439. Early life risk factors for childhood asthma: evidence from birth cohort studies I

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Fetal crown-rump length at ten weeks gestation is an independent predictor of lung function aged five years

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Introduction: Although associations among reduced birth weight and reduced pulmonary function in later life have been reported, the stage of fetal life when reduced growth becomes associated with pulmonary function is unknown.
Objective: To assess relationships among fetal growth and spirometry at age 5 years.
Methods: Ultrasound derived crown rump length (CRL) at 10 weeks and biparietal diameter (BPD) and Femur length (FL) at 20 weeks gestation were retrieved for participants of a birth cohort study recruited antenatally and spirometry at age 5 years.
Results: Of 1924 participants, CRL was recorded in 903 fetuses, BPD in 1562 and FL in 1546; the respective mean measurements were 44mm, 48mm and 33mm. Reliable spirometry was obtained in 639 children of whom fetal measurements were available for 298 at 10 weeks gestation and 503 at 20 weeks gestation. FVC, FEV_1, $FEV_{0.75}$, $FEV_{0.5}$ and FEF_{50} but not FEV_1/FVC, PEF or FEF_{25-75} were positively related to CRL. FVC increased by 5mls (p=0.001), FEV_1 by 4mls (p=0.003) and $FEF_{50}$by 7ml/s (p=0.047) for each 1mm increase in 10 week CRL, independent of maternal smoking and the child's gender height and weight at 5 years. At 20 weeks every 1mm increase in BPD was independently associated with a 8ml increase in FVC at 5 years (p=0.014) but no other spirometric indices. These associations remained when infants of low birth weight (<2.5 kg) were excluded.
Conclusions: Fetal growth at 10 and 20 weeks gestation appear to be associated with lung function at 5years independently of post natal growth.

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Weight-gain in pre-school children and allergic disease: a longitudinal study

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Rationale: The increasing prevalence of allergic disease has occurred in parallel with the obesity epidemic, suggesting a possible association.
Objective: We investigated the relationship of growth from birth to 5 years with wheeze, eczema and atopy within the context of a birth cohort study.
Methods: Children were followed from birth and reviewed at age 3 and 5 years (n=720; male 395). Parents completed questionnaires, and children were weighed, measured, skin tested and examined.
Results: In boys, higher birth weight was associated with decreased risk for wheeze at 3 (Odds Ratio [95%Confidence Interval] per 1 Standardised Deviation Score; 0.66[0.50-0.88], p=0.005) and at 5 years (0.66[0.46-0.96], p=0.03). However, body mass index (BMI) at 3 was positively associated with wheeze at 3 (1.29[1.00-1.66], p=0.048); and BMI at 5 with wheeze at 5 (1.36[1.10-1.68], p=0.004). The risk

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estimates for BMI at 3 years were most strongly predictive of asthma diagnosis by 5 years (1.38[1.04-1.82], p=0.024) and persistence of diagnosis (asthma diagnosis at both 3 and 5 years) (1.83[1.18-2.84], p=0.007) than measures of body size at 5 years. No such associations were seen in girls. In girls, significant positive associations for BMI at 3 and 5 years were observed in relation to eczema but were no longer significant in the adjusted model.
Conclusions: Higher weight-gain was associated with increased risk of allergic disease in early childhood. The strength of this association varied with sex, allergic disease, and the timing of the outcome in the child's development. Excess weight was most strongly associated with wheeze in boys.

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Maternal anxiety during pregnancy is associated with asthma in their children
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Introduction: There is a long standing awareness that exacerbations of asthma may be triggered by psychological and emotional factors and experimental data have confirmed that lung function changes consistent with airway obstruction may occur in response to emotional stimuli in asthmatic subjects.
Objectives: To determine whether prenatal exposure to maternal self-reported anxiety is associated with asthma in children at age $7\frac{1}{2}$ years.
Methods: We investigated 4222 children with data on current asthma and atopy at age $7\frac{1}{2}$ years, bronchial responsiveness at age $8\frac{1}{2}$ years and maternal anxiety scores (Crown Crisp Experiential Index) at 18 and 32 weeks gestation collected prospectively as part of a population-based, longitudinal birth cohort.
Results: There were positive associations between reported maternal anxiety at 18 weeks and 32 weeks gestation and both current asthma and non-atopic asthma at age $7\frac{1}{2}$ years (Odds ratio (95%CI) for highest vs lowest quartile of anxiety scores at 32 weeks gestation = 1.69 (1.30,2.21) and 2.07 (1.29,3.33) respectively) with evidence of a linear trend of increasing asthma prevalence with increasing maternal anxiety ($p<0.001$). We found stronger evidence to support an association between maternal anxiety and non-atopic compared with atopic asthma in their children. These findings persist after adjustment for potential confounders and we have not found evidence to support bias by maternal reporting or differential loss to follow up.
Conclusion: Self-reported anxiety in pregnant women at 18 weeks and 32 weeks gestation was associated with asthma in their children during early life. However, if true, this association did not appear to be mediated through increased risk of atopic asthma.

