the carbon monoxide transfer factor (TLCO, a measure of gas distribution and uptake). On the other hand, the carbon monoxide transfer coefficient (KCO), which is a more direct measure of loss of alveolar gas exchanging surface (emphysema), showed no progressive impairment from stage 0 to stage II–IV, which is consistent with the emphysema being reported as minimal to extensive even in the severe group.

The authors analysed the HRCT scan in two ways—firstly, the expiratory to inspiratory lung density ratio which reflects the degree of air trapping and hence small airways disease and, secondly, the proportion of low density areas on the inspiratory scans which reflects the amount of emphysematous tissue. Using the latter data, there was no correlation with KCO which is at variance with other studies of patients with emphysema.[11 12] This again suggests that the results are influenced by the mild degree of emphysema seen in many of the patients. Indeed, the average proportion of low density areas seen in the three groups on the inspiratory scan (5.8–11.4% in table 1 of the paper[10]) confirms this to be the case. Of particular importance is the failure of the neutrophil counts to correlate with either the CT or physiological assessment of emphysema. This suggests that samples obtained by sputum induction do not reflect the pathological processes at the alveolar level which reflect the development of emphysema, emphasising a compartmentalisation of inflammation and pathology.

On the other hand, the expiratory CT parameters and the expiratory to inspiratory ratios showed good correlation with tests of airflow obstruction and air trapping but not with gas transfer. The degree of neutrophilia of the induced sputum also showed good correlations with these measures, suggesting that the inflammation harvested by this technique reflects pathological processes at the level of the small airways.

This study has important implications. Although associations in cross sectional studies do not reflect cause and effect, the findings of this study suggest that sputum induction does not reveal pathogenic processes involved in emphysema but rather the factors influencing or influenced by small airways pathology. It is therefore more critical that future studies should clarify the phenotype of the patients being studied so that conceptual quantum leaps in pathophysiology are not made. Standardisation of algorithms used in the CT scan and more radiopathological comparisons and analytical techniques offer a real opportunity to study the pathophysiological processes involved in structural changes within the lung and, more importantly, their progression or response to treatment.

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Pi MZ and COPD

Pi MZ and COPD: will we ever know?

N Seersholm

Based on the current evidence, there is no reason to believe that Pi MZ individuals have an increased risk of developing lung disease as long as they do not smoke

Is Pi MZ a risk factor for the development of chronic obstructive pulmonary disease (COPD)? That is the question many authors have tried to answer during the last decades, but the results of published studies are still conflicting.

A very high percentage of patients with COPD have been smokers, but not all smokers develop COPD. There must be other contributing factors and, with a Pi MZ prevalence of 3–5% in many Western countries, it is relevant to determine whether this genotype is an additional risk factor for COPD.[1] Furthermore, if a dose-response relation exists, it is biologically plausible since plasma levels of α_1-antitrypsin (AAT) are reduced to about 60% in Pi MZ subjects compared with those with the normal Pi MM genotype, and Pi Z individuals with very low levels of AAT have a significantly increased risk for emphysema.

There are a number of reasons for the discrepancy between the studies conducted on this subject. Firstly, smoking is a very significant confounder in the development of emphysema which is almost impossible to control for. Secondly, many studies have been subject to various types of bias, particularly selection bias. Thirdly, only a few studies have been sufficiently large to produce a significant result and very few studies have been population based. Finally, the phenotypic appearance of the Pi MZ genotype may be heterogenic.

In the studies of a causal relationship of a risk factor (Pi MZ genotype) and the development of a disease (COPD) there are two types of designs: case-control studies and cohort studies. Cohort studies can be divided into cross sectional studies and follow up studies.

In case-control studies the researchers identify a group with COPD, find a proper control group without the disease, and compare the prevalence of the Pi MZ genotype between the two groups. The major problems are finding a proper control group from the same population as the cases and selection bias. For example, if a person is known to have the Pi MZ genotype, he may be more likely to have his lungs examined because of Pi Z patients with lung disease in his family. If his lung function is reduced, he suddenly becomes a case instead of a control.

