54. Genetic and environmental risk factors for respiratory diseases

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Late-breaking abstract: The forgotten majority: A decrease in persistent but not in intermittent asthma in a large cohort study
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Aim: To evaluate asthma prevalence and severity in Israeli teenage boys over the last decade.

Methods: A representative sample of three hundred thousand medical records of 17-year-old boys, who underwent a comprehensive medical evaluation for eligibility for national service between 1999 and 2008, were reviewed regarding asthma diagnosis and severity. Also monitored in this period were asthma hospitalization rates, corticosteroids inhalers (CSI) sales rates and air pollution in central cities.

Results: Lifetime asthma prevalence decreased from 9.69% to 8.12%. Mild persistent asthma prevalence decreased from 3.4% to 2.4% and moderate to severe asthma from 0.9% to 0.4%. Intermittent (3.5%) and inactive asthma (2%) remained stable.

Conclusions: Prevalence of persistent asthma in Israeli 17-year-old boys decreased significantly over the last decade. Some of this decrease may be attributed to an increase in use of CSI and a decrease in air pollution.

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Rare alpha-1 antitrypsin mutations in the Irish population
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AAT deficiency (AATD) results from mutations in the SERPINA1 gene, classically presenting with early-onset emphysema and liver disease. The most common mutation causing AATD is the Z mutation, with the S mutation weakly associated with lung disease. AAT deficiency is under-diagnosed and prolonged delays in diagnosis are common. ATS/ERS guidelines advocate screening all COPD, poorly-controlled asthma, and cryptogenic liver disease patients, as well as first degree relatives of known AATD patients.

5,000 individuals were screened following ATS/ERS guidelines as part of the Irish national targeted detection programme. AAT levels were determined by nephelometry. AAT phenotyping was performed by isoelectric focusing. Patient DNA isolated from DBS samples was genotyped by PCR (Roche LightCycler). Rare and novel mutations were identified by DNA sequencing of the SERPINA1 gene. A number of rare SERPINA1 mutations including I, V, F, Xchristchurch, Zbirstol, and Mmalton were identified. The I mutation (Arg93Cys) was present at a relatively high frequency (0.0038) in a targeted population, with over 40 cases identified. In addition, a new SERPINA1 mutation was identified.

Current testing of suspected AATD cases is often limited and can miss rare and novel clinically significant SERPINA1 mutations. The rare mutations described in this study were not detected by a commonly used genotyping assay, however, the low AAT levels prompted their correct identification using more detailed genetic analysis. Our findings underline the need for a comprehensive diagnostic work up of all patients with low AAT levels including phenotyping, genotyping and if necessary, DNA sequencing of the SERPINA1 gene.

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Hedgehog-interacting protein (HHIP) polymorphisms and chronic obstructive pulmonary disease (COPD)
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Genome wide association studies (GWAs) have identified single nucleotide polymorphisms (SNPs) in the region of Hedgehog interacting protein (HHIP) to be associated with COPD, level of lung function and height in the general population. We aim to investigate the association of rs1032295 and rs13147758 with lung function level and decline in subjects from the general population, as well as the association with lung function level and decline and small airways function in subjects with established COPD.

Two SNPs rs1032295 and rs13147758 in the HHIP region were genotyped in 1,152 subjects from the general population (Doetinchem) and 110 COPD patients (GLUCOLD). Associations of the SNPs with lung function level and small airways function (FEV1 and FEF25-75%) at baseline were analyzed using linear regression.
Lower-fat yoghurt intake was directly related to increased risk of both childhood asthma and AR, while total milk intake appeared to be protective. Non-fat related nutrient components in yoghurt may be mediating this increase in risk.

**Conclusion:** Low-fat yoghurt intake was directly related to increased risk of both childhood asthma and AR, while total milk intake appeared to be protective. Non-fat related nutrient components in yoghurt may be mediating this increase in risk.
of asthma was observed in rare/never drinkers, OR=1.45 (1.17-1.82), p=0.001, whereas the risk of asthma in heavy daily drinkers was also increased, however not statistically significant, OR=1.26 (0.63-2.50), p=0.514. After adjustment for overall intake of alcohol, preference for beer drinking was associated with an increased risk of asthma compared with no preference, OR=1.29 (1.03-1.61), p=0.01.

Conclusions: Alcohol intake appears to increase the risk of new-onset asthma in adults with a U-shaped association between amount of alcohol intake and the risk of asthma.

