COPD and environmental risk factors other than smoking

11. Atopy, allergy and hyperresponsiveness

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1. Papers identified

The procedures described in "COPD and risk factors other than smoking. 1. Identifying Relevant Papers" were carried out to identify papers (and reviews) that were relevant to atopy, allergy or hyperresponsiveness. In the MEDLINE searches papers relating "COPD" (or "chronic bronchitis" or "emphysema") to any of the terms "atopy", "allergy" or "hyperresponsiveness" were sought.

2. Reviews

A number of the general review papers referred to in the first report refer to atopy, allergy or hyperresponsiveness as risk factors for COPD. A number of these (e.g.[1-5]) do little more than include one or more of the three in their list of risk factors without giving more than a cursory mention of limited evidence or expressing a view as to whether the relationship is causal or not. The 1984 US Surgeon General Report on COLD[6] gives a short discussion of the evidence on atopy and airway hyperresponsiveness, but clearly regard this as insufficient to form any clear judgement. More recent review papers give somewhat conflicting views. For example Jones[7] notes that "Increased AHR is known to be an independent risk factor for development of airways obstruction and smokers are known to have higher levels of immunoglobulin-E (I_gE) and blood eosinophils. However, it is uncertain whether this AHR is related to pre-existing atopy or to structural changes in the airways because of COPD". While Viegi *et al*[8] lists "risk factors for developing COPD", including "atopy (high I_gE)" and "bronchial hyperresponsiveness" among the host factors for which there is good evidence, Sethi and Rochester[9] include an interesting short review of some of the evidence. They note that "The roles of bronchial hyperresponsiveness (BHR) and atopy as risk factors for COPD are

being elucidated. The 'Dutch hypothesis' propounds that COPD is the result of smoking superimposed upon an underlying asthmatic predisposition. In contrast, the 'British hypothesis' suggests that COPD is the result of repeated infections and exacerbations, in the absence of an asthmatic propensity. These mutually exclusive hypotheses have been difficult to prove because non-specific BHR often coexists with many forms of airways disease and cigarette smoking-induced inflammation alone can cause increased BHR", and, after reviewing evidence from a number of studies, conclude that "Atopy and BHR therefore may aggravate smoke-related deterioration of pulmonary function. Conclusive evidence establishing a causal role for these conditions in the development of COPD is lacking, however".

Five reviews specifically relating the factors to COPD were identified in the searches.

The earliest, by deVries *et al*[10], is entitled "Reactivity of the airway to exogenous stimuli". It is not specifically concerned with COPD, but more with chronic non-specific lung disease (CNSLD) generally. It emphasises the difficulties of distinguishing the various factors playing a role but does not make any firm conclusions.

The next, by Weiss in 1987[11] is a brief article in the New England Journal of Medicine centring mainly on results reported by Burrows from the Tucson study (see section 3). It concludes that "it remains to be seen whether atopy and airways responsiveness modify the risk of disease occurrence and whether treatment will influence its prognosis".

Two years later O'Connor, Sparrow and Weiss[12] produced an extensive review, "The role of allergy and non-specific airway hyperresponsiveness in the pathogenesis of chronic obstructive pulmonary disease", with over 200 references. The first part of their summary is repeated below for convenience:

"Although the information that has been reviewed leaves many questions unanswered, some conclusions can be drawn from available data.

(1) Smoking appears to increase the risk of sensitization to certain inhaled antigens encountered in the workplace; however, there is no definite evidence that smoking increases the frequency or intensity of allergy to common aeroallergens in the general population. On average, smokers have higher serum total IgE concentrations and blood eosinophil counts than do nonsmokers, but the mechanisms underlying these alternations are not clear. Analysis of these relationships is complicated by observations suggesting that atopic persons are less likely to become and to remain regular cigarette smokers.

(2) Long-term cigarette smoking may be associated with increased non-specific airway responsiveness, although the magnitude of this effect is relatively small when one adjusts for prechallenge level of pulmonary function. This effect of smoking may be more pronounced in atopic persons.

(3) Atopy, as assessed by skin testing and serum IgE concentrations, is associated with asthma, non-specific airway hyperresponsiveness, and reduced pulmonary function level in population data. However, there is no clear evidence that atopy is a risk factor for irreversible airflow obstruction in persons without asthma. Population data do not indicate how much of the reduction in pulmonary function associated with atopy and asthma is potentially reversible.

(4) Blood eosinophil count appears inversely related to the level of pulmonary function and directly related to the rate of decline of pulmonary function among nonsmokers. Reports vary concerning whether the relationship of eosinophil count to level of pulmonary function remains after excluding subjects with diagnosed asthma. This relationship may be determined largely by a clinically distinguishable subset of nonsmokers with 'asthmatic bronchitis.' Presumably, these observations reflect an adverse impact of eosinophilic inflammation in the airways or lung parenchyma. It is not clear whether this represents an allergic response because skin-test reactivity to common aeroallergens and serum total IgE concentration do not

show similar relationships to reduced level and rapid decline of pulmonary function.

(5) Among smokers, non-specific airway hyperresponsiveness appears to be associated with an accelerated longitudinal decline of pulmonary function, although most studies indicating this association are limited by either a retrospective design or lack of adjustment for prechallenge level of pulmonary function. Perspective [*sic*] data have been reported recently, suggesting that this association exists irrespective of adjustment for prechallenge for FEV_1 and that it is not significantly modified by smoking status. The mechanisms underlying this association remain speculative. It is not clear whether airway hyperresponsiveness is a risk factor that precedes and predisposes to the development of chronic airflow obstruction or is instead a manifestation of the airway inflammation, airway narrowing, and reduction of tractional support of the airways that characterize COPD".

