447. Respiratory diseases at at work: epidemiology, inflammation and challenge studies

P4345
Increased markers of oxidative stress in workers exposed to nanoparticles

Aim: To elucidate the role of HLA-II in adult-onset asthma, we imputed classical HLA-II alleles from 7579 single nucleotide polymorphisms. We explored associations between 25 alleles with frequency >0.001: HLA is a principal candidate gene region for occupational asthma, and HLA-DQ was the only significant locus in the GABRIEL genome-wide association study (GWAS) of late-onset asthma.

Methods: We studied 607 subjects with adult-onset asthma and 2104 adults without asthma from three European cohorts (ESE Consortium: ECRHS, SAPALDIA, EGEA). According to a job exposure matrix, 444 subjects (133 with adult-onset asthma) were exposed to high molecular weight (HMW) agents, with 74% exposed monitored by SMPS and APS spectrometers in size range 15 nm-10 μm. Spatial distributions of total concentrations were determined using monitors of particle number (P-TRAK) and mass concentrations (DustTRAK DRX). Pre-shift and post-shift FeNO and markers in exhaled breath condensate (EBC) were measured in 20 workers, and 17 controls. Malondialdehyde (MDA), 4-hydroxy-2-nonenal (HNE), 4-hydroxy-2-alkenal (HHE), 8-iso-prostaglandin F2α (8-iso), 8-iso-prostaglandin F2α (8-iso), 8-iso-prostaglandin G2 (8-iso), 8-iso-prostaglandin G2 (8-iso), 8-iso-prostaglandin E2 (8-iso), and leukotrienes (LTs) were analyzed by liquid chromatography-electrospray ionization-mass spectrometry.

Results: Total aerosol concentrations in the production plant varied in space and time; number concentrations 1x104-2x105 particles/cm3, mass concentrations 0.1-30 μg/m3. In the workshops, 90% of particles were under 100 nm in diameter. All pre-shift markers, except LTβ4 and FeNO, were increased in workers. Markers of lipid oxidation were elevated (p<0.01): MDA, HNE, HHE, 8-iso and 8-iso, 8-iso-prostaglandin G2 (8-iso), 8-iso-prostaglandin G2 (8-iso), 8-iso-prostaglandin E2 (8-iso), and leukotrienes (LTs) were analyzed by liquid chromatography-electrospray ionization-mass spectrometry.

Conclusion: This first study of EBC in workers suggests deleterious effects of TiO2 exposure to aerosol particles with nano-sized fractions.
to latex. In addition, we studied 946 HMW-exposed workers (392 with asthma) from Dutch and Danish surveys of bakers and farmers.

### Results

In the ESE cohorts, DPB1*0401 (OR 0.76, 95%CI 0.60-0.97) and DQA1*0103 (OR 1.22, 95%CI 1.02-1.44) were associated with adult-onset asthma. DQA1*0301 was associated with asthma, but only in HMW-exposed ESE subjects (OR 0.54, 95%CI 0.29-0.98). In the HMW-exposed bakers and farmers, six other HLA-II alleles were associated with asthma (P<0.05). None of the associations in ESE subjects or workers remained statistically significant after correction for multiple testing.

### Conclusions

Imputation allows a complete evaluation of HLA alleles following GWAS. In a general population and among populations exposed to a variety of occupational allergens, analyses did not reveal a clear association between common classical HLA-II alleles and adult-onset asthma.

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**P4348**

**Work-related asthma among a general asthma population: A cross sectional survey**

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To find the impact of occupational exposure to irritants or sensitizers on the occurrence, recrudescence and worsening of asthma and to identify unrecognized cases of work related asthma (WRA) in a general asthma clinic population sample, we studied 893 subjects from 15 to 46 yrs with diagnosis of asthma identified from the Medical Reimbursement Register of the National Health Service. All subjects were classified in different categories of occupational risk exposure (Low or High: 58.9, 27.9, 13.2% respectively) according to the italian standard classification for industries and job titles, associated with the judgment of occupational hygiene-experts. Subjects with higher occupational risk had a lower lung function (p=0.02) and asthma severity (<0.01). Prevalence of WRA (47%), including occupational asthma (OA; 7%) and work exacerbated asthma (WEA: 40%), was significantly associated with higher occupational risk exposure (OR 6.8, p=0.001). Subjects with WRA had a lower lung function (<0.01) and asthma severity (p=0.01) with respect to subjects without WRA. Two-thirds of OA and half of WEA caused loss of work. In conclusion our study shows a high prevalence of WRA (especially WEA) associated with employment in industries and job titles at risk for airways sensitizers and/or irritants. Control of exposure, an appropriate medical surveillance and an accurate therapeutic management can avoid the loss of job and its socioeconomic consequences in asthmatic subjects.

