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Title: Alpha-1-antitrypsin phenotype and endotoxin exposure are related to BHR but not to change in lung function in a 15 year follow up of young Danish farmers

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Body: We have earlier shown that farming exposure interacts with rare Alpha-1-antitrypsin (α 1-AT) phenotypes in relation to BHR*. We studied 1,964 farming students and 407 controls in 1992/4, and 963 and 172 of these again in 2007/8. Spirometry, a health questionnaire, smoking and occupational history were collected each time. Cumulative dust and endotoxin exposures were estimated from job-exposure matrices based on personal dust measurements. Lung function change was expressed as Δ z-scores using the LMS equations (Stanojevic S, et al. AJRCCM 2008; 177: 253-60). We also studied bronchial hyperresponsiveness using the Yan method with Metacholine. People with an α 1-AT serum concentration <22 mM were tested for phenotype. For subsequent analyses, the different α 1-AT Pi-groups were collapsed into three groups: 1) MM & MX; 2) MS & MZ; 3) SZ, SS, ZZ. Table 1 shows the OR (95% c.i.) for BHR at follow up according to Pi-group, endotoxin exposure and smoking in the cohort. It can be seen, that all three variables were significantly associated to an increased OR for BHR. This confirms our earlier finding in the cohort. However we were not able to show any significant interaction between Pi-types and exposure. No effect of the Pi types were found on lung function change, neither for FEV1 nor for FVC.

The association between alfa-1-antitrypsin Endotoxin and BHR

| | OR | 95% low | 95% high |
|--------------|------|---------|----------|
| Alfa 1 MM | 1 | | |
| Alfa 1 MSZ | 1.04 | 0.50 | 2.15 |
| Alfa 1 SZ | 7.60 | 1.13 | 51.3 |
| Endotoxin Q1 | 1 | | |
| Endotoxin Q2 | 1.12 | 0.62 | 2.02 |

| | | | |
|--------------|------|------|------|
| Endotoxin Q3 | 1.42 | 0.81 | 2.50 |
| Endotoxin Q4 | 2.04 | 1.16 | 3.57 |

Corrected for smoking, atopi, FEV1

*Sigsgaard et al ERJ 2000.