Postma and Rijcken (1997)[13]is a shorter review of "the role of atopy and hyperresponsiveness in the development of COPD". The abstract states that "Smoking is the main risk factor for development of chronic obstructive pulmonary disease (COPD), leading to disease in 15% of smokers. Susceptible smokers appear to be those with atopy and hyperresponsiveness. Studies have investigated atopy by serum levels of immunoglobulin E (IgE), positive skin tests or peripheral blood eosinophilia. The interrelationships of these factors and the different populations studied for these relationships limit interpretation of results. Nevertheless, the general feeling is that atopy may predispose to the development of COPD.

More insight has been gained into hyperresponsiveness as a risk factor for development and progression of disease. The risk for COPD increased with more severe hyperresponsiveness independent of atopy, smoking and level of forced expiratory volume in one second (FEV_1). The extent to which these factors are determining small and large airway disease has yet to be

established. Whether intervention targeting these factors prevents rapid decline in lung function, is also unknown, at present."

The final review, by Weiss in 2000[14] concerned "Atopy as a risk factor for chronic obstructive pulmonary disease. Epidemiological evidence". It is quite brief, concluding that "Atopy appears to be an important factor in at least three ways. First, it is the primary influence on persistence of asthma in childhood and, hence, may contribute to decrease in maximal attained level of lung function. Second, it appears that, independent of airway responsiveness and level of FEV_1, it is related to accelerated decline in FEV_1 in later adult life, independent of cigarette smoke. Finally, and this is not proven, it may have relationships that enhance inflammation by interacting with cigarette smoking and airway responsiveness to produce disease".

3. Specific studies

Åhman *et al* (1995)[15] studied 130 industrial arts teachers and 112 other school employees in Sweden. Medical Research Council (MRC) chronic bronchitis (CB) was associated with atopy (self-reported atopic dermatitis, hay fever or asthma during adolescence), after adjustment for smoking and other risk factors, with an OR of 3.67 (95% CI 1.35-9.98).

Annesi *et al* (1987)[16] surveyed 912 working men in 1980/81 and 1985/86 in France. Methacholine BHR was assessed at the end of follow-up in 329 men. Skin prick tests were also performed at this time. In a multiple regression analysis among ever smokers, FEV_1 decline over the five-year period was significantly ($p = 0.04$) greater in methacholine reactors but no relationship to atopy was seen. Neither BHR nor atopy was related to FEV_1 decline in never smokers or in the whole population.

Armentia *et al* (2007)[17] carried out a case-control study in Spain with various groups including 60 patients with nonallergy bronchial obstructive disease, 20 of which were diagnosed as having COPD, and 60 healthy non-smoking controls. It is stated that tobacco sensitivity was 8% in COPD patients and 0%

in the controls. However, the 8% was given as 5/60 and presumably relates to all the patients with nonallergy bronchial obstructive disease, which also includes patients with intrinsic asthma and with lung cancer. It is also noted that "a delayed bronchial and patch response was more common in patients with COPD ($p<0.001$)" though which comparison group is unclear. Generally, the paper is difficult to follow.

Brutsche *et al*[18] reported results from the SAPALDIA prospective study in Switzerland in which BHR to methacholine was evaluated in 1991, with prevalence of COPD (defined by a ratio of forced expiratory volume in 1 second [FEV_1] to forced vital capacity [FVC] <0.70 and no physician's diagnosis of asthma) determined in 2002 in 4852 of the subjects. After adjustment for a range of factors, including atopy at baseline and smoking in 2002, the OR for COPD was 4.5 (3.3-6.0). A strong association of BHR to CB (presence of chronic cough or phlegm) was also noted. Participants diagnosed with asthma between 1991 and 2002 were excluded from these analyses.

Burrows *et al* (1982)[19] reported cross-sectional results from the Tucson study in which serum immunoglobulin E (IgE) was related to various respiratory symptoms. In the total population of some 2400 subjects aged 15+, no relation was seen between IgE and the prevalence of CB. However, in a subset of 425 allergy skin test-negative smokers aged 55+ a significant positive association was seen.

Further results from the Tucson study were reported by Burrows *et al* in 1983[20]. Based on 1182 subjects aged 35+ with no past history of cardiorespiratory disease, impairment of FEV_1 showed "a definite relationship to total serum IgE", but only if the low FEV_1 was accompanied by symptoms suggesting asthma or CB. Allergy skin test reactivity to a battery of common aeroallergens showed no overall relationship to FEV_1. However, after accounting for total serum IgE, positive allergy skin tests tended to be associated with high rather than low FEV_1 values.

Later, in 1988, Burrows *et al*[21] carried out further analyses in subjects aged 40-74, for which asthmatics had been excluded. Atopy, eosinophilia and IgE no longer appeared to be significant risk factors for ventilatory impairment, and nonasthmatic non-smokers showed almost no remaining inhibitory impairment.

Later still, in 1991, Burrows *et al*[22] reported further results from the Tucson study for subjects who provided follow-up information after the age of 60. Though the paper mainly concerns factors affecting newly diagnosed asthma, some results are given for COPD, including the statement that "there was virtually no trend for .. COPD .. to increase with increasing levels of IgE ..".