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**P4349**

**Shield 1992-2012: 20 years of a reporting scheme for occupational asthma**

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**SHEILD is the Midland Thoracic Society’s rare surveillance scheme for occupational asthma in the West Midlands, England, UK (working population 2.2 million). The database is a useful tool to locate outbreaks within a particular field of work and discover causative agents. There have been 1644 notifications of occupational asthma since January 1992.**

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**P4350**

**The effect of work on asthma in middle-aged men having asthma from youth**

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**Aims:** We studied the effect of current workplace exposure on current asthma severity, asthma control and occurrence of exacerbations in a population of approximately 40-year old men having asthma since their youth.

**Methods:** We used Finnish Defence Force registers, 1986-1990, to select: (1) conscripts with asthma to represent a mild/moderate asthma group (n=485), (2) asthmatics who were exempted from military service to represent a relatively severe asthma group (n=393) and (3) a control group (n=1506) without asthma. A questionnaire consisting of validated questions on asthma and occupations was sent out in 2009 and current occupational exposure was estimated with asthma Job Exposure Matrix (JEM). Asthma severity was evaluated with the modified GINA guidelines and control with the Asthma Control Test. Logistic regression was used in risk factor analyses. A total of 54% of the men in asthma group 1, 44% of those in asthma group 2 and 44% of the controls answered.

**Results:** A total of 17.7% of the subjects in asthma group 1 and 40.5% of the subjects in asthma group 2 had had current moderate or severe persistent asthma. Asthma was more often uncontrolled in asthma group 2 (28.0% vs. 15.1%, p=0.002) and exacerbations during last 12 months were more frequent (19.3% vs. 11.6%, p=0.036). Being currently not-employed (OR 2.0, 95%CI 1.0-4.0) and self-reported occupational exposure to abnormal temperatures (OR 1.7, 95%CI 1.0-3.0) were associated with asthma exacerbations, while occupational exposure based on JEM was not related to current asthma status.

**Conclusion:** Current workplace exposure seems to have only minor effect on asthma severity, control and exacerbations in 40-year old men having asthma since their youth.
Postcard Discussion

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P4352

Occupational asthma and rhinitis in champagne vineyard workers
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Background: Vineyard workers (VW) are exposed to various inhaled respiratory allergens. However, the prevalence and risk factors of occupational asthma (OA) and rhinitis (OR) in Champagne VW have not been studied.

Aims: The objectives of this cross-sectional study were to determine the prevalence of OA and OR in Champagne VW and to analyze the relationships between occupational symptoms (OS), occupational exposure and sensitization profile.

Methods: Champagne VW were recruited from the Department of Occupational Medicine in May and June 2010. Demographic and occupational characteristics were recorded. Nasal and respiratory symptoms were scored for each month of the past year. OS were defined by symptoms related to work exposure. Diagnosis of asthma was based on symptoms and skin prick tests (SPT) were performed on respiratory allergens, grape mould (botrytis) and grape pollen. FEV1/FEV6 ratio was measured.

Results: Sixty-six workers were included. The prevalence of rhinitis and asthma was 38% and 13% respectively. The prevalence of OR and OA was 21% and 3% respectively. SPT showed sensitization for grape moulds (18%), D. pteronyssinus (12%), D. farinae (11%), vine pollen (11%), botrytis (5%). Compared to VW without OS, VW with OS were more frequently sensitized to betacellulase (20% vs 2% respectively, p=0.03) and were involved in the activities of disbudling, straightening and/or hooking (35% vs 6% respectively, p=0.04). OS were present in May and June only for 67% of patients, corresponding to disbudding, straightening and hooking.

Conclusion: The prevalence of OR in Champagne VW is high, whereas OA is relatively rare. OR and OA are associated with a sensitization to betacellulase and with direct exposure to vine.

