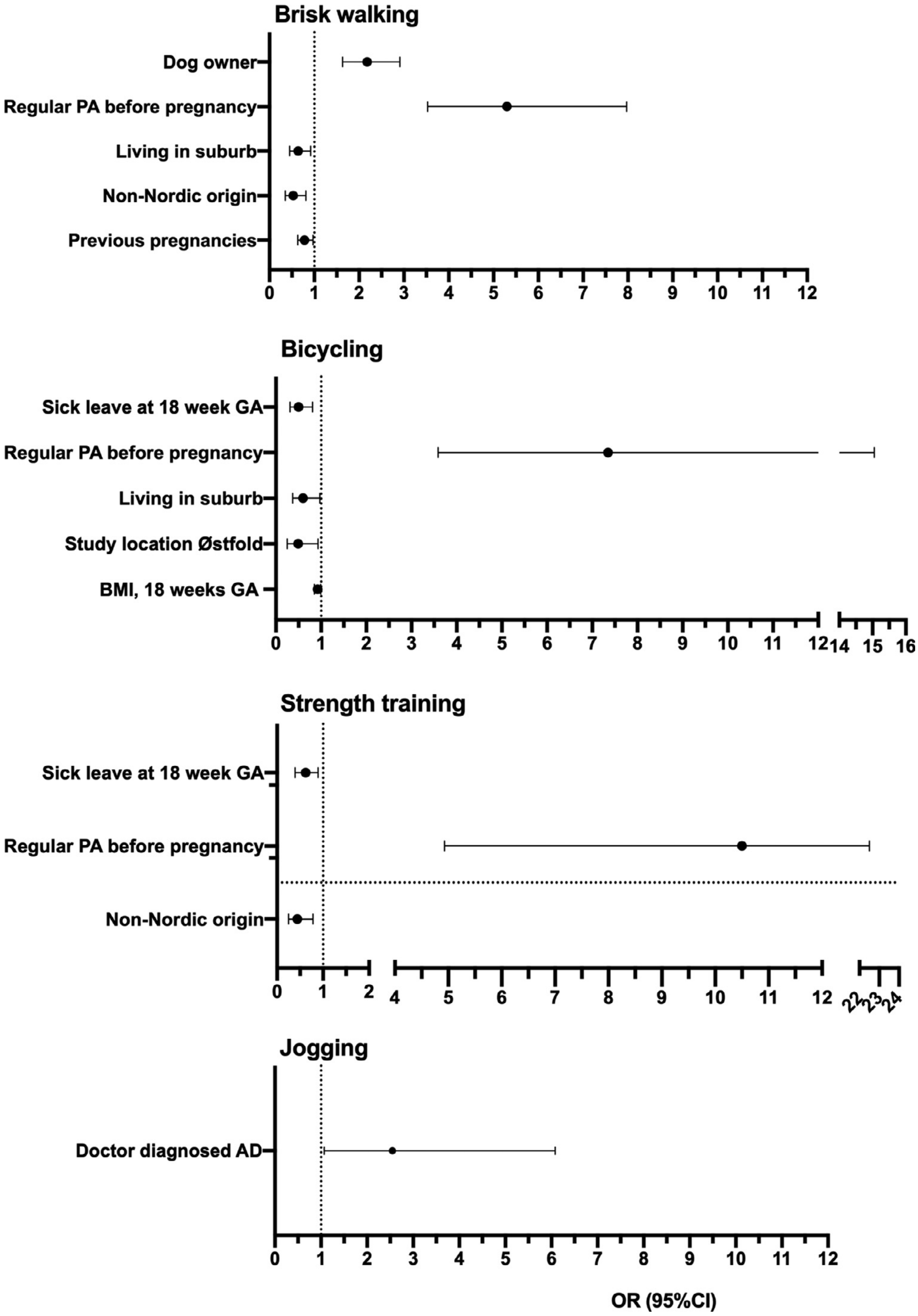
women reported in a Danish cross-sectional study of almost 8000 pregnant women in their first trimester of pregnancy[17] and the 0.3% of women in the ALSPAC study reported at 18 weeks' gestation.[16] Jogging at least twice weekly was less common in the PreventADALL study (5%) compared with the Danish study (10%)[17] but was more common than in the ALSPAC study (0.3%).[16] Less than 10% of the women in our study reported other PAs performed at least twice weekly, in line with both the Danish and ALSPAC studies.[16,17]

The higher PA levels observed among 5% (jogging) to 24% (brisk walking) of the women in our study were not directly comparable with studies assessing the proportion of women reaching national recommendations. A Danish study reported that 38% of pregnant

FIGURE

Factors associated with meeting higher levels of PA



Factors associated with meeting higher levels of PA by brisk walking (n=553), bicycling (n=263), strength training (n=287), and jogging (n=114) among 2349 pregnant women. Results are shown as ORs with 95% CIs.