Celli *et al* (2005)[23] evaluated airway obstruction (FEV_1/FVC <0.70) in US adults aged 30 to 80 interviewed in the third National Health and Nutrition Examination Survey (NHANES3) who had never smoked and had valid spirometry. Reported allergy (doctor diagnosed hay fever, two or more episodes of defined nasal or eye symptoms in the last year, or severe reactions to food, pets or allergy tests) was associated with an increased risk of airway obstruction (OR 1.63, 1.11-2.38) after adjustment for a range of other risk factors.

Chaudemanche *et al* (2003)[24] reported results from a longitudinal study in France of 215 dairy farmers and 110 controls. Subjects underwent skin prick tests, total IgE was measured and serum IgE antibodies against a mixture of inhalant allergens was performed using the Phadiatop test. No relation between any indices of allergy and respiratory function changes between 1994 and 1999 were detected, except for FEV_{25-75}.

Chen *et al* (2000)[25] described an analysis of 7210 subjects aged 35-64 who participated in the 1994-95 Canadian National Population Health Survey. COPD, defined as a report of CB or emphysema diagnosed by a health professional, was significantly related to a history of allergy (again diagnosed

by a health professional) in both men and women. ORs were 2.29 (1.23-4.28) in men and 4.00 (2.61-6.13) after adjustment for smoking and other variables.

Choy *et al* (2002)[26] carried out a cross-sectional study of 179 subjects in Hong Kong aged 70+, in which skin prick tests were conducted, and IgE and lung function measured. Presence of positive skin test was unrelated to a history of CB or to a history of emphysema.

In their book "The natural history of chronic bronchitis and emphysema" published in 1976, Fletcher *et al*[27] describe results of an eight-year study of early COPD in working men in London. Data on lung function, recent bronchial infections and mucus hypersecretion were collected in six-monthly surveys conducted between 1961 and 1969. Detailed smoking data were also collected. Allergy was assessed by questions on personal history of asthma and hay fever in 1961, by a detailed allergy questionnaire in 1965, and by the presence of eosinophils in the sputum specimen at three of the surveys. Their detailed analyses divided factors into those that caused irreversible airflow obstruction (smoking) and those that did not (bronchial infection and allergy). For allergy, the authors noted that "Our indices of allergy are imperfect, but the complete lack of correlation of FEV level or slope with a personal or family history of allergic disorders, with variability of FEV readings, or with hyperreactivity to the inhalation of cigarette smoke provides no support for the hypothesis that allergy plays an important part in progressive loss of FEV."

Frew *et al* (1992)[28] reported combined results of four longitudinal occupational health surveys in Canada in which BHR to methacholine was determined, and skin prick tests conducted, at baseline, and in which lung function was recorded at baseline and about 5 years later. In multiple regression analyses conducted in nonasthmatics, the rate of decline of FEV_1 was significantly increased in relation to both BHR ($p = 0.009$) and atopy ($p = 0.04$) in current smokers but no associations were seen in never or in exsmokers.

Gottlieb *et al* (1996)[29] investigated the relationship between skin prick reactivity (dust, mixed grasses, mixed trees, and ragweed) to the rate of decline of lung function in 1,025 US non-asthmatic men in the Normative Aging Study. Changes in lung function over a six-year period were related to reactivity after adjustment for age, height, smoking status and initial lung function. Mean wheal diameter was related to FEV_1/FVC ($p = 0.001$), FEV_1 ($p = 0.05$), but not FVC.

Hospers *et al* (1999)[30] carried out a number of surveys in the Netherlands in 1964 to 1972 during which allergen skin testing was carried out. The subjects were followed until 1995, during which there were 121 primary deaths and a further 137 secondary deaths from COPD. In multivariate analysis, smoking and various other factors were associated with risk of COPD (primary only, or all), but a positive skin test was not. For primary COPD the RR was 1.21 (0.63-2.33) for a positive skin test.

A further analysis of the same cohort study was reported by Hospers *et* al a year later[31], but based on those 2008 subjects who had had a histamine challenge test in 1964-1972. Based on 60 combined primary and secondary COPD deaths, and after adjustment for smoking and other factors, mortality from COPD increased with more severe hyperresponsiveness. "Relative risks of 3.83 (95% CI 0.97-15.1), 4.40 (1.16-16.7), 4.78 (1.27-18.0), 6.69 (1.71-26.1), and 15.8 (3.72-67.1) were associated with histamine thresholds of 32 g/L, 16 g/L, 8 g/L, 4 g/L, and 1 g/L, respectively, compared with no hyper-responsiveness." These analyses also showed no relationship of COPD to a positive skin test.

Itabashi *et al* (1990)[32] carried out a case-control study in Japan which included 60 patients with COPD and 60 age-matched healthy volunteers. Serum IgE was significantly ($p<0.05$) higher in the COPD cases than in the controls, but no difference was seen as regards skin test scores.

In the cohort study in the Netherlands referred to above[30,31], Jansen *et al* (1999)[33] examined whether skin test positivity assessed at the first survey increased the risk of developing respiratory symptoms (including CB) at the second survey, and whether these relationships were the same in subjects with and without airway hyperresponsiveness (AHR) to histamine. Development of all respiratory symptoms tended to be higher in those with AHR but was reduced in those with a positive skin test. These findings were only presented graphically without CI and did not appear to be adjusted for smoking.