P4353

Quartz exposure and lung function
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Occupational exposure to quartz not only leads to silicosis but also to chronic bronchitis and obstructive lung disease. In Austria more stringent occupational limit values for dusts have been introduced in 2007. We assumed that (a) workers exposed to mineral dusts (quartz) have a poorer lung function (LF) than other workers that did not work with dusts, and (b) workers that work at the highest dust exposure limits have lower LF values. We hypothesized that (a) the LF decline is fastest in the quartz-group, and (b) the decline slowed down after the introduction of stricter limit values.

We examined repeated LF data (FVC, FEV1, MEF50) from the routine examination (usually every 2 years) performed by one occupational health centre from the years 2002 through 2010. Three main linear regression models were analysed on each LF parameter. (a) The effect of quartz exposure on the raw parameter after controlling for age, height, weight, smoking, gender, and smoking. (b) The effect of quartz exposure on the difference between actual value and the age-sex-height-dependent Austrian norm value. This approach allowed us to additionally control for the impact of duration of exposure. (c) The impact of quartz exposure on the intra-individual decline in LF parameters per year. In this analysis we could also check for differences in the slope before and after the introduction of new limit values.

We analysed 7315 data-sets (on average 5 per person, mostly males). Nearly 40% of these were from workers exposed to quartz dusts. The remaining workers were welders or were exposed aluminium or other dusts. Both smoking and quartz exposure lead to lower LF values. Duration of quartz exposure also was a significant predictor of LF decline. The decline slowed after the introduction of stricter limit values.

P4354

Reduction of particles by using a particle separator in pig barn environment reduces inflammatory response in healthy volunteers
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The pig farming environment is a well-known inducer of upper and lower airway inflammation and it is unknown what causes the strong inflammatory response. The objective was to investigate if the number or size distributions of particles in the barn dust affect the airway inflammatory reaction in healthy volunteers. Two identical barns were cleaned and a particle separator (CentriClean System AB) was installed in one stable before the pigs were housed for ten weeks. Twelve non-smoking volunteers were exposed while weighing pigs for 3 hours to normal pig house environment and particle separated pig house environment (6 in each group, cross over design) with 2-4 weeks between the exposures. Initial particle (0.3-5μm) analyses showed e.g. 2.4 fold higher particle numbers in an ordinary pig barn than in particle separated barn.

There were increase in body temperature, exhaled NO and almost all perceived symptoms while FEV1, PDE20, FEV1 (methylcholine), VC and PEFR were reduced in all subjects after exposure to pig barn in comparison to filtered milieux. No significant changes were seen between the exposures except for body temperature (p=0.034) and IL-8 and IL-6 in nasal lavage fluid and CD14-expressing monocytes in blood increased more after exposure to swine barn in comparison to the air filtered swine barn (p=0.040, p=0.021 and p=0.034 respectively).

The results indicate that reduction in particles exposure of pig barns affect both local and systemic inflammatory responses in healthy persons after acute exposure to swine barn environment.

P4355

Specific inhalation challenges to metal working fluids
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Metal working fluid (MWF) is a recognised cause of occupational asthma and is becoming increasingly prevalent. In Birmingham, UK there are a large number of industries using metal working fluid to machine automotive and aircraft parts. The oil in water emulsion can be used at varying ratios generally ranging from 3-5% oil in water up to 10%.

Methods: 20 workers underwent specific inhalation challenge (SIC) tests to metal working fluid. Challenges were set up to mimic occupational exposures using indirect (into the room) and direct (into breathing zone) methods of nebulisation of new and used MWF. Exposures lasted from 5 minutes up to 70 minutes in total (spread over 3 exposures). Workers were also exposed to metal contaminants of the MWF by nebulisation of cobalt chloride (cobalt exposure can be from carbide tips used for machining) and potassium dichromate (chromium exposure can be from the machining of stainless steel).

Results: Overall, 15 workers had positive SIC tests to either MWF or metal contaminants (cobalt/chrome). The Venn diagram in Figure 1 shows the results. 8 workers had a >2 fold change in methacholine reactivity between pre and post challenge.