A cohort study compares either the prevalence of COPD in a cross sectional setting or the incidence of COPD in a longitudinal setting of a group of Pi MZ individuals with a matched control group which can be derived from the general population. The longitudinal design is often superior to the case-control design but is much more expensive and time consuming and it may be underpowered. In a longitudinal cohort study it is critical to start counting person years from the date the genotype was established and only to use data collected afterwards. Some authors have used data collected before this date in the calculation of the rate of decline in forced expiratory volume in 1 second (FEV_1), and it can produce biased results.[2] The best cohort studies are population based with large sample sizes, long follow up times, and no selection bias, but only a few have been conducted on Pi MZ and COPD.[3]

When published studies are small and inadequate for drawing a firm conclusion, a meta-analysis may be the solution. In this issue of *Thorax* Hersh and colleagues have combined published case-control studies and cross sectional cohort studies in a meta-analysis and tried to determine whether Pi MZ is a risk factor for COPD.[4] Their conclusion is the same as that of previous review papers—namely, that case-control studies are in favour of an increased risk and cohort studies are not.[5] Their final conclusion is that Pi MZ individuals have a small increased risk for COPD or a fraction of Pi MZ individuals carry a larger risk.

Seersholm *et al* came to the same conclusion in a study of Pi MZ individuals identified through relatives of Pi Z patients either because of lung symptoms (index cases) or through family screening.[6] The study showed an increased risk for hospitalisation for COPD in Pi MZ individuals, but subanalysis showed the increased risk to be present only in Pi MZ individuals who were close relatives to Pi Z index patients.

If only a percentage of Pi MZ individuals are at increased risk for COPD, they must carry additional risks—either environmental, genetic, or both. Smoking is the major environmental confounder and only five of the 16 studies included in the meta-analysis corrected for smoking. The pooled odds ratio for these five studies was not significantly increased after adjustment for smoking habits. It is tempting to conclude that the apparent increased risk for COPD found in Pi MZ individuals is caused by differences in smoking habits and not by the Pi MZ genotype. If this is true, Pi MZ individuals should be more susceptible to start smoking and therefore their smoking habits are determined by their genotype. This is not unlikely if the Pi MZ persons were identified through family screening and thus are subject to selection bias. The vast majority of Pi Z index cases have been smokers and smoking habits are influenced by parents and siblings and thus aggregate in families.[7]

The difficulty in discriminating between environment and genes is further demonstrated in a recently published study by Svanes and colleagues who concluded that intrauterine and environmental exposure to parental smoking was related to the development of lung disease in adulthood.[8] It is, however, also possible that modifier genes (Z allele or others) were responsible for some of the increased risk for lung disease.

Silverman *et al* investigated quantitative phenotypes in 52 Pi MZ first degree relatives of Pi Z patients with or without significant airflow obstruction. They found a trend towards lower FEV_1 in Pi MZ relatives of Pi Z subjects with airflow obstruction, a trend that could not be explained by differences in smoking habits.[9] A Danish study of Pi Z patients found that Pi Z index cases have a worse prognosis than Pi Z non-index cases even after controlling for smoking habits, and never smoking non-index cases had no increased mortality compared with the general population.[10] These studies suggest that other genetic factors contribute to the development of lung disease.

Besides protease inhibitor deficiency alleles, no candidate genes for the development of COPD have yet been identified although several have been proposed—including α_1-antichymotrypsin, glutathione S-transferase, and tumour necrosis factor α.[11] Linkage analysis of pedigrees ascertained through probands with severe early onset COPD who had normal AAT levels have shown a susceptibility locus on chromosome 2 and possibly several other genomic regions.[12]

The development of COPD is a complex interaction between environmental exposure and possible many genes, and whether Pi MZ is one of the genotypes remains to be shown. Observational studies and meta-analyses based on them should be interpreted very carefully, particularly in view of the impact of smoking and biased case selection. For example, if the study by Seersholm *et al* had included Pi MZ relatives of Pi Z index cases only, the conclusion would have been that all Pi MZ individuals are at increased risk of hospitalisation for COPD. The variability of quantitative phenotypes of homozygous AAT patients is ideal for the further study of modifier genes but, because of the rarity of the disease, international collaboration will be necessary.

To determine whether Pi MZ is a risk factor for COPD requires a large population based study with long follow up time. The most recently published study found no accelerated decline in FEV_1 in 57 Pi MZ individuals followed for an average of 15 years, but the study may be underpowered.[3] In 1991–4 the Copenhagen city heart study genotyped a sample of 9000 individuals from the general population and identified 450 Pi MZ subjects. They have completed questionnaires on smoking habits and have undergone extensive testing including spirometry and, with a follow up time of more than 10 years, the study should soon come up with a sound conclusion. In the meantime, we have to advise individuals with the Pi MZ genotype about their risk for developing lung disease and, based on the current evidence, there is no reason to believe they have an increased risk as long as they do not smoke.