AD, atopic dermatitis; *CI*, confidence interval; *GA*, gestational age; *OR*, odds ratio.

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women met the Danish guidelines of 3.5 hours of moderate-intensity activity per week[17] and the ALSPAC study with 49% of women engaging in strenuous exercise at least 3 hours per week.[16] Our estimates suggested that at least 27% and no more than 50% of women performed 150 minutes or more of PA with moderate or high intensity in our study. This is higher than the 15% of women at 32 weeks' gestation who performed ≥20 minutes of moderate-intensity activity at least 3 times per week in the Norwegian Akershus Birth Cohort study, which included 3482 women.[18] This may in part be explained by differences in data collection methods and response categories and, more importantly, by the different duration of pregnancy. Gjestland et al[18] reported that primiparity, higher education (college or university), and prepregnancy BMI of <30 were associated with increased probability of meeting the national guidelines of 20 minutes of moderate-intensity PA ≥3 times per week.

Women in the PreventADALL study who were physically active before pregnancy were more likely to have higher levels of PA (≥30 minutes ≥2 times per week of at least moderate intensity) during pregnancy, in line with previous studies.[17,19] Dog ownership more than doubled the likelihood of higher levels of brisk walking in our study, supported by 50% increased likelihood in the ALSPAC study[23] and a recent multinational cross-sectional study showing that dog owners walked more and spent more time in outdoor environments.[28]

The Danish cross-sectional study conducted in 2012−2014 identified the following risk factors for not meeting the recommendations of daily PA of 30 minutes at moderate intensity during pregnancy: lack of exercise before pregnancy, being overweight, <4 years of higher education, not being proficient in the Danish language, multiparity, a previous miscarriage, smoking before pregnancy, and becoming pregnant after assisted reproductive technology.[17]

In line with previous studies, higher pregnancy BMI[16−18] and previous pregnancy or pregnancies[16−19] were associated with decreased likelihood of higher levels of PA. The reduced likelihood of higher PA levels by women of non-Nordic origin agrees with the Danish findings.[17] Being on sick leave was associated with reduced likelihood of higher PA levels by strength training and bicycling.

In contrast to other studies,[16−19,27] neither education nor age was significantly associated with higher levels of the 4 most commonly performed PAs. However, these findings were supported by a Portuguese study, including 133 women during the first 2 trimesters of pregnancy.[29] Our cohort was somewhat biased in terms of education, as more than 50% of the women had ≥4 years of higher education; however, the women in the previous Norwegian,[18] Danish,[17] and ALSPAC[16] studies had similar educational levels.

Higher levels of PA were not significantly associated with doctor-diagnosed asthma or AR. This may suggest that mild or well-regulated allergic disease does not limit PA. However, we did find that doctor-diagnosed AD was positively associated with higher levels of jogging. To the best of our knowledge, this is a novel finding with unclear implications. A recent study from the United States[30] found that AD was associated with less PA in US adults, whereas a systematic review from 2016[31] found insufficient evidence to conclude whether AD was associated with more or less PA. In addition, we are not aware of any previous studies reporting higher levels of jogging in women with AD.

Strengths and limitations

This study offered study participation to all pregnant women at 16 to 22 weeks' gestation who attended the national routine fetal ultrasound screening in their midtrimester of pregnancy. Unintentionally, the enrolled study population had higher education attainment, had slightly higher age than the national average, and was predominantly of Norwegian and Swedish origins but is relatively representative of city populations.[32,33] Furthermore, our population matched that of other similar cohort studies in terms of age, parity, education, and income levels.[17,18] The skewing of our population toward higher education may have bearings on the generalizability of our results, with PA observed in our study possibly overestimating that of the general population.

However, if our finding that 29% of the women had been inactive at midpregnancy is an overrepresentation, the general population may be even less active than the population in the PreventADALL study.

A limitation in the PreventADALL study was that women without sufficient Norwegian or Swedish language skills were excluded from participation. Therefore, our study is not generalizable for some minority populations. Furthermore, the questionnaire was not appropriate for direct comparison with the current Norwegian guidelines published in April 2019. The information on PA in pregnancy included questions in line with those reported by Haakstad et al[25] in a Norwegian pregnancy cohort but were modified to fit our electronic questionnaire. Because of the study design, it was not feasible to include accelerometer or other objective measures of PA; therefore, the data presented in this article were exclusively self-reported. Contraindications for PA were not explored in this study, as the study population consisted of relatively healthy women, pregnant with 1 or 2 fetuses.

