147. Asthma: from childhood environment to adult phenotypes

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Feasibility of measurements of fraction of exhaled nitric oxide (FENO) in a large population based study (ADONIX)
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FENO is used in epidemiological studies as a non-invasive marker of airway

inflammation. Some patients do not manage to fulfill the measurement criteria. The objective was to examine if there are any differences between subjects that do and do not manage to perform a correct FENO measurement, mainly relating to respiratory disease and differences in lung function.
The Adonix-cohort comprises a general population sample of 6,296 subjects (52% women), aged 25 to 75 years. They have all been examined with FENO (NIOX, Aerocrine™), lung function, questionnaires and blood samples. To fulfill the measurement criteria for FENO the subjects had to exhale at a 50 mL/s ±10% (mean level 45-55 mL/s and allowed instant flow 40-50 mL/s) during the last 3 seconds of the exhalation, in accordance to international guidelines.
217 subjects (3.4%, 67% women) were unable to perform a correct test. These subjects were characterized by significantly lower lung function; FVC 3.6 vs 4.2 L ($p<0.001$) and FEV1 2.8 vs 3.3 L ($p<0.001$), but also lower predicted lung function; FVCpred 105.3 vs 109.9% and FEV1pred 98.3 vs 103.4%. In addition, we found a statistically significant over representation of subjects with asthma (13.1 vs 8.8%) in the group that did not manage to perform the test.
In conclusion, the overall success-rate of FENO measurement was high. Subjects that failed the test were more likely to have lower lung function and more likely to have asthma than subjects that fulfilled the measurement criteria.

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Maternal obesity and inhaled corticosteroid use in childhood

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Background: It has been proposed that maternal obesity during pregnancy may increase the risk that the child develops asthma and allergic disease, although the mechanisms underpinning this relationship are currently unclear.
Methods: The study population comprised a Swedish national cohort of term children born between 1992 and 2008 to native Swedish parents. Maternal BMI was measured at 8-10 weeks gestation. Unconditional logistic regression models were used to determine if maternal obesity was associated with increased risk of inhaled corticosteroid (ICS) in 431,718 first-born children, while adjusting for potential confounders. An age-matched discordant sib-pair analysis was performed for 38,296 children, taking into account shared genetic and environmental risk factors.
Results: Maternal over-weight and obesity were associated with increased risk that the child would require ICS (for BMI >35kg/m^2, aOR=1.30, 95%CI=1.10-1.52 compared with normal weight mothers) in children aged 6-12 years. Similar effects were seen in younger children, but in children aged 13-16 years, maternal obesity (BMI>30) was related to increased risk of ICS use in girls (aOR= 1.28, 95%CI=1.07-1.53) but not boys (OR=1.05, 95%CI=0.87-1.26). The sib-pair analysis failed to find any evidence that increasing maternal weight was related to increased risk of ICS use in children older than six years
Conclusion: Maternal obesity is associated with increased risk of childhood ICS use up to approximately 12 years of age, but only in girls after this age. These effects could not be confirmed in a sib pair analysis, suggesting the effects of maternal BMI may be due to shared genetic or environmental risk factors.

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Relationships between school indoor toluene and respiratory symptoms in children of five European countries (HESE study)

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Aim: To assess whether indoor toluene may affect respiratory health in schoolchildren.
Methods: Health status and related risk factors were assessed through questionnaire in 628 children (mean age 10yrs) of five European countries: Sweden, Norway, Denmark, France, Italy (EU-funded HESE Study, Health Effects of School Environment). Measurements of pollutants were performed in 46 classrooms. Toluene was measured by active sampling using charcoal tubes.
Results: The levels of toluene were relatively low: median concentration was 4.57, significantly higher in France (12.12) than in the other four countries (range: 2.82 in Sweden to 5.09 μg/m^3 in Italy). Prevalence rates of dry cough at night and wheeze were respectively 35% (range: 17 in Sweden to 48% in Italy) and 13% (range: 10% in Northern countries to 18% in France). Multiple logistic regression, accounting for centre, gender, age, presence of asthma, passive smoking at home, other indoor pollutants (PM_{10}, CO_2, viable moulds) indicated toluene to be associated with higher risk of dry cough (OR 4.37, 95%CI 2.19-8.75 per 1 μg/m^3 increment) and wheeze (OR 3.24, 1.25-8.45). These associations were significant after further accounting for the fixed effect of the classroom.
Conclusion: Although toluene levels in classrooms were relatively low, long-term exposure seems to be a risk factor for respiratory health of schoolchildren.