Kaukiainen *et al* (2005)[34] carried out a study on 1000 male Finnish construction painters and 1000 carpenters. In a multivariate analysis based on 1028 of those subjects, the OR for CB in relation to atopy after adjustment for smoking, age and occupation was 1.81 (1.16-2.81). Atopy was defined in terms of ever having had asthma, allergic rhinitis or atopic dermatitis.

Kotaniemi *et al* (2005)[35] carried out a cross-sectional study in Finland in adults aged 21-70. COPD, as defined by the GOLD or BTS criteria, was not related to skin-prick positivity, after adjustment for smoking and other risk factors, with ORs of 1.59 (0.60-4.19) and 0.62 (0.19-2.06) respectively.

Krawczyk *et al* (1975)[36], in a study in Poland, compared the results of various indices of allergy in 230 cases of CB and 50 healthy individuals. The authors report in their abstract that "In 31 per cent of chronic bronchitics, at least two traits of allergy were found as well as positive skin tests to various allergens. In this group of the patients examined the role of an allergic factor in their disease seemed the most likely" and that "It was found that house dust played the most important role in allergic manifestations of the respiratory tract." However, the abstract does not mention any results in the controls. Assessment of this paper would require a translation of the Polish text, only the abstract being in English.

Lebowitz *et al* (1995)[37] described further results from the Tucson study. Comparison was made between subjects with diagnosed CB and other

subjects, having removed those with diagnosed emphysema and asthma from the data set. The paper mainly concerns eosinophilia, but the authors did report (without giving detailed results) that "persistent and newly diagnosed CB without diagnosed asthma was not associated with high IgE or skin test reactivity, and eosinophilia was also independent of these factors. Likewise, diagnosed CB was not related to allergic rhinitis (or other allergic diseases)."

Leino *et al* (1997)[38] reported results from a cross-sectional study in Finland of hairdressers and saleswomen. In a logistic regression model, hairdressing, smoking, age and atopy (OR 2.1, 1.0-4.3) were significantly associated with CB defined by questions on symptoms. Presence of atopy was based on ever having had asthma, allergic rhinitis or atopic dermatitis.

Meijer *et al* (2001)[39] evaluated 314 dust-exposed workers in the Netherlands. COPD was defined as an FEV_1/FVC ratio outside the 5^{th} percentile. There was no significant difference between the frequency of a history of allergic symptoms between workers with COPD (5/24 = 21%) and without COPD (40/290 = 14%).

Mensin *et al* (1992)[40] studied the relationship of skin test reactivity and eosinophilia to the level of FEV_1 in a community cohort in the Netherlands. After adjustment for height, age, area of residence and smoking habits, and comparing to those with no skin test reactivity or eosinophilia, FEV_1 was nonsignificantly higher in those with skin test reactivity alone, but was significantly ($p<0.01$) lower in those with eosinophilia alone, or skin test reactivity in combination with eosinophilia. Based on approximate significance tests from the data presented, skin test reactivity was associated with a significantly ($p<0.05$) lower FEV_1 in those with eosinophilia, but not in the whole population.

Miller *et al* (1976)[41] compared 111 US subjects with COPD who had an FEV_1 less than 70% of that predicted with control subjects matched for age, sex, occupation and smoking history with an FEV_1 85% or more of that predicted.

The authors noted a similar frequency of reported hives, eczema, hay fever, nasal polyps, or sinus surgery and "allergy" in the two groups. The types of allergy noted were also similar in both groups.

In a study in Newcastle-upon-Tyne, Ogilvie and Newell (1957)[42] compared 464 confirmed chronic bronchitics and 485 controls with a confirmed diagnosis of no bronchitis. "A personal history of allergic manifestations (asthma, rhinitis, eczema, or nettle rash) was significantly associated with the disease in each sex. 31 per cent. and 39 per cent. of the male and female bronchitics respectively had a history of allergy, as compared with 15 per cent. for each sex of the controls ($P < 0.001$ in each)."

Omenaas *et al* (1995)[43] carried out a cross-sectional community study in Norway in which serum IgE and level of lung function were measured in 1233 adults aged 18-73. Increasing IgE was associated with reduced FEV_1 ($p<0.01$), with the relationship similar by sex, age and smoking habits.

Based on a study showing a relationship of total serum IgE level to a decreased level of FEV_1, Orie *et al*, in 1961[44] hypothesized that increased airway responsiveness and allergy might be endogenous factors predisposing individuals to the development of CB and emphysema. [The paper was not obtained, the summary being based on statements by Weiss[14,45].]

Parker *et al* (1990)[46] reported on 790 US men aged 40-79, free of known chronic medical conditions upon entry to the study, who were followed for at least 14 years. They had regular FEV_1 measurements taken and, at the end of follow-up, had a methacholine challenge test; IgE was measured and atopic status was measured by a skin prick test. The annual rate of adjusted FEV_1 decline was associated with greater methacholine responsiveness in current, former and never smokers. No significant correlation was seen between FEV_1 decline and IgE. Within groups stratified by smoking and methacholine responsiveness, there were no consistent differences in the rate of FEV_1 decline between skin test positive and skin test negative subjects.

Rijcken *et al* (1995)[47] studied the association of AHR to histamine with FEV_1 decline in a prospective study of a random sample of the Dutch population. 1682 paired observations were used in analyses, which adjusted for smoking, baseline FEV_1 residuals, symptom prevalence and other factors. A highly significantly ($p<0.001$) greater decline was seen in both sexes in those with AHR.