Clinical implications

Despite the acknowledged benefits to maternal and offspring health by regular PA in pregnancy, our data showed that less than 50% of the women were regularly active at a high level in midpregnancy. This pointed to a need to address the importance of PA during pregnancy follow-up visits.

Research implications

The potential benefits of high levels of PA in pregnancy for the mother and her offspring in terms of noncommunicable disease development need further investigations, as do the potential effects of suboptimal levels of PA in pregnant women.

Conclusion

At midpregnancy, almost one-third of women reported no regular PA in the last 2 weeks before answering the questionnaire, whereas less than 50% of women had 2 hours or more of regular moderate-intensity PA per week during pregnancy. The most common activities performed at least twice weekly were brisk walking, bicycling, and strength training. Being physically active before pregnancy, owning a dog, and having AD were associated with higher levels of 1 or more of the most commonly performed physical activities. Awareness of PA in pregnancy should be discussed at pregnancy follow-up visits, particularly among women with higher BMI, on sick leave, with previous pregnancy or pregnancies, and of non-Nordic origin—groups who often do not reach higher levels of PA. ■

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.xagr.2020.100002.

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Paper II

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

II

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

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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,

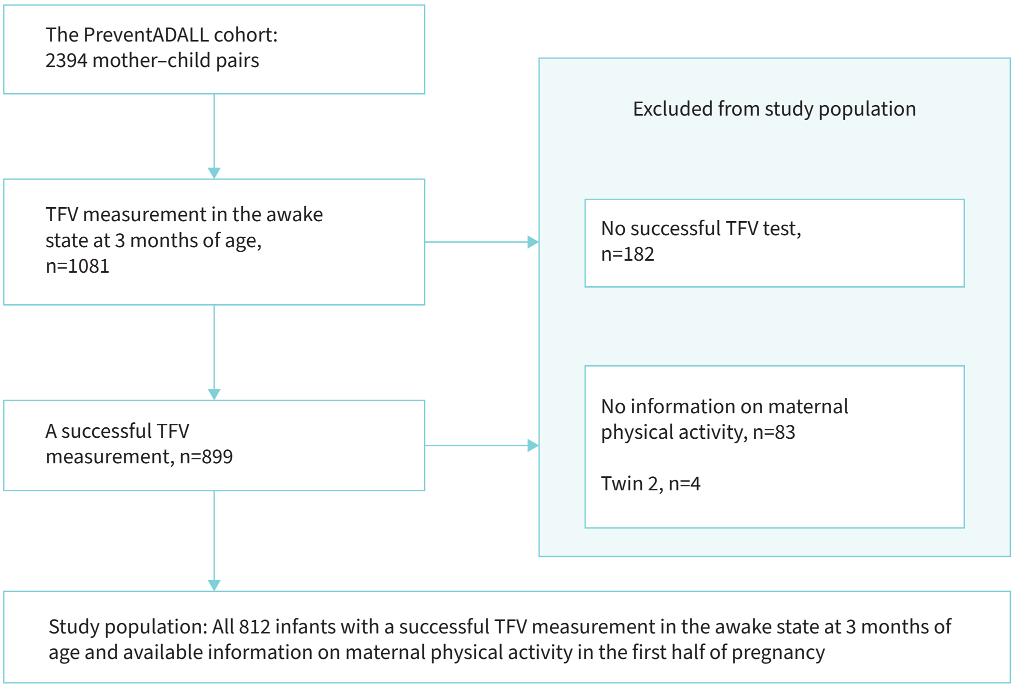

FIGURE 1 Study population. The present study population includes all 812 infants from the Preventing Atopic Dermatitis and Allergies in Children (PreventADALL) cohort with a successful tidal flow–volume (TFV) measurement in the awake state at 3 months of age and available information on maternal physical 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_{PTEF}/t_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[ƒ]	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); [ƒ]: 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).