Conclusion: Specific inhalation challenge tests to MWF did not produce non-specific reactions. Contaminants of the MWF can be the cause of occupational asthma even with a negative challenge to MWF.

P4356

Occupational asthma to quaternary ammonium compounds: Clinical features of 16 positive bronchial challenge tests using didecyl dimethyl ammonium chloride
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Introduction: Quaternary ammonium compounds (QACs) are used as detergents or disinfectants and known to induce occupational asthma. Moreover, clinical reports with bronchial challenge tests (BCTs) that demonstrated the role of QACs are rare.

Objectives: To analyse the clinical response obtained during a positive BCT in 16 patients with occupational asthma to QACs.

Methods: A realistic BCT was performed in an experimental chamber with didecyl dimethyl ammonium chloride. The concentration corresponded to the lowest concentration of DDAc to which patients were exposed at workplace. A positive BCT was defined as a 20% drop in FEV1 or a change of 2 doubling dose in non-specific BCT to methacholine.

Results: 14 women and 2 men (mean age = 47.8 y.) were included from 2008 to 2011. 11 of them (62.5%) were healthcare workers: 1 dentist, 1 dentist-assistant, 2 nurses, 5 auxiliary nurses, 1 janitor. 5 of them (37.5%) were cleaners 69% had also occupational rhinitis and 19% occupational contact dermatitis to QACs. The mean duration of exposure during BCT was 28 minutes [3-60]. Same BCTs were done only in 3 workers.

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P4357

Persistence of the asthmatic response after exposure to ammonium persulfate in an animal model

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Introduction: The aim of the study is to evaluate the persistence of respiratory symptoms after the end of exposure to ammonium persulfate (AP) in a validated model of occupational asthma (OA).1

Material and methods: BAL/Bc mice received dermal applications of AP or dimethylsulfoxide (DMSO) (control) on days 1 and 8. On day 15, they receive a single nasal instillation of AP or saline. The ventilatory function (Pnch) was monitored by whole body plethysmography for 40 minutes after the nasal instillation. Bronchial hyperresponsiveness was assessed using methacholine provocation, while pulmonary inflammation was evaluated in BAL and total serum IgE was measured in blood, 1 day (day 16), 2 days (day 17), 3 days (day 18), 4 days (day 19), 1 week (day 23) or 2 weeks (day 30) after the single challenge on day 15.

Results: There was a significant increase in bronchial hyperresponsiveness (and the percentage of neutrophils (12%) 24 hours after the challenge with AP in AP-sensitized mice. The peak response in AHR and neutrophil inflammation was found 48h post-challenge. From then onwards, both the bronchial hyperresponsiveness and the percentage of neutrophils decrease gradually. Levels of total serum IgE increased significantly, reaching a peak three days after challenge, after which the level returned to baseline 23 days post-challenge. Overall, after two dermal sensitizations, followed by a single challenge, the asthmatic response decreases in time, with initially only decreases in respiratory and inflammatory responses, but later also in the immunological responses.

Conclusion: The finding that an occupational factor (i.e., working in traditional farms) is associated with respiratory symptoms and bronchial hyperresponsiveness in dairy farmers is significant and should be considered in future studies.

P4358

Metalworking fluids, machine operator’s lung and serological diagnosis evolution

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Machine operator’s lung (MOL), has been related to Mycobacterium immunogenum (MD) growing in metalworking fluids (MWF). Our contribution to the serological evolution of MOL diagnosis is a 3 step story:

1. Sera from 13 MOL cases from the same plant, and 30 controls were tested again MOL antigen (Ag). MI was identified in 40% of used MWF (n=83/1 plant).
2. The threshold for differentiating MOL cases from controls was 5 arcs (sensitivity (Se) 77% and specificity (Sp) 92%), as determined by electrosyneresis (ES). Using ES, the agglutination index (MI) antigen (Ag). MI was identified in 40% of used MWF (n=83/1 plant).
3. Recombinant antigens (rAg) were expressed in Escherichia coli and tested by ELISA. From the 350 spots visualized, 6 immunogenic proteins were obtained by using rAg. But whereas other strains was isolated in Germany from 3 new farms, MD was identified in 40% of used MWF.

Several studies have suggested an increased risk of chronic obstructive pulmonary disease (COPD) among dairy farmers despite a lower prevalence of smoking compared with general populations. The prevalence of COPD among farmers, and the occupational factors associated with COPD are however unknown.

