379. Early wheezing conditions in childhood

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Association of wheezing phenotypes in the first 7 years of life with fractional exhaled nitric oxide and lung function in adolescence. The ALSPAC study

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Background: Patterns of wheezing during early childhood are associated with lung function and bronchial hyperresponsiveness in mid childhood. Little is known about the associations of early wheezing phenotypes with fraction of exhaled nitric oxide (FeNO), a marker of allergic airway inflammation, and lung function in adolescence.
Methods: This study was based on 6,841 children in a population-based prospective birth-cohort study. Latent class analysis identified 6 wheezing phenotypes (never/infrequent, transient early, prolonged early, intermediate, late, persistent) based on wheezing patterns from birth to 7 years. FeNO levels and airway function (forced expiratory volume in 1 s (FEV1), forced expiratory volume in 1 s/forced expiratory volume ratio (FEV1/FVC), mid forced expiratory flow (FEF25-75)) were measured at age 15.
Results: Intermediate onset wheezing (18 months) was the most strongly associated with increased FeNO levels (ratio geometric means 2.01, 95% confidence interval: (1.63, 2.48)), compared with the reference group never/infrequent wheezing. Wheezing phenotypes were not associated with FEV1, but showed associations with decreased levels of FEV1/FVC and FEF25-75 (most strongly for persistent wheezing: mean differences -0.50 (-0.62, -0.38) and -0.42 (-0.54, -0.29), respectively).
Conclusions: Wheezing phenotypes with onset after the age of 18 months and persistent wheezing were the most strongly associated with FeNO levels and lung function, respectively, in adolescence. Our results suggest that specific patterns of asthma-related symptoms in early life are associated with markers of lung morbidity at older ages.

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International study of wheezing in infants (EISL): How latitude modifies the associations between risk and protective factors for recurrent wheeze during the first year of life

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Background: The influence of latitude on the strength of the association of risk/protective factors of recurrent wheeze (RW) has never been reported.
Methods: The "Estudio Internacional de Sibilancias en Lactantes" (EISL) included 30,093 infants 12 to 15 months of age, recruited from 13 Latin American centres (n=25,030) and from 5 European centres (n=5,063). Adjusted odd ratios (aOR) of factors associated to RW reported previously were used to build a meta-regression between the strength of the aORs of each factor and centre latitude (distance from equator either N or S). The meta-regression was further adjusted for continent and the slope expressed as adjusted regression coefficient (aRC).
Results: We found significant correlations between latitude (the higher the distance from equator the higher the strength of the association) and the magnitude of the aOR between RW and: 1. Cold(s) in the 1st 3 months (aRC +0.19; p=0.004); 2. Nursery school (aRC +0.25; p=0.01); 3. Siblings (aRC +0.024 per additional sibling; p=0.002); and 4. Breast feeding >=3 months: the higher the latitude the higher the protection (aRC -0.17; p=0.047). Heterogeneity of the strength of aORs between centres was: 73.9% for colds, 67.1% for nursery school, 59.7% for siblings and 22.4% for breast feeding. Latitude explained (by R-squared) much of heterogeneity: 66.1% for colds, 54.9% for nursery school; 83.1% for siblings and 100% for breast feeding.
Conclusion: The magnitude in which some risk or protective factors are associated to recurrent wheeze during the first year of life varies significantly with latitude.

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Effect of late preterm birth on longitudinal lung spirometry in children

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Introduction: Rates of preterm birth have increased in most industrialised countries (Goldenburgh, R.L. et al. Lancet 2008; 371:75-84) but data on later lung function of late preterm birth is limited.
Aims and objectives: To compare lung function at 8-9 and 14-17 years in a population-based cohort of children born at 25-32, 33-34 and 35-36 weeks gestation with similar aged children born at term (≥37 weeks gestation).
Methods: From the Avon Longitudinal Study of Parents and Children (ALSPAC, n = 14062), children who had spirometry at 8-9 (n=6712) and/or 14-17 (n=4513) years of age were divided into 4 groups: 25-32, 33-34, 35-36 and ≥37 weeks (term control) of gestation.
Results: At 8-9 years of age, all spirometry measures (except FVC, in the 25-32 weeks gestation group) were significantly lower in both 25-32 and 33-34 weeks gestation groups compared to term controls (FEV_1, mean z-score ± SD -0.461±0.876, -0.498±1.09 and 0.011±1.00 respectively). The 35-36 weeks gestation (FEV_1 0.008±0.908) and term groups had similar values. At 14-17 years of age, most spirometry measures in the 25-32 and 33-34 week gestation groups were not different from term controls except lower FEF_{25-75} and FEF_{25-75}/FVC in both 25-32 and 33-34 weeks gestation groups and lower FEV_1/FVC in the latter group.
Conclusions: Children born at 33-34 weeks gestation have significantly lower lung function values at 8-9 years of age similar to decrements observed in the 25-32 weeks group although most of these differences were reduced by 14-17 years of age.