P320 Aspirin-induced asthma is strongly associated with obesity: Large population study on prevalence and risk factors

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Background: Population-based studies on aspirin-induced asthma are few and no comprehensive risk factor analysis for the condition has been published. We sought to investigate the prevalence and risk factors of aspirin-induced asthma in the general population.

Methods: A questionnaire on respiratory health was mailed to 30,000 randomly selected subjects aged 16-75 years in West Sweden, 29,218 could be traced and 18,087 (62%) responded. The questionnaire included questions on aspirin-induced dyspepsia, asthma, respiratory symptoms and possible determinants.

Results: The prevalence of aspirin-induced asthma was 0.5%, 0.3% in men and 0.6% in women (p=0.014). The prevalence increased with increasing body mass index (BMI) (3.0% vs. BMI>35; 2.2%; p=0.001).

Conclusion: Aspirin-induced asthma was common in the study population. Increasing body mass index increased the risk of aspirin-induced asthma in a dose-response manner. A number of risk factors including obesity were considerably stronger for aspirin-induced asthma than for aspirin-tolerant asthma.

P321 Physical fitness and asthma development in a random population during three decades. The Odense schoolchild study

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Aim: To investigate the longitudinal association between physical fitness and the development of asthma and asthma-like symptoms in a general population sample. 1369 children from the Odense schoolchild study were assessed from 1985 to 2007 at age 9, 15, 20 and 29 years. The same physical fitness test was applied at all occasions and fitness was stratified into quintiles for each sex.

Results: The following analysis is based all subjects who performed a satisfactory fitness test: 1369 children at age 9 (mean 9.7), 1072 (78%) at age 15 (mean 15.6), 881 (64%) at age 20 (mean 20.3) and 814 (60%) at age 29 (mean 29.3) performed a satisfactory fitness test respectively. The results showed that fitness levels at each age was associated with lower lung function at same age (p<0.001). The was no significant difference in the occurrence of asthma-like symptoms in the sex specific fitness quintiles at age 9 years. Higher fitness at age 9 was associated with a lower occurrence of asthma at age 20 (p=0.001) and 29 years (p=0.04), but not significant at age 15 years. On the other hand, at age 15 there was a significant trend of higher occurrence of asthma-like symptoms the lower the fitness quintile at age 9 years (p<0.05). In the sex specific analyses the association between physical fitness at age 9 years and asthma at age 20 and 29 years was only significant in women (age 20; p=0.01); (age 29; p=0.04) and men (age 20; p=0.07); (age 29; p=0.7) respectively.

Conclusion: In conclusion, our results point toward the importance of a moderate-high fitness level before puberty to reduce the impact of asthma development in adulthood but this effects seems mainly present in women.

P322 Impact of physical inactivity on cognitive function in adults with obstructive lung disease (OLD)

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Background: OLD may increase risk of cognitive deficits.

Objective: Examine the role of physical inactivity in cognitive impairment (CI).

Methods: Members of a population-based cohort with self-reported physician-diagnosed COPD, emphysema, or chronic bronchitis (n=140; 63% female, mean age 67 yrs, 19% current smokers) completed baseline (T1) and 2-year follow-up (T2) in-person assessments that included spirometry; completion of the CHAMPs Questionnaire to estimate energy expenditure in vigorous/moderate intensity activities (M/V) and overall; and a 10-test cognitive function battery. We defined physical inactivity as no expenditure in M/V activities. We transformed cognitive test scores to age-adjusted z-scores and defined CI as z-scores ≤ -1.5 or ≥ +3.3 of cognitive tests. Logistic regression tested relationships between physical inactivity and CI at both T1 and T2, controlling for sex, education, smoking, comorbid conditions, low O2 saturation, depression, and arthritis.

Results: At T1, 31% were physically inactive. CI was more frequent among inactive subjects (27% vs. 12%; adjusting for covariates: OR=9.8 [95% CI 1.8, 53.1]). Adjusting for covariates plus T1 CI, inactive subjects were more likely to be cognitively impaired at T2 (OR=4.4 [1.2, 15.8]). Among 120 subjects not impaired at T1, inactive subjects were more likely to develop CI at T2 (26% vs. 15%; OR=0.6 [1.5, 2.4]).