Silva *et al* (2004)[48] reported further results from the Tucson study based on 3099 adult subjects followed for a total of 20 years. In Cox proportional hazards analyses, smoking and active asthma were strongly associated with the development of CB, emphysema or COPD. However, no significant associations were seen with IgE or a positive skin test.

Sparrow *et al* (1987)[49] carried out a cross-sectional analysis relating BHR to methacholine to the occurrence of respiratory symptoms and pulmonary function in 458 US male participants in the Normative Aging Study. After adjustment for smoking, age and height FEV_1 and FEF_{25-75} were significantly ($p<0.001$) lower in those with BHR.

Sunyer *et al* (2000)[50] carried out a cross-sectional study in Spain of 1472 subjects aged 20-44. After adjustment for smoking, FEV_1 in females was significantly reduced in relation to methacholine reactivity, and was also reduced in relation to skin reaction to Alternaria and IgE antibodies against cat and Timothy grass. FEV_1 in males was similarly related to methacholine reactivity, and was also reduced in relation to olive. Although these associations were highlighted by the authors, only the associations with methacholine reactivity were highly significant and those with Alternaria, cat and prick olive were not significant at all. Given the range of prick tests and IgE test conducted, it is unclear statistically whether there is any true association except with methacholine reactivity.

Tabona *et al* (1984)[51] studied host factors affecting decline in lung function over 6 years in 267 Canadian male grain elevator workers who did not change

their occupation, or smoking habits over the follow-up period. Atopy, as measured by skin prick tests, was unrelated to the decline in lung function adjusted for age and smoking. In contrast, BHR to methacholine was associated with a significantly ($p<0.05$) greater decline in FEV_1 in current smokers and exsmokers, in FVC in current smokers, and in FEF_{25-75} in current smokers.

Talini *et al* (2003)[52] carried out a study of 461 agricultural workers in Italy. Atopy was noted not to be significantly associated with CB symptoms, but detailed results were not given.

Taylor *et al* (1985)[53] examined the relationships between smoking, BHR to histamine, baseline FEV_1 and annual decline of FEV_1 over 7.5 years in 227 UK men. Men with asthma were excluded. In smokers, FEV_1 decline was associated with BHR and a personal history of allergy, but was not related to a family history of allergic disease, serum IgE, blood eosinophil count or skin prick test score. No significant association of BHR or allergy to FEV_1 decline was seen in exsmokers or never smokers.

Terho *et al* (1987)[54] reported results based on 9483 Finnish farmers participating in postal surveys. Atopy was defined based on past or present eczema, atopic dermatitis or allergic rhinitis. CB was twice as common among atopic as among non-atopic subjects and twice as common among smokers as among non-smokers. Atopy and smoking seemed to have an additive effect on both the prevalence and incidence of CB. Similar results were also reported in another paper[55].

Based on the same study, Terho *et al* (1987)[56] related lung function to atopy and smoking based on 1831 farmers with no symptoms of the lower respiratory tract. Atopy was found to have no effect on mean FEV_1, but mean FVC was lower in atopic subjects within both smokers and non-smokers. The significance of these differences is unclear.

Terho *et al* (1995)[57] reported results from postal surveys carried out in 1975 and 1981 as part of the Finnish twin cohort study. Atopy was defined based on whether a diagnosis of allergic rhinitis or allergic dermatitis had been made by a doctor. CB was defined based on coughing up phlegm on most days for at least 3 months a year. Subjects with diagnosed asthma were excluded. Based on cross-sectional analysis of 1975 data from 18351 subjects, with 1025 prevalent cases, a multiple logistic analysis showed that atopy was associated with CB (RR 1.41, 1.20-1.65), after adjustment for age, sex, smoking and working as a farmer. Based on 553 incident cases occurring during the six year follow-up, similarly adjusted analyses also showed an association with atopy (1.28, 1.02-1.59).

Villar *et al* (1995)[58] reported results from a prospective study in the UK. At baseline, 324 subjects completed a respiratory questionnaire, and underwent measurement of FEV_1 and FVC, BHR to methacholine, skin prick testing and estimation of total serum IgE. 212 underwent further spirometry four years later. In multiple regression analysis, FEV_1 decline was almost significantly ($0.05<p<0.1$) greater in those with BHR, but was not significantly related to atopy or IgE. In ever smokers significant ($p<0.05$) relationships were seen with BHR and atopy.

In a cross-sectional study in 169 farmers in Finland Vohlonen *et al*[59] related the prevalence of CB to smoking and atopy based on a skin prick test. After adjustment for smoking there was a significantly ($p<0.01$) higher CB prevalence in those who were skin test reactive.

Weiss *et al* (1998)[45] investigated the relationship between home allergen exposure and decline in FEV_1 (over a mean 3.8 years) in 10 asthmatic and 30 non-asthmatic US participants in the Normative Aging Study. Concentrations of cockroach allergens in house dust specimens were highly significant ($p<0.001$) predictors of decline in FEV_1 after adjustment for age, smoking and baseline FEV_1, these results being unchanged after eliminating the asthmatic participants. Decline in FEV_1 was not associated with dust mite or cat allergens.

Woolcock *et al* (1987)[60] carried out a cross-sectional study in Australia involving 916 subjects in which BHR to histamine and atopic response to skin prick tests were measured. There was a significant ($p<0.001$) association of BHR to respiratory symptoms, atopy, smoking and abnormal lung function (FEV_1 < 70%, or FEV_1/FVC < 80% of predicted) but no association with age, sex or recent respiratory tract infection. No multivariate analysis was conducted, BHR being related to each factor individually.