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Reduced neonatal lung function and wheezing illnesses during the first 5 years of life

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Introduction: Studies about reduced neonatal lung function and wheezing illnesses in childhood showed conflicting results. No study analyzed the association between the single occlusion technique (SOT) and wheezing illnesses during the first 5 years of life.
Objectives: The aim was to assess the association between resistance and compliance of the respiratory system (Rrs, Crs) measured shortly after birth and wheezing-associated primary care consultations during the first 5 years of life, different wheezing phenotypes, and asthma at age 5.
Methods: Infants participate in WHISTLER, a birth cohort on wheezing illnesses. SOT was performed during natural sleep before 2 months of age. Wheezing-associated consultations were collected from the electronic patient file. Poisson regression was used to study the association between Rrs and Crs and the number of consultations. Median Rrs and Crs values of children with different wheezing phenotypes and with and without asthma were compared by non-parametric tests.

Results: 549 infants had successful SOT and complete medical files. Every kPa/l/s increase in Rrs was associated with 9% more consultations in the first 3 years of life. Every cl/kPa increase in Crs was associated with a 17% reduction of consultations in the first 3 years of life and 29% in the 4th-5th year of life. Children with late-onset or persistent wheezing and with asthma had significantly lower Crs values than their peers.
Conclusion: An increased neonatal Rrs is associated with more wheezing illnesses during infancy, while a reduced neonatal Crs is associated with more wheezing illnesses during the first 5 years of life, a late-onset or persistent wheezing phenotype, and asthma at age 5.

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Factors associated with elevated FeNO in infants with recurrent respiratory symptoms
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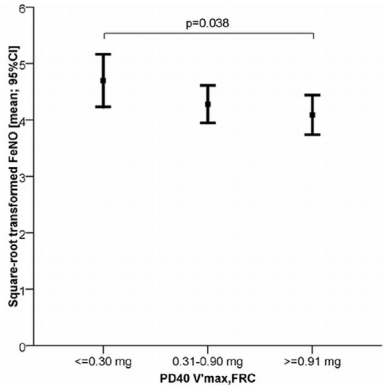
Fractional concentration of exhaled nitric oxide (FeNO) is a non-invasive biomarker reflecting eosinophilic inflammation in bronchial mucosa. Its role in early childhood respiratory disorders is not clear. 136 infants with recurrent lower respiratory tract symptoms underwent measurement of FeNO, lung function tests, and a methacholine challenge test. The median level of FeNO was 19.3 ppb (interquartile range 12.3-26.9 ppb). Children with increased airway responsiveness to methacholine (i.e. the provocative dose of methacholine causing a 40% fall in maximal expiratory flow at functional residual capacity (PD_{40} $V'_{max,FRC}$) ≤0.30 mg) had significantly higher FeNO when compared to those with only mild or no airway responsiveness to methacholine (PD_{40} $V'_{max,FRC}$ ≥0.91 mg).



Elevated FeNO (≥27 ppb, i.e. the highest quartile) was associated with maternal asthma, and increased airway responsiveness, but not with atopy, eosinophilia, or lung function.

Factors associated with elevated FeNO. Results of the multivariate analysis

Parameter	Adjusted OR[#]	95% CI	p-value
Maternal history of asthma	3.2	1.3; 8.1	0.012
Atopy	0.4	0.1; 1.1	0.064
Height	1.0	1.0; 1.1	0.252
PD_{40} $V'_{max,FRC}$			
≤0.30 mg	4.1	1.4; 12.7	0.012
0.31-0.90 mg	1.4	0.4; 4.7	0.547
≥0.91 mg	1.0	–	–

[#]Adjusted for maternal history of asthma, atopy, height, and PD_{40} $V'_{max,FRC}$.

In conclusion, maternal history of asthma, and increased airway responsiveness are associated with elevated FeNO in symptomatic infants.