Conclusion: Physical inactivity is a significant risk factor for presence and incidence of cognitive impairment among adults with OLD.

Clinical relevance: In OLD, participation in a program of even moderate physical activity may offer protection from cognitive impairment.

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P323 Decrease in smoking is related to a decrease in respiratory symptoms but not asthma

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Aim: To compare the prevalence of respiratory symptoms and asthma among adults in 1996 and 2006 by smoking habits.

Methods: In 1996, 7104 randomly selected subjects (response rate 85%) in Northen Sweden aged 20-69 answered a postal questionnaire about respiratory symptoms, and respiratory history. In 2006, a new sample of 6165 subjects (77% responded) of same age answered the same questionnaire.

Results: All respiratory symptoms were strongly related to smoking. The prevalence of most respiratory symptoms decreased significantly from 1996 to 2006 parallel to a decrease in smoking, which decreased from 27 to 19%. The prevalence of spumon production decreased from 19.1 to 15.0%; longstanding cough 12.4-10.8%; chronic bronchitis 7.4-6.3%; and recurrent wheeze 13.4-12.1%. The prevalence of these symptoms was similar among smokers, and decreased among non-smokers. Physician-diagnosed asthma increased among both smokers and non-smokers, totally from 9.3 to 11.5%. However, the proportion of medicine users and symptomatics among the asthmatics were lower in 2006. In multivariate analysis adjusted for confounders, a significant increase of asthma by study year was found (OR 1.4). Corresponding analysis for chronic bronchitis yielded a significant decreased effect by study year (OR 0.8).

Conclusions: The decreased prevalence of respiratory symptoms was parallel to a decrease in smoking. The decrease in bronchitis symptoms among non-smokers may be related to a reduction of environmental tobacco smoke and occupational airborne exposures. Increased diagnostic activity can explain the increase in asthma.

P324 Recent trends in COPD prevalence in Italy

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Aim: To compare prevalence rates and risk factors associated with COPD in an Italian population sample surveyed 20 years apart.

Methods: The family cluster random sample living in Central Italy (Pisa) was enrolled in 1991-93 (n=2529, age range 20-97 yrs, males 44.4%); the survivors, with the inclusion of new family members, were studied again in 2009-10, within the framework of the European Union funded project IMCA2 (Indicators for Monitoring COPD and Asthma in EU) (n=1341, age range 20-103 yrs, male 46.5%). Lifestyle, health status and chronic respiratory diseases information were collected at T2 (n=18 087 (62%) responded. The questionnaire included questions on aspirin-induced dyspepsia, asthma, respiratory symptoms and possible determinants.

Results: At T1, 31% were physically inactive. CI was more frequent among inactive subjects (27% vs. 12%; adjusting for covariates: OR=9.8 [95% CI 1.8, 53.1]). Adjusting for covariates plus T1 CI, inactive subjects were more likely to be cognitively impaired at T2 (OR=4.4 [1.2, 15.8]). Among 120 subjects not impaired at T1, inactive subjects were more likely to develop CI at T2 (26% vs. 15%; OR=0.6 [1.5, 2.4]).

Conclusion: Physical inactivity is a significant risk factor for presence and incidence of cognitive impairment among adults with OLD.

Clinical relevance: In OLD, participation in a program of even moderate physical activity may offer protection from cognitive impairment.

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COPD among non-smokers

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Methods: In 1986 a postal questionnaire responders (response rate 88%) aged 46-77 years from a stratified sample of the general population of Norrbotten, Sweden, a random sample of 1500 subjects were invited to structured interviews and lung function tests, and 1237 completed a lung function test with acceptable quality. Never smokers were defined as those who had smoked <1 cigarette/day for <31 year. COPD was defined as GOLD stage ≥II, as several medical conditions are associated with a FEV1/FVC <0.7.

Results: The prevalence of COPD among non-smokers was 3.4% and tended to be more common among women than men (4% vs 2.3%, NS) and was strongly age related particularly among men. For comparison the overall prevalence in ages 45-77 yrs was 16% (12% in men and 21% in women). Among never smokers the prevalence of severe COPD (FEV1 <50% of predicted) was 0.8 (women 0.9% men 0.6%; NS). In contrast to men, severe cases of COPD were found among women aged ≥65 years. Of all men with COPD, 15% were never smokers versus twice that much among women. Increasing age was a significant risk factor, while passive smoking, manual work in industry and female sex tended to be associated with COPD among never smokers.