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Physical activity trajectories and lung function: The 1993 Pelotas birth cohort

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Background: Practice of physical activity is stimulated by the United Nations. Ithas been considered a protective factor for several chronic diseases. Inconsistencies are found in the literature to evaluate the association between physical activity and parameters of lung function in adolescents.
Objective: To evaluate the association between physical activity trajectories from 11 to 15 years old and lung function at 15 years.
Methods: The original cohort comprised 5,249 hospital born children during the calendar year of 1993 in Pelotas, Brazil. In 2004-5 and 2008-9, all cohort members were sought for follow-up visits. Physical activity was measured at ages 11 and 15 and then classified into active or inactive (>300 min/week) in both periods. At the 2008-9 visit, when participants were 15 years-old, pre and post-bronchodilator spirometry was performed. Linear regression was used and all analyses were stratified by sex.
Results: Out of the 5,249 original members of the cohort, 4,325 were located at 15 years of age, and 4,100 performed spirometry. In girls, those who were active in leisure time in both periods have better % predicted FVC [β=3.239 (95%CI 0.638; 5.840)] and FEV6 [β=0.086 (95% CI 0.007; 0.165)] than those who where inactive in the two time periods. Also in girls, those who became active at 15 years of age had higher PEF than those inactive at 11 and 15 years of age. In boys, only those who became inactive in leisure time had worse PEF [β= -0.170 (95% CI -0.331; -0.009)] than boys inactive at ages 11 and 15.
Conclusions: It was concluded that leisure-time physical activity during adolescence mainly among girls was associated with better lung function parameters effort dependent.

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IgE-associated phenotypes in 8-year old children. Cluster analysis of European birth cohorts

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MeDALL (Mechanisms of the Development of ALLergy) is a FP7 project that aims to generate novel knowledge on the mechanisms of initiation of allergy. We aimed to identify phenotypes of allergic diseases in children using hypothesis-free statistical analyses. A total of 14,625 children (50% female) aged 8 years from 5 European birth cohorts (MAS, BAMSE, PIAMA, LISA, and GINI) were included in a common database with 83 variables obtained through harmonization of standardized questionnaires. Children were grouped, using partitioning cluster analysis (k-means), according to the distribution of 21 variables (phenotypic traits), covering asthma, rhinitis, dermatitis, food allergy, specific IgE levels, and child characteristics. Two groups emerged as the best separation maximizing between- and minimizing within- groups distances. The prevalence of most allergic diseases

	Group 1 n=11,712 (80%) (51% female)	Group 2 n=2,913 (20%) (39% female)
Wheezing ever	28%	78%
Number of wheezing attacks in the past 12 months: >3 times	1%	13%
Wheezing after exercise ever	7%	51%
Asthma ever	5%	54%
Any asthma treatment in the past 12 months	3%	34%
Bronchitis or Bronchiolitis ever	33%	63%
Cough at night (when no cold) ever	35%	73%
Sneezing or runny or blocked nose ever (when no cold)	32%	82%
Sneezing or runny or blocked nose in the last 12 months (when no cold)	13%	62%
Itchy watery eyes in the last 12 months (when no cold)	5%	42%
Allergic Rhinitis ever	6%	54%
Itchy rash (coming and going for at least six months) ever?	40%	76%
Itchy rash (coming and going for at least six months) in the last 12 months?	12%	27%
Eczema ever	26%	69%
Urticaria ever	16%	39%
Allergy to food ever	11%	46%
IgE sensitization (serum specific IgE)	28%	64%
Weight (kg), m (SD)	32.1 (7.7)	33.1 (8.7)
Height (cm), m (SD)	137.6 (9.4)	139.0 (11.1)

was different between groups (see Table): 5% *vs* 54% for ever asthma, 6% *vs* 54% for ever allergic rhinitis, and 26% *vs* 69% for ever eczema, in Groups 1 and 2, respectively. Specific IgE positivity was observed in 28% and 64% of children, respectively.
Thus, Group 1 could correspond to healthy children from the general population, while Group 2 puts together children with the different allergic diseases. These data suggest that allergic diseases could be better approached as one single entity rather than as independent, solely organ-related diseases.