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Breastfeeding and the risk of childhood asthma: a population-based cohort study
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Aim: s: Data relating to breastfeeding and risk of childhood asthma are contradictory, especially a potential effect modification by maternal atopy. We determined the association between duration of breastfeeding and childhood wheeze using data from a large community-based cohort study.
Methods: Repeated questionnaire surveys to a random sample of 8700 children (1998, 2001, 2003) aged 1-4 years initially. Breastfeeding was assessed in the first questionnaire, respiratory outcomes repeatedly. Multivariable logistic regression was used for analysis.
Results: We analysed data on 4229, 5214 and 4071 children at the ages of 1, 3-5 and 6-8 years respectively. 42% were not breastfed, while 28%, 12% and 18% were nursed for 1-3, 3-6 and >6 months respectively. Adjusting for risk factors and confounders, breastfeeding >6 months was associated with a reduced risk of wheeze at age 1 (OR 0.65, 95% CI 0.53-0.78), at age 3-5 (0.75 (0.59-0.94) but not at age 6-8 (1.05 (0.83-1.33)). We found no effect modification by maternal asthma or ethnic group, and results were similar for viral-induced wheeze and multiple trigger wheeze. The population-attributable risk fraction of current wheeze caused by lack of breastfeeding was calculated as 22% and 12% for wheeze at the age of 1 and 3-5 years respectively.
Conclusions: Our data support a modest protective effect of breastfeeding on childhood wheeze. Importantly, there was no evidence for a detrimental effect in children of atopic mothers. Our analysis will be complemented with a longitudinal approach (Cox regression), and we will also study objective outcomes (atopy, BHR, lung function).

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Early daycare: more infections and asthma symptoms in infancy, no prevention of (allergic) asthma at 8 years
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Background: Daycare attendance leads to more frequent respiratory infections early in life, but the preventive effect on the development of (allergic) asthma remains unclear.
Objective: Prospectively observe the effect of daycare attendance on the development of respiratory infections, allergic sensitization and asthma symptoms during the first 8 years of life.
Methods: In the PIAMA birth cohort, daycare attendance and respiratory health was assessed yearly by questionnaires (n=3936). At 8 years, sensitization to airborne allergens (n=1713) and bronchial hyperresponsiveness (BHR) (n=938) was tested. Daycare was defined as Early (age 0-2); Late (age 2-4); or None (no daycare before age 4). Associations of daycare with respiratory symptoms, asthma (at least one episode of wheezing, shortness of breath or steroid use last year), BHR and sensitization were assessed in a repeated-event analysis.
Results: Children with early daycare attendance had more respiratory infections and wheezing in the first years of life. After the age of 3 years these children had less respiratory infections, wheezing and asthma. At 8 years, daycare was not protective for any outcome (OR_{asthma}: 0.82; CI95%: 0.61–1.10). Also, no significant association was found between early daycare attendance and sensitization (OR: 1.06; CI95%: 0.83–1.37), BHR (OR: 0.77; CI95%: 0.57–1.05) or allergic asthma (OR: 1.05; CI95%: 0.71–1.55).
Conclusions: Early daycare attendance leads to increased airway symptoms in the first years of life, and less symptoms between 4 and 8 yrs. No protection against airway symptoms, asthma, BHR or sensitization was seen at the age of 8. Hence, our data do not support the "hygiene hypothesis".