4. Summary of the evidence

45 papers were summarized in the previous section. These are not independent as there are a number of cases of multiple publications based on the same study, notably including the study in Tucson[19-22,37,48] and the study in Vlagtwedde and Vlaardingen in the Netherlands[30,31,33,40,47]. The majority of the studies take smoking into account, but some do not.

The evidence relating to BHR (to methacholine or histamine) is very consistent. In prospective studies associations have been consistently reported (which are virtually always significant and often highly so) with COPD death[31], with increased decline in FEV_1 (and in some cases other lung function parameters)[16,28,46,47,51,53,58], and with the development of COPD[18] or CB[33]. Cross-sectional studies have also reported an association of BHR with lung function[49,50,60]. Some of the studies (e.g.[16,28]) report associations only in smokers.

The evidence relating to IgE is far less convincing. Publications based on prospective studies have reported no significant association with change in lung function[24,46,58] or with COPD development[48]. While there are some reports from cross-sectional studies of associations of IgE with lower lung function[43,44,50] and a report from a case-control study of an association with diagnosed COPD[32], various cross-sectional analyses (all based on the Tucson study) find no clear associations of IgE with lung function[20,21], diagnosed COPD[22], diagnosed CB[37] or symptoms of CB[19].

36 of the 45 papers relate allergy (usually measured by a skin prick test) to various indices of COPD. Of those based on prospective studies, most concern decline in lung function, some finding no significant relationship with allergy[16,24,27,46,51], and some finding a relationship[28,29,45,53,58], though in some cases only in smokers or only with specific allergens. (In that context the strong association with lung function decline seen with concentration of cockroach allergens[45] is of interest.) The remaining prospective studies report no association of allergy with COPD death[30,31], or with the development of COPD[48] or CB[33]. Cross-sectional and case-control studies also report variable conclusions. Studies of lung function that do not report an association with allergy[20,21,26,39,40] clearly outnumber those that do[50,55], and these latter two references are unconvincing in any case. There is more evidence of an association with symptoms of CB, with various reports of an association[15,34,38,54,57,59], interestingly all from Scandinavia, and only one of no association[52]. The remaining cross-sectional studies concern diagnosed COPD or COPD defined based on GOLD (or similar) criteria. Here some studies report an association[17,23,25,42] and some do not[32,35,37,41].

A number of these studies also relate eosinophilia, as a marker of allergy, to indices relating to COPD. The evidence here was considered earlier, in report 5.

5. Conclusions

There are a variety of indices of allergy, atopy and BHR and a variety of endpoints related to COPD. There are also, as discussed in the review papers in section 2, considerable difficulties in interpreting associations as cause and effect and difficulties in removing confounding by other factors. Even where smoking is adjusted for, this is often fairly crude. Nevertheless the strong evidence of an association of BHR with decline in FEV_1 and onset of COPD, and the weaker evidence for an association with skin test sensitivity and other indices of allergy suggest that atopy, allergy and BHR may have a causal relationship to COPD.

6. References

1. Higgins M. Risk factors associated with chronic obstructive lung disease. *Ann N Y Acad Sci* 1991;**624**:7-17.

2. Mannino DM. Chronic obstructive pulmonary disease: definition and epidemiology. *Respir Care* 2003;**48**:1185-91.

3. Mannino DM. Epidemiology and global impact of chronic obstructive pulmonary disease. *Semin Respir Crit Care Med* 2005;**26**:204-10.

4. Silverman EK, Speizer FE. Risk factors for the development of chronic obstructive pulmonary disease. *Med Clin North Am* 1996;**80**:501-22.

5. Snider GL. Chronic obstructive pulmonary disease: risk factors, pathophysiology and pathogenesis. *Annu Rev Med* 1989;**40**:411-29.

6. US Surgeon General. *The health consequences of smoking. Chronic obstructive lung disease. A report of the Surgeon General*. Rockville, Maryland: US Department of Health and Human Services; Public Health Service; 1984. DHHS (PHS) 84-50205. http://www.cdc.gov/tobacco/sgr/index.htm

7. Jones A. Causes and effects of chronic obstructive pulmonary disease. *Br J Nurs* 2001;**10**:845-50.

8. Viegi G, Scognamiglio A, Baldacci S, Pistelli F, Carrozzi L. Epidemiology of chronic obstructive pulmonary disease (COPD). *Respiration* 2001;**68**:4-19.

9. Sethi JM, Rochester CL. Smoking and chronic obstructive pulmonary disease. *Clin Chest Med* 2000;**21**:67-86, viii.

10. de Vries K, Booy-Noor D, van der Lende R, Tammeling GJ, Sluiter JH, Orie NGM. Reactivity of the airway to exogenous stimuli. *Progr Respir Dis* 1971;**6**:66-77.

11. Weiss ST. Atopy and airways responsiveness in chronic obstructive pulmonary disease. *N Engl J Med* 1987;**317**:1345-7.

12. O'Connor GT, Sparrow D, Weiss ST. The role of allergy and nonspecific airway hyperresponsiveness in the pathogenesis of chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989;**140**:225-52.

13. Postma DS, Rijcken B. The role of atopy and hyperresponsiveness in the development of COPD. *Eur Respir Rev* 1997;**7**:159-62.

14. Weiss ST. Atopy as a risk factor for chronic obstructive pulmonary disease: epidemiological evidence. *Am J Respir Crit Care Med* 2000;**162**:S134-S136.

