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## 146. Prognosis and outcome of respiratory infections

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**Dynamic changes of serum sTREM-1 and its gene polymorphisms associated with sepsis prognosis**

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**Introduction:** More and more studies have confirmed that sepsis is an acquired genetic disease.

**Objectives:** To explore how sepsis prognosis is associated with the dynamic changes of serum sTREM-1, as well as with gene polymorphisms.

**Methods:** 80 subjects were selected from inpatients in the RICU, SICU, and EICU. 80 healthy volunteers acted as control. To detect the dynamic changes of serum sTREM-1 over a 14-day observation, ELISA was performed. Four exons of TREM-1 gene were sequenced on ABI3730.

**Results:** The nonsurvivors' sTREM-1 levels remain significantly higher than the survivors' over period of 14 days ( $P < 0.01$ ). The curves show that the nonsurvivors

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register higher sTREM-1 levels at the initial stage, which steadily go up with the passage of time. In contrast, the survivors'sTREM-1 levels are on the decline all the time. Three TREM-1 SNPs (rs144672509,rs2234237 and rs2234246) are detected from four exons. In three inherited models, rs2234237 is clearly related to sepsis prognosis( $P<0.05$ ). The log-rank test shows that patients with the rs2234237 genetic variation stand a greater probability of a 28-day death( $P<0.05$ ). However, no relationship is spotted between TREM-1 gene polymorphism and the dynamic concentrations of serum sTREM-1. Logistic regression analysis shows that sTREM-1,APACHE II score,and TREM-1 rs2234237 genetic variation are risk factors affecting the prognosis.

**Conclusions:** Dynamic changes in serum sTREM-1 may be more accurate and valuable for sepsis monitoring and for dynamic assessments of prognosis. It is proved that TREM-1 rs2234237 polymorphism is associated with high 28-day mortality among sepsis patients, constituting a risk factor affecting prognosis.

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#### Vitamin D level predicts clinical outcome in community-acquired pneumonia

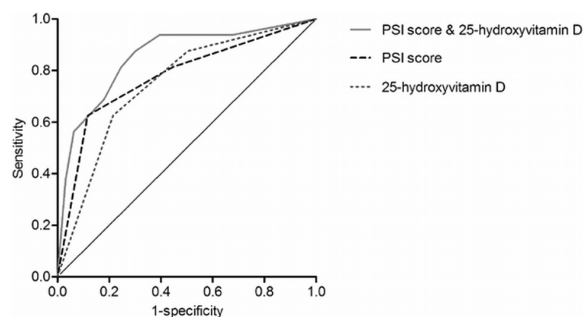
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**Rationale:** Vitamin D plays a role in host defense against infection. Vitamin D deficiency is common. The prognostic value of vitamin D in pneumonia is unknown.

**Objective:** To examine the impact of vitamin D status on outcome in community-acquired pneumonia (CAP).

**Methods:** Subanalysis of a prospective study in 272 adults presenting to the emergency department with CAP. 25-hydroxyvitamin D, leukocytes, C-reactive protein, total cortisol, the Pneumonia Severity Index (PSI) score and the CURB-65 score were measured. Intensive care unit (ICU) admission during hospitalization and 30-day mortality were assessed.

**Results:** 143/272 patients (53%) were vitamin D deficient ( $\leq 50$  nmol/L), of which 65 patients were severe deficient ( $< 30$  nmol/L). (Severe) vitamin D deficiency was associated with an increased risk of ICU admission and 30-day mortality. Vitamin D was an independent predictor of 30-day mortality (area under the curve (AUC) 0.75, 95% confidence interval (CI) 0.63-0.87). When combined with the PSI score, the prognostic accuracy was superior to that of the PSI score alone (AUC 0.85, 95% CI 0.75-0.96 vs. AUC 0.78, 95% CI 0.64-0.91). The association between severe vitamin D deficiency and the combined endpoint mortality/ICU admission persisted after thorough adjustment for confounding, adding to a possible causal relationship.



**Conclusion:** The vitamin D level is an independent predictor of 30-day mortality, and adds prognostic value to the PSI score.

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#### Obesity is associated with improved outcome in community-acquired pneumonia

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**Background:** Obesity was shown to be an independent risk factor for adverse outcome from 2009 pandemic H1N1 influenza. There is a relative paucity of information regarding whether this link applies to other pulmonary infections. We aimed to investigate whether body mass index (BMI) correlates with outcome in community-acquired pneumonia (CAP).

**Methods:** We performed a prospective observational study of consecutive patients presenting to hospital with a primary diagnosis of CAP between January 2005 and December 2009. BMI measured on admission was used to classify patients into 2 groups: obese (BMI $\geq 30$ ) and non-obese (BMI $< 30$ ). Outcomes of interest were 30-day mortality and need for mechanical ventilation or vasopressor support (MV/VS). Multivariable logistic regression was used to compare outcomes in obese patients to non-obese patients, adjusting for admission severity of illness (CURB65 criteria), diabetes mellitus, COPD and prior statin use.