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Temporal stability of asthma phenotypes identified by a clustering approach: An ECRHS-SAPALDIA-EGEA study
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Background: The temporal stability over time of asthma phenotypes identified using clustering methods has never been addressed.
Aims: To assess whether repeated Latent Class Analysis (LCA) applied in asthma a decade apart leads to the identification of comparable phenotypes, and to characterize the transition between them.
Methods: The LCA was applied twice, 10 years apart, on data from 2399 asthmatic adults recruited in 3 epidemiological surveys using standardized protocols: ECRHS (European Community Respiratory Health Survey, n=1450), SAPALDIA (Swiss cohort study on air pollution and lung disease, n=589) and EGEA (Epidemiological study on Genetics and Environment of Asthma, n=360). 14 variables covering personal characteristics, asthma symptoms, treatment, age of asthma onset, allergic characteristics, lung function and bronchial hyperresponsiveness were considered at both time points.
Results: A model with four latent classes was selected at each time point (prevalence between 14%-36%, mean posterior probability 84%). Two of them were predominantly composed of subjects with active asthma, mainly differing by allergic status and age at onset. Two others were predominantly composed of subjects with inactive-mild asthma, mainly differentiated by allergic status. Most of the population (60%) was assigned to the same asthma phenotype at both time points, although stability varied between phenotypes (from 47% for "active adult-onset asthma" to 68% for "inactive-mild non-allergic asthma").
Conclusion: Asthma phenotypes identified by a clustering approach 10 years apart were comparable. Further analyses will be conducted using Latent transition analysis.

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Serum eosinophilic cationic protein (ECP) in adult monozygotic and dizygotic twins
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Aim: To identify predictors for variation in serum levels of eosinophilic cationic protein (ECP) and to determine the relative proportion of the variation in ECP that is due to genetic and non-genetic factors in an adult clinical twin sample.
Methods: ECP was measured in 256 complete twin pairs and 63 single twins, who were selected through a questionnaire survey of 21,162 adult twins from the Danish Twin Registry. Interview data and tests for atopic diseases were collected. Data were analysed with regression and variance components models.
Results: The median level of serum ECP was 5.75, range (0.84-91.95). Sex (p=0.002) and airway responsiveness to methacholine measured as logDRS (p=0.001) were significant predictors of serum ECP. The intra-class correlation of serum ECP was 0.48 in monozygotic and 0.31 in dizygotic twins. Genetic factors explained 53% (39-67%), p=0.000, of the variation in serum ECP, whereas the remainder of the variation was attributable to random non-genetic variation. The genetic correlation between serum ECP and airway responsiveness was small and insignificant.
Conclusions: About half of all variance in serum ECP is due to genetic factors. Moreover, serum ECP levels are influenced by sex and airway responsiveness but this is not due to genetic similarity between this trait and serum ECP.

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Gender differences in bronchial responsiveness: A population-based cohort
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Background: Incidence of adult asthma, particularly non-allergic asthma, is higher in women but underlying mechanisms remain unclear. Cross-sectional studies have shown that bronchial hyper-responsiveness (BHR) is more frequent in women but gender differences in the onset and prognosis of BHR have been little studied.
Methods: Gender differences in BHR were studied in men and women without asthma or asthma-like symptoms participating in the European Community Respiratory Health Survey (baseline 1991-93; n=7521, age 20-44 years). BHR was defined as $\geq$20% decrease in FEV_1 for a methacholine dose $\leq$1 mg.
Results: At baseline, BHR was more frequent in women (12.6%) than in men (6.0%) (adjusted odds-ratio (OR); 2.33 95%CI 1.82-2.98). In subjects without BHR at baseline, BHR at follow-up (1998-2002) was observed in 8.2% (119/1449) women and 4.1% (76/1834) men (adjusted OR 2.74; 95%CI 1.92-3.91). Gender difference in BHR onset was significant in never-smokers, smokers and non-atopic subjects but was not observed in atopic subjects. In subjects with BHR at baseline, no gender difference in BHR persistence and prognosis of BHR as regards asthma was observed: in 172 women and 105 men with BHR at baseline, respectively 54.6% vs. 48.6% still had BHR at follow-up (p=0.33); 20.4% vs. 23.8% had developed asthma-like symptoms (p=0.50), and 12.8% vs. 15.2% had asthma-like symptoms and BHR (p=0.56). BHR was a significant predictor for asthma development in both sexes.
Conclusions: This study suggests that female sex is a risk factor for the development of BHR during adult life. Further research on the influence of sex-specific factors on BHR is needed to understand the mechanisms underlying the development of asthma in men and women.