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Environmental allergen exposure, sensitisation and asthma

Environmental allergen exposure, sensitisation and asthma: from whole populations to individuals at risk

A Custovic, A Simpson

To prevent asthma and allergies we need to design interventions appropriate for individual susceptibilities, taking account of both genes and the environment

Sensitisation to inhalant allergens remains a major risk factor for asthma,[1] but the size of the effect is hotly debated.[2,3] Several cross sectional studies have suggested a simple dose-response relationship between dust mite allergen exposure and specific sensitisation, both within communities[4–7] and between communities exposed to differing levels of mite allergens.[8] The threshold concentration of 2 μg Group 1 mite allergen per gram of dust for developing mite sensitisation in children at high risk has been suggested, but a much higher cut off level of 80 μg/g appeared significant in low risk children.[4] For other allergens the relationship between exposure and sensitisation is less well defined. Several studies in the US inner city areas reported that children are more likely to become sensitised to cockroach with increasing cockroach allergen exposure,[9] and that high exposure to mouse allergen appears to be associated with an increased prevalence of sensitisation to mouse.[10] Some studies in older children and adults reported a close relationship between specific allergen sensitisation and current domestic exposure for mite and cockroach, but not cat allergen.[5,11] This, together with studies reporting a protective effect of high cat allergen exposure on sensitisation,[12,13] raises the question of whether the dose-response relationship between exposure and sensitisation may be different for different allergens. However, there are remarkably few published data on the longitudinal relationship between allergen exposure and the development of specific sensitisation.

EVIDENCE FROM LONGITUDINAL STUDIES

Several observational birth cohort studies investigating risk factors for the development of allergen sensitisation and asthma have measured allergen levels in dust samples collected in early life to examine the association between allergen exposure and the development of specific sensitisation. The studies were based in Germany,[14] Sweden,[15] Holland,[16] and the UK (Manchester[17] and Ashford cohorts[18]). While this is the optimal study design for conditions which manifest early in life and progress into adulthood, these studies are difficult and expensive to run and it takes many years to obtain meaningful results.

Following several reports by the German Multicenter Allergy Study (MAS-90),[19,20] in this issue of *Thorax* Cullinan *et al* become only the second birth cohort to report the exposure-outcomes relationship presenting their results for sensitisation and atopic wheeze at age 5 years in 552 children.[18] This cohort from Ashford, UK is truly population based; the investigators approached every woman presenting for antenatal care to three general practices in the area. By skin prick testing the children at the age of 5 years to three common allergens (mite, cat and pollen) they identified a rate of allergic sensitisation of 17%, a figure similar to the 19.6% reported in the Isle of Wight cohort at age 4 years.[21] A total of 7% of the children had atopic wheeze. Mite and cat allergen levels were measured in the living room floor at one time point (8 weeks after birth) and the levels were similar to other contemporaneous data from the UK. For the whole population there was no linear dose-response relationship between mite and cat allergen levels and the respective specific sensitisations. For mite, there was an increase in the proportion of sensitised children on moving from the 1st to the 2nd quintile of exposure, after which rates of sensitisation appeared to tail off. For cat, sensitisation increased steadily from the 2nd to the 4th quintile and then tailed off. While this pattern was not significantly altered when children with paternal atopy were considered separately, there was a significant interaction between paternal atopy and mite exposure with a considerably higher proportion of high risk children being sensitised at any given quintile of exposure (except for the lowest).

These results are markedly different from those in the MAS-90 study.[19,20] The population sample in the German study was larger (939 at age 7 years) and differs from the Ashford cohort as it is enriched with high risk children. Rates of sensitisation were compared between children in the lowest and highest quartiles of mite allergen exposure. At the age of 7 those in the highest quartile were significantly more likely to be sensitised than those in the lowest quartile (~14% *v* ~4%). A similar effect was seen for cat allergen exposure and sensitisation to cat.

How do we assimilate these two apparently different sets of results? It is likely that the relationship between exposure and sensitisation differs markedly between children at high risk and those at low risk of allergic sensitisation. The MAS-90 study was weighted with high risk children and the strongest dose-response relationship was seen in this group.[19] On the other hand, the study by Cullinan *et al* is more representative of the general population with allergen exposure likely to be of little relevance for the majority of subjects. In a population of this composition and size with a modest (by Australian