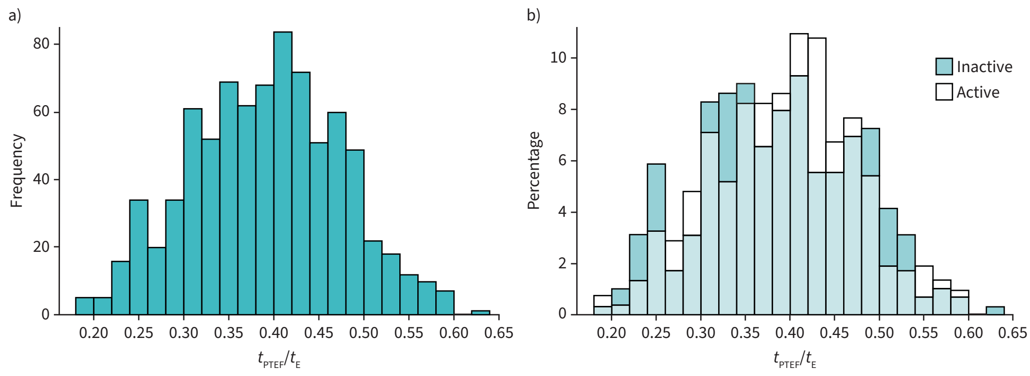

FIGURE 2 Histograms showing the distribution of the infant ratio of time to peak tidal expiratory flow to expiratory time (t_{PTEF}/t_E) in a) all included infants (n=812) and b) infants of inactive (n=290) compared to all active (n=522) mothers, presented with partly overlapping bars. While the *y*-axis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

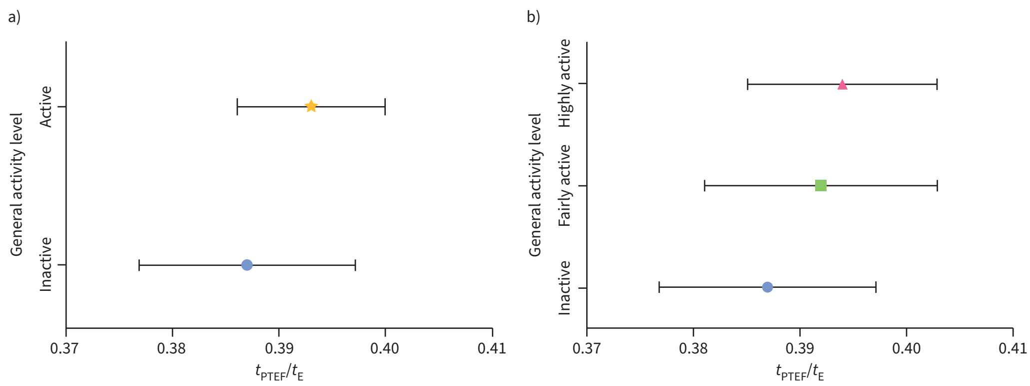

FIGURE 3 Infant ratio of time to peak tidal expiratory flow to expiratory time (t_{PTEF}/t_E) at 3 months of age according to maternal general activity level, shown for infants of a) inactive and active mothers, and b) inactive, fairly active and highly active mothers. Mean t_{PTEF}/t_E for infants of 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

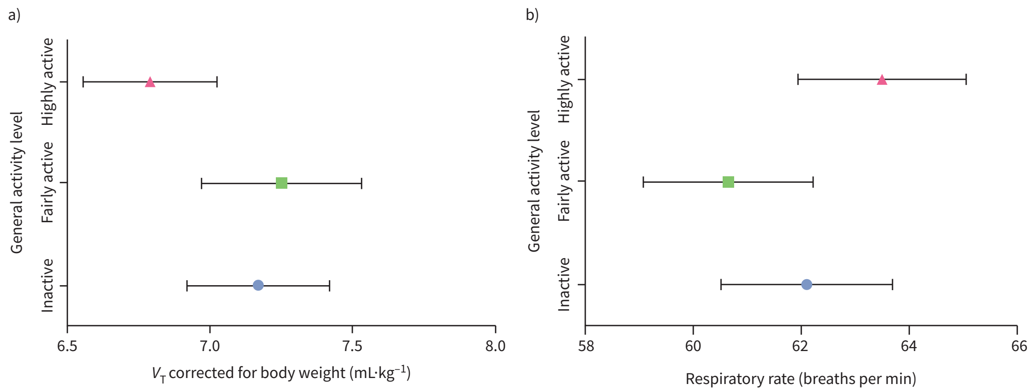

FIGURE 4 Infant a) tidal volume (V_T) corrected for body weight and b) respiratory rate at 3 months of age according to maternal general activity level in three categories. a) Mean V_T corrected for body weight was compared between groups with one-way ANOVA (p=0.023). Mean V_T corrected for body weight 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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Conflict of interest: M. LeBlanc reports personal fees from MSD, outside the submitted work. E.M. Rehbinder reports personal fees from Sanofi-Genzyme, Novartis, Leo-Pharma, Perrigo, and The Norwegian Asthma and Allergy Association, outside the submitted work. The other authors have no financial relationships relevant to this article to disclose.