We therefore retrospectively analyzed respiratory symptoms (forced vital capacity [FVC], and forced expiratory volume in one second [FEV1]), occupational and medical questionnaires in 3 cohorts of dairy farmers. All studied subjects (n=590) were males without asthma and/or hyperresponsiveness problems.

COPD (15.9 vs. 7.9%, p=0.03 and 30.3% vs. 10.6%, p<0.0001 respectively). On multivariate analysis, the three independent factors associated with COPD were an older age (adjusted odds ratio [95% confidence interval]: 1.04 [1.02-1.07]), tobacco smoking (2.83 [1.29-6.19]) and low modernity of farms (2.89 [1.48-5.63]).

Moreover, the association between tobacco smoking and working in traditional farms seemed to be synergistically linked with COPD in this population.

The finding that an occupational factor (i.e., working in traditional farms) is independently associated with COPD in dairy farmers suggests that prospective studies should be conducted in this population in order (1) to identify etiologic factors of COPD and (2) to characterize the COPD patients in terms of distortion, exercise capacity and cardiovascular comorbidities.

P4361

Prevalence of chronic respiratory symptoms, ventilatory capacity and bronchial responsiveness in welders

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Objective: To evaluate the prevalence of chronic respiratory symptoms, ventilatory capacity abnormalities and bronchial hyperresponsiveness in welders and to clarify the role of workplace exposure.

Methods: A cross sectional study was performed including 40 male workers working as stainless steel welders (mean age=43.9±7.4; duration of exposure 15.2±6.8 yrs) and 40 male office workers as a control group (mean age=42.8±7.1) matched for age, duration of employment, smoking habits and socioeconomic status. Evaluation of examined subjects included completion of a questionnaire on respiratory symptoms in the last 12 months (cough, phlegm, dyspnea, wheezing, and chest tightness), spirometry and histamine challenge (PC20≤8 mg/mL).

Results: We found non-significantly higher prevalence of respiratory symptoms in the last 12 months in welders with significant difference for cough (P=0.036).
and phlegm (P=0.007). Mean values of spirometric parameters was lower in welders with significant difference for MEF25 (P=0.006) and MEF75 (P=0.000). Prevalence of bronchial hyperresponsiveness (BHR) was higher in welders with significant difference for borderline BHR (P=0.041). Multivariate analysis showed that current smoking (OR=8.4, 1.6 to 81.7) and total exposure to welding fumes with duration of more than 10 years (OR=8.2, 1.7 to 69.8) were independent risk factors for development of chronic respiratory symptoms.

Conclusion: Our data suggest that workplace exposure in welders may lead to respiratory impairment that on the other hand is closely related to its duration.

P4362
The effect of radiographic abnormalities on mental health of former workers and residents of Wittenoom in Western Australia
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Introduction: Exposure to asbestos causes radiographic abnormalities such as pleural plaque (PP), diffuse pleural thickening (DPT) and asbestosis. Knowledge of presence of these radiographic abnormalities may affect individuals’ mental health (MH).

Aim: The aim of this study is to examine the effect radiographic abnormalities on the MH of people exposed to crocidolite.

Method: Subjects were former workers and residents of Wittenoom, a crocidolite mining town in Western Australia, who had participated in an Asbestos Review Program. The diagnosis of PP, DPT or asbestosis was determined from plain chest x-rays. In 2007, participant had completed a questionnaire that included questions on mental health status (SF-12) and sense of personal control (SOPC). Generalised linear modelling was used to relate the presence of PP, DPT and asbestosis to MH scores and SOPC scores controlling for asbestos exposure measurements, smoking status, other cancers, general physical health and demographic variables.

Results: A diagnosis of asbestosis was significantly associated with worse MH status (β = -0.04; 95% CI -0.079 -0.004; p=0.031) but not SOPC. The presence of PP and DPT were not related to either poor mental health or reduced SOPC.

Conclusion: The presence of PP or DPT, in the absence of other disease, do not seem to affect the mental health of crocidolite exposed subjects from Wittenoom compared to exposed persons without radiographic abnormalities. However, patients with asbestosis have evidence of worse MH compared to other asbestos exposed individuals.