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Cord blood gene expression of ILT3 and ILT4 and its relation to prenatal farm exposure
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Background: Previous studies have consistently shown that growing up on a farm confers protection from the development of atopic sensitization. The underlying mechanisms are unclear. T suppressor cells have been shown to play an important role in the preservation of central and peripheral tolerance thus potentially influencing the development of atopy. These cells can tolerize antigen presenting cells (such as dendritic cells) by up-regulating the cell surface expression of the inhibitory receptors immunoglobulin-like transcript (ILT)-3 and ILT4 and by down-regulating the expression of costimulatory molecules.
Objectives: To evaluate the relation between the gene expression of ILT3 and ILT4 and the prenatal exposure to a farming environment.
Methods: A multicenter birth cohort was established in rural areas of five European countries. Information on maternal farm-related exposures was collected by questionnaires during pregnancy. The expression of the genes of ILT3 and ILT4 was analysed by real time RT-PCR in the cord blood (CB) of 938 children (446 farm and 492 non-farm).
Results: Median gene expression was higher in farm children compared to non-farm children: ILT3 (0.182 vs. 0.166, p=0.037), ILT4 (0.291 vs. 0.277, p=0.049). Ordinal logistic regressions additionally showed a relation between ILT3 and maternal contact to farm animals during pregnancy with a center and farmer adjusted OR of 1.46 [95-CI 1.06-2.02].
Conclusions: Maternal exposure to a farm environment during pregnancy may increase the expression of cord blood ILT3 and ITL4. These findings indicate that the activation of T suppressor cells may contribute to the allergy protective effect in these environments.

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Environmental factors in early life and atopy in an urban birth cohort up to age 5 years
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Background: Early environmental exposures have been suggested to modulate

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the subsequent risk of atopic disease. However, it is not yet clear whether this also holds for urban and affluent populations.
Objective: Aim of this study was to prospectively investigate the role of perinatal factors for the development of atopy in an urban birth cohort.
Methods: 526 children were recruited from a consecutive series of pregnant women presenting for antenatal care at an obstetric department in a Munich clinic. Assessed data comprised yearly interviews on atopic symptoms and environmental factors, allergen and endotoxin exposures at 3 months, specific IgE at 1 year and a skin prick test at 5 years.
Results: Crowding defined as the number of persons per room during pregnancy was inversely associated with early atopic dermatitis (adj.OR=0.43, 95%-CI 0.20-0.95 adjusted for family history of atopy), early sensitisation to food allergens (adj.OR=0.09, 95%-CI 0.01-0.62) and allergic rhinitis at age 5 years (adj.OR=0.19, 95%-CI 0.05-0.66). Similarly, early exposure to endotoxins showed an inverse association with atopy at age 5 years, especially with sensitisation to mites (adj.OR=0.71, 95%-CI 0.55-0.92). This effect was contrasted by early exposure to mites: children with mite exposure below median and endotoxin exposure above median merely had 0.15-times the risk of being sensitised to mites later in life compared to the contrasting reference group (95%-CI 0.03-0.81).
Conclusion: As early as pregnancy, environmental factors showed a protective effect on atopic outcomes, thus underlining that the hygiene hypothesis not only holds for rural and farming environments, but also in an urban and affluent setting.

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Air pollution during pregnancy and lung function in newborns: a birth cohort study

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Background: Exposure to air pollution is associated with diminished lung growth during school age. The effect of air pollution during pregnancy on lung development of the newborn is unknown. We thus determined whether prenatal exposure to air pollution is associated with lung function changes in the newborn.
Methods: In a prospective birth cohort of 241 healthy term-born neonates we measured tidal breathing, lung volume, ventilation inhomogeneity and exhaled nitric oxide (eNO) during unsedated sleep at age 5 weeks. We measured maternal exposure to particulate matter with an aerodynamic diameter of less than 10 μm (PM_{10}), nitrogen dioxide (NO_2), ozone (O_3), and distance to major roads during pregnancy. The association between these exposures and lung function was assessed using linear regression.
Results: Minute ventilation was higher in infants with higher prenatal PM_{10} exposure (24.7 mL/min per $\mu g/m^3$ PM_{10}; 95%-CI, 8.9 to 40.5; p=0.002). This association was stronger in newborns of mothers who lived within 200 m to a major road. Exhaled NO was increased in infants with higher prenatal NO_2 exposure (0.96 ppb per $\mu g/m^3$ NO_2; 95%-CI, 0.44 to 1.48; $p<0.001$). Postnatal exposure to air pollution did not influence these findings.
No association was found between air pollution and lung volume or ventilation inhomogeneity. Exposure to ozone was not associated with any of the investigated outcomes.
Conclusions: Our results suggest that prenatal exposure to air pollution is associated with higher respiratory need and airway inflammation in newborns. Such alterations during early lung development may contribute to long-term respiratory morbidity.

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