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Paper III

Fetal thoracic circumference in mid-pregnancy and infant lung function

III

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ORIGINAL ARTICLE

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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

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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Children's Hospital; The Cancer- and Allergy Foundation; Barnestiftelsen at Oslo University Hospital; The Samaritan Foundation for Pediatric research; The Regional Health Board South East; Oslo University Hospital; The Norwegian Research Council; The Swedish Heart-Lung Foundation; The Swedish Research Council – the Initiative for Clinical Therapy Research; Østfold Hospital Trust; SFO-V Karolinska Institutet; Health and Rehabilitation Norway; The University of Oslo; The Swedish Asthma- and Allergy Association's Research Foundation; The Foundation for Healthcare and Allergy Research in Sweden – Vårdalstiftelsen

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.

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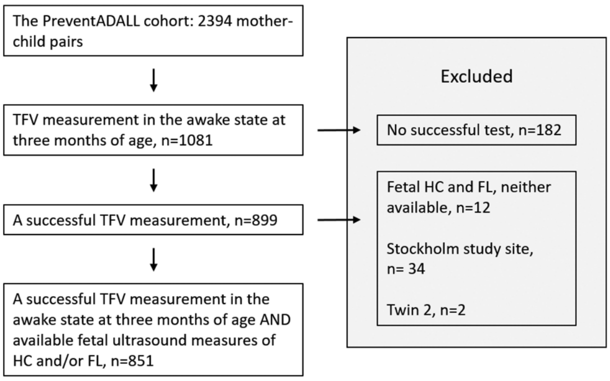

FIGURE 1 Study population. From the PreventADALL mother–child birth cohort, all 851 infants from the Oslo study site with available tidal flow-volume (TFV) measurement in the awake state at 3 months of age as well as mid-pregnancy ultrasound measurements of fetal head circumference (HC) and/or femur 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.

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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	Included infants (*n* = 851) *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)

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TABLE 1 (Continued)

Background characteristics	Included infants (*n* = 851) *n*	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

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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)

	Univariable regression (*n* = 726)				Multivariable regression (*n* = 726)			
t_{PTEF}/t_E ~ TC/HC	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)

	Univariable regression (*n* = 725)				Multivariable regression (*n*= 725)			
t_{PTEF}/t_E ~ TC/AC	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)

	Univariable regression (*n*= 724)				Multivariable regression (*n*= 724)			
t_{PTEF}/t_E ~ TC/FL	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).

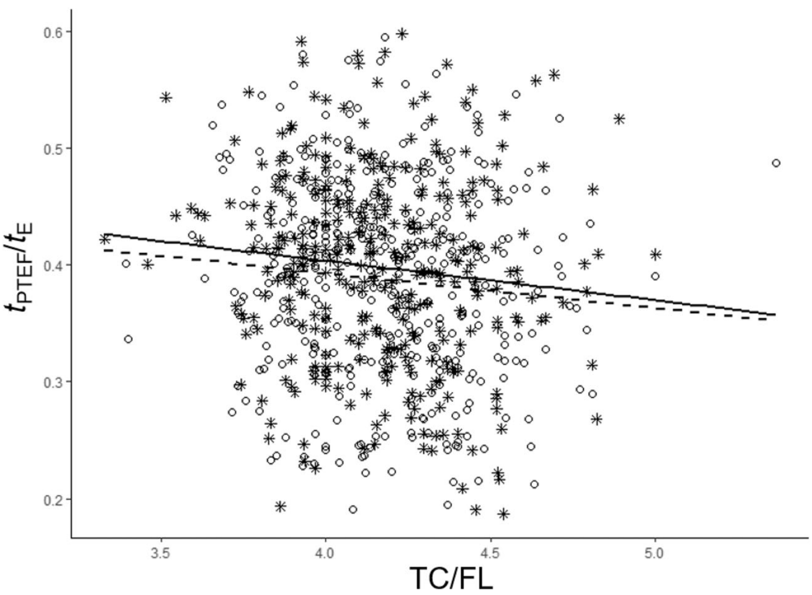

FIGURE 2 The variation in infant t_{PTEF}/t_E in relation to fetal TC/FL ratio. In the unadjusted model, the TC/FL ratio explained 1.0% of the variation in t_{PTEF}/t_E in all infants (R^2 = 0.010). R^2 for girls was 0.011 and R^2 for boys was 0.009. TC/FL, fetal thoracic circumference relative to femur 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.

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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.

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

	n	R^2	$\hat{\beta}$	95% CI	*p* value
a) TC/HC					
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					
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					
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).

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

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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 ~ 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 ~ 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 ~ 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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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.

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

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