Conclusion: The prevalence of clinically relevant COPD among never smokers aged ≥45 yrs was 3.4% and was associated with increasing age. One out of seven men with COPD versus one out of three women had never been smokers.

BMI and risk in COPD

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Methods: A stratified sample of subjects from a population survey was invited to clinical examinations including lung function tests in 1986. Out of 1506 (91% of the invited) we identified 266 subjects, 64% men, fulfilling the spirometric GOLD criteria of COPD. The subjects with COPD reflected well COPD in the society. The subjects were followed-up to 20 years or until death. Risks for death of these subjects were determined by survival analysis (Cox regression) adjusting for baseline sex, age, heart disease, smoking habits and BMI.

Results: After 20 years, 46% of the COPD cohort was still alive. At baseline, underweight (BMI<18.5) was found in 4% and obesity (BMI≥30) in 9%; 24% were non-smokers and 46% current smokers. Heart disease, i.e. myocardial infarction or heart failure was reported by 10.2% of the cohort. In the adjusted survival analysis (Cox regression) significant risk factors for death included GOLD stage 3-4 (HR=3.0, 95% CI: 1.6-5.5), myocardial infarction or heart failure (HR=3.1, 95% CI: 1.9-5.1), and increasing age. There was no significant association between BMI categories and risk of death, not even in COPD stage 3-4.

Conclusion: Mortality in COPD seems to be associated with heart disease where overweight is a risk factor. In a long-term perspective, low BMI was not associated with increased mortality.

Professional exposure to goats increases the risk of pneumonic-type lung adenocarcinoma.

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Background: Pneumonic-type lung adenocarcinoma (P-ADC) represents a distinct subset of lung cancer with specific clinical, radiological, and pathological features. The weak association with tobacco-smoking and the striking similarities with JSRV-induced ovine pulmonary adenocarcinoma, it has often been suggested that a viral agent infecting pulmonary cells may predispose to P-ADC in humans.

Aims and objectives: Our objective was to explore whether exposure to domestic ungulates may represent a risk factor for P-ADC.

Methods: We performed an exploratory multicenter case-control study recruiting patients with P-ADC as cases and patients with non-P-ADC non-bronchioloalveolar non-small cell lung cancer as controls. A dedicated 356-item questionnaire was built to evaluate domestic ungulates exposure. A total of 44 cases and 132 controls were included.

Results: At multivariate analysis, P-ADC was significantly associated with female gender (Odds-ratio (OR)=3.23, 95% confidence interval (CI): 1.32-7.82, p=0.010), never-smoker status (OR=3.57, 95% CI: 1.27-10.00, p=0.015), personal history of

Cured meat consumption increases risk of readmission in COPD patients

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Rationale: Recent studies have shown that a high dietary intake of cured meat increases the risk of COPD readmission. However, its potential effects on COPD evolution have not been tested.

Objective: To assess the association between dietary intake of cured meat and risk of COPD readmission in COPD patients.

Methods: 274 COPD patients were recruited during their first COPD admission between 2004 and 2006, provided information on dietary intake of cured meat during the previous 2 years, and were followed through December 31st 2007 (median follow-up 2.6 years). Associations between cured meat intake and COPD admissions were assessed using parametric regression survival-time models.

Measurements and main results: Mean (SD) age was 68 (8) years, 93% of patients were males, 42% were current smokers, mean post-bronchodilator FEV1 was 53 (16)% predicted, and median cured meat intake was 23g/day. After adjusting for age, FEV1, and total caloric intake, high cured meat intake (> median value) increased the risk of COPD readmission (unadjusted Hazard Ratio (95% confidence interval) 2.02 (1.31 - 3.12), p=0.001). Smoking and socioeconomic status were not included in final models because they did not relate to cured meats consumption.

Conclusions: High cured meat consumption increases the risk of COPD readmission in COPD patients, which suggests potential public health benefits from recommending dietary shifts to reduce intakes of these foods in COPD patients.
any cancer (OR=3.43, 95% CI: 1.10-10.72, p = 0.034), and professional exposure to goats (OR=5.09, 95% CI: 1.05-24.69, p = 0.043).

**Conclusions:** This exploratory case-control suggests a link between professional exposure to goats and P-ADC, and prompts for further epidemiological evaluation of potential environmental risk factors for P-ADC.