15. Åhman M, Söderman E, Cynkier I, Kolmodin-Hedman B. Work-related respiratory problems in industrial arts teachers. *Int Arch Occup Environ Health* 1995;**67**:111-8.

16. Annesi I, Neukirch F, Orvoen-Frija E, Oryszczyn MP, Korobaeff M, Doré MF, *et al*. The relevance of hyperresponsiveness but not of atopy to FEV_1 decline. Preliminary results in a working population. *Bull Eur Physiopathol Respir* 1987;**23**:397-400.

17. Armentia A, Bartolomé B, Puyo M, Paredes C, Calderón S, Asensio T, *et al*. Tobacco as an allergen in bronchial disease. *Ann Allergy Asthma Immunol* 2007;**98**:329-36.

18. Brutsche MH, Downs SH, Schindler C, Gerbase MW, Schwartz J, Frey M, *et al*. Bronchial hyperresponsiveness and the development of asthma and COPD in asymptomatic individuals: SAPALDIA Cohort Study. *Thorax* 2006;**61**:671-7.

19. Burrows B, Halonen M, Lebowitz MD, Knudson RJ, Barbee RA. The relationship of serum immunoglobulin E, allergy skin tests, and smoking to respiratory disorders. *J Allergy Clin Immunol* 1982;**70**:199-204.

20. Burrows B, Lebowitz MD, Barbee RA, Knudson RJ, Halonen M. Interactions of smoking and immunologic factors in relation to airways obstruction. *Chest* 1983;**84**:657-61.

21. Burrows B, Knudson RJ, Cline MG, Lebowitz MD. A reexamination of risk factors for ventilatory impairment. *Am Rev Respir Dis* 1988;**138**:829-36.

22. Burrows B, Lebowitz MD, Barbee RA, Cline MG. Findings before diagnoses of asthma among the elderly in a longitudinal study of a general population sample. *J Allergy Clin Immunol* 1991;**88**:870-7.

23. Celli BR, Halbert RJ, Nordyke RJ, Schau B. Airway obstruction in never smokers: results from the Third National Health and Nutrition Examination Survey. *Am J Med* 2005;**118**:1364-72.

24. Chaudemanche H, Monnet E, Westeel V, Pernet D, Dubiez A, Perrin C, *et al*. Respiratory status in dairy farmers in France; cross sectional and longitudinal analyses. *Occup Environ Med* 2003;**60**:858-63.

25. Chen Y, Breithaupt K, Muhajarine N. Occurrence of chronic obstructive pulmonary disease among Canadians and sex-related risk factors. *J Clin Epidemiol* 2000;**53**:755-61.

26. Choy DKL, Hui DSC, Li ST, Ko FWS, Ho S, Woo J, *et al*. Prevalence of wheeze, bronchial hyper-responsiveness and asthma in the elderly Chinese. *Clin Exp Allergy* 2002;**32**:702-7.

27. Fletcher C, Peto R, Tinker C, Speizer FE. *The natural history of chronic bronchitis and emphysema. An eight-year study of early chronic obstructive lung disease in working men in London*. New York, Toronto: Oxford University Press; 1976.

28. Frew AJ, Kennedy SM, Chan-Yeung M. Methacholine responsiveness, smoking, and atopy as risk factors for accelerated FEV_1 decline in male working populations. *Am Rev Respir Dis* 1992;**146**:878-83.

29. Gottlieb DJ, Sparrow D, O'Connor GT, Weiss ST. Skin test reactivity to common aerollergens and decline of lung function. The Normative Aging Study. *Am J Respir Crit Care Med* 1996;**153**:561-6.

30. Hospers JJ, Schouten JP, Weiss ST, Rijcken B, Postma DS. Asthma attacks with eosinophilia predict mortality from chronic obstructive pulmonary disease in a general population sample. *Am J Respir Crit Care Med* 1999;**160**:1869-74.

31. Hospers JJ, Postma DS, Rijcken B, Weiss ST, Schouten JP. Histamine airway hyper-responsiveness and mortality from chronic obstructive pulmonary disease: a cohort study. *Lancet* 2000;**356**:1313-7.

32. Itabashi S, Fukushima T, Aikawa T, Yanai M, Sekizawa K, Sasaki H, *et al*. Allergic sensitization in elderly patients with chronic obstructive pulmonary disease. *Respiration* 1990;**57**:384-8.

33. Jansen DF, Schouten JP, Vonk JM, Rijcken B, Timens W, Kraan J, *et al*. Smoking and airway hyperresponsiveness especially in the presence of blood eosinophilia increase the risk to develop respiratory symptoms. A 25-year follow-up study in the general adult population. *Am J Respir Crit Care Med* 1999;**160**:259-64.

34. Kaukiainen A, Riala R, Martikainen R, Reijula K, Riihimäki H, Tammilehto L. Respiratory symptoms and diseases among construction painters. *Int Arch Occup Environ Health* 2005;**78**:452-8.

35. Kotaniemi J-T, Sovijärvi A, Lundbäck B. Chronic obstructive pulmonary disease in Finland: prevalence and risk factors. *COPD* 2005;**2**:331-9.

36. Krawczyk Z. Udział alergii wczesnej w etiopathogenezie przewlekłego zapalenia oskrzeli u dorosłych (The role of early allergy in the etiopathogenesis of chronic bronchitis in adults). *Gruzlica* 1975;**43**:633-9.