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Association between breastfeeding and lung volumes and alveolar size
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Aim: In a previous study we found that non-breastfed children of asthmatic mothers (CAM) had lower FVC and FEV_1 compared with non-breastfed children of non-asthmatic mothers (CnAM), but breastfeeding (BF) compensated, improving these values in CAM (Dogaru 2010 ERJ 678s). We extended this study, analyzing plethysmographic lung volumes (LV) and alveolar size in a different group.
Method: In 132 UK-born subjects (7-21yrs) we measured FRC and TLC by plethysmography and Apparent Diffusion Coefficient (ADC, proxy for alveolar size) by He^3-magnetic resonance. We used linear regressions adjusting for LV predictors and potential confounders and stratified by maternal asthma (MA).
Results: 32 (24%) of children were not BF, 38 (29%) were BF ≤3mo and 53 (40%) BF>3mo; 24 (18%) had asthmatic mothers. We found no significant associations between BF and alveolar size, FRC or TLC in the whole group. However, stratification by MA showed a) that non-breastfed CAM have lower FRC and TLC but similar ADC means compared with non-breastfed CnAM and b) a trend for higher FRC and TLC in CAM if breastfed (Table).

Table: Association between BF and ADC, FRC and TLC*

	group mean†	BF ≤ 3 months‡ N=38	BF > 3 months‡ N=53
ADC (cm^2/second)			
non-asthmatic mothers	0.094	0.004 (0.259)	0.003 (0.434)
asthmatic mothers	0.090	0.016 (0.111)	0.013 (0.244)
FRC (liters)			
non-asthmatic mothers	2.185	-0.036 (0.745)	-0.050 (0.756)
asthmatic mothers	2.087	0.175 (0.621)	0.372 (0.372)
TLC (liters)			
non-asthmatic mothers	4.569	-0.046 (0.748)	0.023 (0.902)
asthmatic mothers	4.245	0.491 (0.435)	0.898 (0.281)

ADC = Apparent Diffusion Coefficient; FRC = Functional Residual Capacity; TLC = Total Lung Capacity
N (%) non-asthmatic mothers: 102 (77%)
N (%) asthmatic mothers: 24 (18%)
[*]adjusted for height, weight, age, sex, birth weight, gestational age, ethnicity, parental asthma, child's wheezing history, smoking exposure and family education
[†]the group mean represents the average value in non-breastfed children
[‡]mean difference from the group mean (p-value)

Conclusion: These results support previous findings that reduced LV in non-BF CAM compared with non-BF CnAM are compensated by BF. Since alveolar size was similar in CAM and CnAM, we suggest that alveolar number is reduced in CAM without BF, but can be partially increased with BF. Confirmation will require larger samples.
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Early life exposure to locally-generated PM_{10} and lung function measurements at school-age
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Aim: Although multiple studies have linked short-term exposure to particulate matter (PM_{10}) with respiratory symptoms and lung function (LF) in children, little is known about effects of early lifetime exposure.
Methods: In a population-based cohort study (n=4400) we collected information on residential history from birth to early school-age (6-9 yrs) and modelled primary PM_{10} exposure throughout childhood using Airviro. We assessed wheeze symptoms by parental questionnaires and performed spirometry in a sample of children aged 9-13 yrs (n=399). We analysed association between early life exposure to PM_{10} and LF using linear regressions controlling for a number of confounders and attacks of wheeze at school-age.
Results: Median (interquartile range) of early life exposure to PM_{10} was 1.83 (0.93-2.70) µg/m^3. Mean (SD) FVC, FEV_1 and MEF_{50} were 2.42 (0.44) l, 2.11 (0.39) l and 2.82 (0.73) l/s respectively. After adjustment FVC was lower with higher exposures to PM_{10}.We found no significant association with FEV_1 or MEF_{50}. When adjusting for number of attacks results were similar.

Table: Association between early life exposure to PM_{10} and lung function measurements

	Mean*	Difference†*	p-value	Mean‡	Difference†‡	p-value
FVC (l)	2.276	-0.036	0.023	2.265	-0.035	0.029
FEV_1 (l)	1.947	-0.019	0.186	1.925	-0.016	0.250
MEF_{50} (l/s)	2.525	0.033	0.317	2.460	0.041	0.207

* adjusted for sex, age, height, weight, preterm, breastfeeding, heating, cooking, smoking exposure, parental education, type of diet, parental history of asthma
† Difference from the mean for 1 µg/m^3 change of PM_{10}
‡ adjusted for previous confounders and number of attacks of wheeze at school-age

Conclusions: Lifetime exposure to primary PM_{10} was associated with lower FVC at school-age which might be independent of wheezing disorders. This result is compatible with a chronic effect of air pollution on normal lung function growth, resulting in a restrictive rather than an obstructive pattern.
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