**Results:** 1079 patients were included in the study with 21% classified as obese. Mean age was 62.5 years. There was no difference in admission severity (mean CURB65 score 1.44 vs 1.39) or immediate requirement for MV/VS between obese and non-obese groups. Despite this, obese patients had lower 30-day mortality compared with non-obese patients (6.7% vs 10.3%,  $p=0.3$ ). After multivariable adjustment for confounders, obesity remained significantly associated with reduced 30-day mortality (OR= 0.54, 95% CI 0.30-0.97,  $p=0.04$ ).

**Conclusions:** In our prospective study, obesity was shown to exert a protective effect on mortality from CAP. The mechanism of this effect is unclear. Further correlation from clinical and scientific studies is warranted.

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**Cigarette smoke extract (CSE) alters the secretion profile of the *Pseudomonas aeruginosa* strain PA14**

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**Background:** In North America, a major cause of morbidity and mortality is due to chronic obstructive pulmonary disease (COPD), an emerging epidemic that requires a better understanding of the pathobiology of the disease<sup>1</sup>. The single most important factor in the development of COPD is cigarette smoke; where the mechanisms and pathogenesis of the disease remain unclear. The airways of COPD patients are colonized with potential pathogens, including *Pseudomonas aeruginosa* (Ps)<sup>2</sup>. However, the effect of cigarette smoke on the cellular physiology of Ps is not known. Since Ps utilizes a variety of secreted virulence factors during infection, we sought to assess whether CSE affects protein secretion in the Ps strain PA14.

**Methods:** An overnight growth of Ps strain PA14 (Ps) was inoculated into cell culture media 1) Ps only 2) Ps +0.1% CSE 3) Ps+0.5% CSE and 4) Ps+1% CSE and harvested (OD 0.8). The cultures were then filter sterilised and the proteins precipitated by acetone; culture secreted profiles were then determined by SDS-PAGE.

**Results:** CSE increased the production of low molecular weight proteins in a dose dependent manner by the virulent Ps strain PA14 when stimulated with 0.1, 0.5 and 1% CSE as observed on an acrylamide gel.

**Conclusion:** We have shown that CSE causes a significant physiological response in PA14 by up-regulating the production of its secreted proteins. Enhanced production of these proteins can potentially cause severe damage to the upper and lower airways of smokers which can therefore influence the development of progressive COPD.

**References:**

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- [2] Laan M et al. *J Immunol*. 2004 Sep 15;173(6):4164-70.

1365

**Obesity and outcomes in patients hospitalized for pneumonia**

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**Background:** Obesity is a risk factor for acquiring pneumonia, but studies also suggest it is associated with better pneumonia-related outcomes. We examined the impact of obesity on short-term mortality in patients hospitalized with pneumonia.

**Methods:** For 2-years clinical data were prospectively collected on all consecutive adults admitted with pneumonia to 6 hospitals in Edmonton, Alberta, Canada. We identified 907 patients who also had body mass index (BMI, kg/m<sup>2</sup>) collected. Patients were categorized as underweight (BMI<18.5), normal (18.5 to <25), overweight (25 to <30) and obese (>30).

**Results:** Overall, 65% were >65 years, 52% were female and 15% reported recent weight loss. 84 (9%) were underweight, 358 (39%) normal, 228 (25%) overweight, and 237 (26%) obese. Two-thirds had severe pneumonia (63% PSI Class IV/V) and 79 (9%) patients died. In-hospital mortality was greatest among the underweight (12 [14%]) vs normal (36 [10%]) vs overweight (21 [9%]) vs obese (10 [4%], p<0.001 for trend). Compared with normal weight, obese patients had lower rates of in-hospital mortality (4% vs 10%, unadjusted odds ratio (OR) 0.39, 95%CI 0.19-0.81) that remained significant in multivariable analyses adjusted for age, sex, comorbidities, and clinical-radiographic severity of pneumonia (adjusted OR 0.44, 95%CI 0.21-0.94, p=0.035). However, compared with normal weight, neither underweight (adjusted p=0.47) nor overweight (adjusted p=0.64) were associated with mortality.

**Conclusion:** In patients hospitalized with pneumonia, obesity was independently associated with lower short-term mortality, while neither underweight nor overweight were. This suggests a protective influence for BMIs>30 kg/m<sup>2</sup> that requires better mechanistic understanding.

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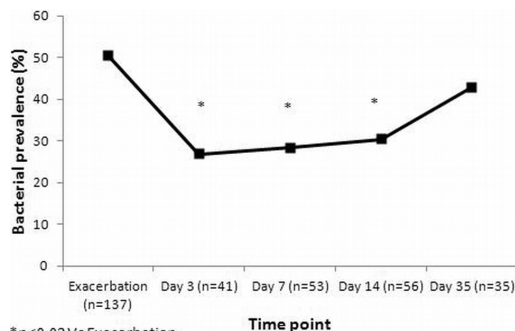
**Bacterial prevalence and load during COPD exacerbation and recovery**

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Bacteria are a common aetiological trigger of COPD exacerbations, with prevalence and load increasing from stable state (Garcha et al, *Thorax* 2011; 66:A11). We investigated prevalence and load of *H. influenzae*, *S. pneumoniae* and *M. catarrhalis* during exacerbation recovery using quantitative PCR (qPCR).