37. Lebowitz MD, Postma DS, Burrows B. Adverse effects of eosinophilia and smoking on the natural history of newly diagnosed chronic bronchitis. *Chest* 1995;**108**:55-61.

38. Leino T, Tammilehto L, Luukkonen R, Nordman H. Self reported respiratory symptoms and diseases among hairdressers. *Occup Environ Med* 1997;**54**:452-5.

39. Meijer E, Grobbee DE, Heederik DJJ. Health surveillance for occupational chronic obstructive pulmonary disease. *J Occup Environ Med* 2001;**43**:444-50.

40. Mensinga TT, Schouten JP, Weiss ST, van der Lende R. Relationship of skin test reactivity and eosinophilia to level of pulmonary function in a community-based population study. *Am Rev Respir Dis* 1992;**146**:638-43.

41. Miller RD, Hepper NGG, Kueppers F, Gordon H, Offord KP. Host factors in chronic obstructive pulmonary disease in an upper Mid-west rural community: design, case selection, and clinical characteristics in a matched-pair study. *Mayo Clin Proc* 1976;**51**:709-15.

42. Ogilvie AG, Newell DJ. *Chronic bronchitis in Newcastle-upon-Tyne*. Edinburgh: E and S Livingstone Limited; 1957.

43. Omenaas E, Bakke P, Eide GE, Elsayed S, Gulsvik A. Total serum IgE and FEV_1 by respiratory symptoms and obstructive lung disease in adults of a Norwegian community. *Clin Exp Allergy* 1995;**25**:682-9.

44. Orie NGM, Sluiter HJ, deVries K, Tammeling GJ, Witkop J. The host factor in bronchitis. In: *Bronchitis*. Assen, The Netherlands: Van Gorcum Press, 1961;43-59.

45. Weiss ST, O'Connor GT, Demolles D, Platts-Mills T, Sparrow D. Indoor allergens and longitudinal FEV_1 decline in older adults: the Normative Aging Study. *J Allergy Clin Immunol* 1998;**101**:720-5.

46. Parker DR, O'Connor GT, Sparrow D, Segal MR, Weiss ST. The relationship of nonspecific airway responsiveness and atopy to the rate of decline of lung function. The Normative Aging Study. *Am Rev Respir Dis* 1990;**141**:589-94.

47. Rijcken B, Schouten JP, Xu X, Rosner B, Weiss ST. Airway hyperresponsiveness to histamine associated with accelerated decline in FEV_1. *Am J Respir Crit Care Med* 1995;**151**:1377-82.

48. Silva GE, Sherrill DL, Guerra S, Barbee RA. Asthma as a risk factor for COPD in a longitudinal study. *Chest* 2004;**126**:59-65.

49. Sparrow D, O'Connor G, Colton T, Barry CL, Weiss ST. The relationship of nonspecific bronchial responsiveness to the occurrence of respiratory symptoms and decreased levels of pulmonary function. *Am Rev Respir Dis* 1987;**135**:1255-60.

50. Sunyer J, Soriano J, Antó JM, Burgos F, Pereira A, Payo F, *et al*. Sensitization to individual allergens as risk factors for lower FEV_1 in young adults. *Int J Epidemiol* 2000;**29**:125-30.

51. Tabona M, Chan-Yeung M, Enarson D, MacLean L, Dorken E, Schulzer M. Host factors affecting longitudinal decline in lung spirometry among grain elevator workers. *Chest* 1984;**85**:782-6.

52. Talini D, Monteverdi A, Carrara M, Paggiaro PL. Risk factors for chronic respiratory disorders in a sample of farmers in middle Italy. *Monaldi Arch Chest Dis* 2003;**59**:52-5.

53. Taylor RG, Joyce H, Gross E, Holland F, Pride NB. Bronchial reactivity to inhaled histamine and annual rate of decline in FEV_1 in male smokers and ex-smokers. *Thorax* 1985;**40**:9-16.

54. Terho EO, Husman K, Vohlonen I. Prevalence and incidence of chronic bronchitis and farmer's lung with respect to age, sex, atopy, and smoking. *Eur J Respir Dis* 1987;**71(Suppl 152)**:19-27.

55. Terho EO, Husman K, Vohlonen I, Heinonen OP. Atopy, smoking, and chronic bronchitis. *J Epidemiol Community Health* 1987;**41**:300-5.

56. Terho EO, Husman K, Vohlonen I, Tukiainen H. Lung function of farmers with respect to atopy and smoking. *Eur J Respir Dis* 1987;**152(Suppl)**:183-7.

57. Terho EO, Koskenvuo M, Kaprio J. Atopy: a predisposing factor for chronic bronchitis in Finland. *J Epidemiol Community Health* 1995;**49**:296-8.

58. Villar MTA, Dow L, Coggon D, Lampe FC, Holgate ST. The influence of increased bronchial responsiveness, atopy, and serum IgE on decline in FEV_1: a longitudal study in the elderly. *Am J Respir Crit Care Med* 1995;**151**:656-62.

59. Vohlonen I, Terho EO, Horsmanheimo M, Heinonen OP, Husman K. Prevalence of chronic bronchitis in farmers according to smoking and atopic skin sensitisation. *Eur J Respir Dis* 1987;**152(Suppl)**:175-80.

60. Woolcock AJ, Peat JK, Salome CM, Yan K, Anderson SD, Schoeffel RE, *et al*. Prevalence of bronchial hyperresponsiveness and asthma in a rural adult population. *Thorax* 1987;**42**:361-8.