We collected sputum from subjects in the London COPD cohort at exacerbation presentation (n=137), day 3 (n=41), 7 (n=53), 14 (n=56) and 35 post-exacerbation (n=35). All exacerbations were treated with ≥7 days of antibiotics (±oral steroids) and defined by our usual symptomatic criteria (Seemungal et al, *AJRCCM*, 1998).

Characteristics of 102 COPD patients: mean(SD) age 68.7(8.2) years; FEV<sub>1</sub> 1.2(0.5)L, 48.6(24.8)% predicted. Bacterial prevalence was higher at exacerbation than Day 3 (50.4 vs 26.8%; p=0.008), Day 7 (28.3%; p=0.006) and Day 14 (30.4%; p=0.011) (Fig. 1). In recovery samples paired with bacteria-positive exacerbations (different patients at each time point), load [median (IQR) Log<sub>10</sub> CFU/ml] was significantly higher at exacerbation compared with Day 3 (n=15): 10<sup>8.1(5.9-8.7)</sup> vs 10<sup>9(0-4.0)</sup>, p=0.001; Day 7 (n=17): 10<sup>8.2(6.3-8.8)</sup> vs 10<sup>4.2(0-6.6)</sup>, p=0.01; Day 14 (n=14): 10<sup>8.0(6.3-8.7)</sup> vs 10<sup>4.4(0-6.6)</sup>, p=0.022; and Day 35 (n=15): 10<sup>7.7(5.7-9.3)</sup> vs 10<sup>5.9(0-6.74)</sup>, p=0.047.



\*p&lt;0.02 Vs Exacerbation

Bacterial prevalence and load detected by qPCR falls within 3 days of antibiotic therapy for COPD exacerbations, with load remaining low for at least 35 days post-onset.

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**Acute respiratory infections in lung transplant recipients: Use of a novel multiplex-PCR assay**

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**Background:** Acute respiratory infections (ARI) share features with common, non-infectious complications after lung transplantation (LTx) making accurate and rapid diagnosis crucial for the management of LTx recipients.

**Objectives:** To evaluate the performance of a novel multiplex-PCR assay in addition to routine evaluation.

**Methods:** In this ongoing prospective cohort study, LTx-outpatients with any new symptom of ARI were screened for 24 respiratory viruses (RV) and atypical bacteria by a multiplex-PCR assay performed on throat swabs. Routine evaluation included PCR for 14 RV on throat washes and lower respiratory tract (LRT) sampling (BAL for quantitative microbiology, direct immunofluorescence, viral culture, PCR, and transbronchial biopsy), if indicated.

**Results:** Between Sept. 2011 and Feb. 2012, among 104 episodes from 95 LTx recipients, 30 RV were detected in 29 patients (31%): 9 rhino-, 7 parainfluenza, 6 metapneumo-, 4 corona-, 3 adenovirus, 2 RSV, 2 CMV, and 3 viral coinfections. The multiplex-PCR detected RV in 12% (12/104 episodes) compared to 26% (23/90) with routine evaluation (κ=0.20, p=0.03), including additional 4 RV. RV were more frequently detected in LRT than in URT samples (24% vs. 14%; κ=0.10, p=0.40). Agreement between both PCR assays in URT specimens was moderate (RV detected in 7 of 21 throat washes; κ=0.54, p=0.011). Definite clinical diagnoses were suspected (28 subjects) and proven viral infection (26), BOS (23), AR (10), bacterial infection (9), obstructive airway complication (4), pneumonia (3), and CMV infection (1).

**Conclusions:** In LTx recipients, virological methodology and sampling are complementary, with LRT specimens resulting in higher diagnostic yield.

**147. Asthma: from childhood environment to adult phenotypes**

1368

**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

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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  $\pm$  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 overrepresentation 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.

### 1369

#### 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  $> 35 \text{ kg/m}^2$ , 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.

### 1370

#### 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  $\mu\text{g}/\text{m}^3$  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<sub>10</sub>, CO<sub>2</sub>, viable moulds) indicated toluene to be as-

sociated with higher risk of dry cough (OR 4.37, 95%CI 2.19-8.75 per 1  $\mu\text{g}/\text{m}^3$  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.

### 1371

#### 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. It has 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 ( $>300 \text{ min/week}$ ) 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 [ $\beta=3.239$  (95%CI 0.638; 5.840)] and FEV6 [ $\beta=0.086$  (95% CI 0.007; 0.165)] than those who were 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 [ $\beta= -0.170$  (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.

### 1372

#### 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<br>n=11,712 (80%)<br>(51% female) | Group 2<br>n=2,913 (20%)<br>(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)                             |

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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<sub>1</sub> 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.