Histamine airway hyper-responsiveness and mortality from chronic obstructive pulmonary disease: a cohort study

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Summary

Background Smoking and airway lability, which is expressed by histamine airway hyper-responsiveness, are known risk factors for development of respiratory symptoms. Smoking is also associated with increased mortality risks. We studied whether airway hyper-responsiveness is associated with increased mortality, and whether this risk was independent of smoking and reduced lung function.

Methods We followed up 2008 inhabitants of the communities of Vlagtwedde, Vlaardingen, and Meppel (Netherlands), who had histamine challenge test data, from 1964–72 for 30 years. Follow-up was 99% successful (29 patients lost to follow-up) with 1453 participants alive and 526 deaths (246 died from cardiovascular disease, 54 from lung cancer, and 21 from chronic obstructive pulmonary disease [COPD]).

Findings Mortality from COPD increased with more severe hyper-responsiveness; 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 risks were adjusted for sex, age, smoking, lung function, body-mass index, positive skin tests, eosinophilia, asthma, and city of residence.

Interpretation Increased histamine airway hyper-responsiveness predicts mortality from COPD. Although this trend was more pronounced in smokers, an increasing proportion of COPD deaths with increasing hyper-responsiveness was also present among individuals who had never smoked.

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Introduction

Airway hyper-responsiveness, the sensitivity of the airways to a variety of pharmacological and physical stimuli that induce bronchoconstriction, is common in general population samples with a prevalence of 6–35%.[1] Airway hyper-responsiveness is associated with an increased risk of developing respiratory symptoms and asthma[2–4] and more rapid than normal decline in lung function.[5–8] The presence of airway hyper-responsiveness worsens the prognosis of patients with chronic obstructive pulmonary disease (COPD).[9] Airway hyper-responsiveness is also known to be associated with cigarette smoking and reduced lung function,[10] which are in turn associated with mortality.[11,12] Whether airway hyper-responsiveness is directly associated with increased mortality is not known.

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We investigated whether airway hyper-responsiveness was associated with all-cause and cause-specific mortality, and whether these mortality risks were independent of cigarette smoking and reduced lung function. We also studied whether the association was present in individuals without asthma.

Methods

Participants and questionnaire

The study population was selected from several epidemiological surveys on risk factors for asthma and COPD in three Dutch communities.[13,14] In 1964, in Meppel, all men aged 40–65 years were invited to complete a questionnaire on respiratory symptoms. Those who indicated symptoms of asthma or COPD and a random sample of the remainder underwent clinical analysis. In 1965, individuals aged 40–64 years from two additional communities were invited to participate in a questionnaire survey. In Vlagtwedde, 50% (randomly selected) of those surveyed were also invited to undergo clinical analysis. In Vlaardingen, a random sample of all inhabitants in the General District Register were invited to complete the questionnaire and undergo clinical analysis. These surveys were followed by a survey of young people aged 15–39 years in 1967, in Vlagtwedde, and in 1969, in Vlaardingen, as part of a prospective study.

Data on sex, age, smoking habits, and respiratory symptoms were collected by trained interviewers by means of a Dutch version of the UK Medical Research Council's standard questionnaire.[15,16] Ex-smokers were individuals who had stopped smoking at least 1 month before the examination, and current smokers were those who smoked at least one cigarette a day. Pipe and cigar smokers were defined as smokers. Asthma was self-reported and recorded in those who had ever experienced attacks of shortness of breath with wheezing at rest (asthma attacks). Chronic cough and chronic phlegm were defined when present on most days or nights for up to three consecutive months each year during the winter. Dyspnoea grade III or more was present if individuals reported being troubled by shortness of breath when walking with their peers on level ground. Wheeze was defined as a wheezing or whistling sound in the chest on most days or nights.

Clinical analysis

We measured inspiratory vital capacity by deep expiration with a water-sealed spirometer (Lode Spirograph D53, Lode Instruments, Groningen, Netherlands), followed by forced expiratory volume in 1 s (FEV_1). Participants performed the manoeuvres until two technically satisfactory tracings were produced. The higher value of these tracings was taken as the baseline measurement.[14,17] Percentage predicted reference values were calculated with regression coefficients derived from analysis of all symptom-free individuals, irrespective of their smoking habits, who took part in the first survey in 1965, 1967, and 1969 or the second survey in 1970 and 1972 in Vlagtwedde and Vlaardingen. We calculated regression equations for FEV_1 for both sexes separately as a function of age and height, with an age cut-off of 21 years.

We used a histamine threshold test as an index of non-specific histamine airway responsiveness. Histamine

International Classification of Diseases (ICD) codes, 1964–1995, with disease groups classified according to Mackenbach

Cardiovascular disease
ICD 7: 330–334, 400–416, 420–422, 430–434, 440–447, 450–456, 460–468, 782.4
ICD 8: 390–398, 400–404, 410–414, 420–429, 430–438 (excluding 444.2), 450–458, 782.4
ICD 9: 390–398, 401–405, 410–417, 420–438, 440–448, 451–459. 785.4
Lung cancer
ICD 7: 162, 163
ICD 8: 162, 163.0, 163.9
ICD 9: 162, 163, 165
COPD
ICD 7: 501–502, 526, 527.1
ICD 8: 490–492, 518
ICD 9: 490–492, 494, 496

challenge test was assessed by the method of Tiffeneau in a random sample of 25% of the study population.[18,19] After baseline measurements of pulmonary function, participants inhaled nebulised distilled water from a Wiesbaden Doppel inhalator (Wiesbadener Inhalator, Wiesbaden, Germany). If inspiratory vital capacity or FEV_1 decreased by at least 10%, the test was stopped. Otherwise, the test proceeded with the application of sequential aerosols of histamine biphosphate (1 g/L, 4 g/L, 8 g/L, 16 g/L, 32 g/L). Each concentration was inhaled for 30 s, after which two inspiratory vital capacity and FEV_1 manoeuvres were done. A concentration that produced a persistent decline of 10% or more of inspiratory vital capacity or FEV_1 compared with baseline was defined as the threshold value. Individuals with an FEV_1 below 1·5 L, who could not perform a forced expiration, or who suffered from heart disease or hypertension, were not tested. Histamine airway hyperresponsiveness was defined by a threshold value of 16 g/L histamine or less.[2,7] We used both the dichotomous variable and the actual threshold values for data analysis.

Eosinophil counts were assessed in a 1:11 dilution of peripheral blood with a Bürker counting chamber.[14,20] Eosinophilia was defined as at least $2{\cdot}75\times10^8$ cells/μL.

Participants also underwent allergen skin testing. Four common aeroallergens were applied intracutaneously to the volar forearm: house dust, mixed pollen, epidermal products, and mixed moulds[14,20] (Diephuis, Groningen, Netherlands). Wheal diameters for each allergen were coded on a six-point scale (0, 0–5 mm; 1, 5–7·5 mm; 2, 7·5–10 mm; 3, 10–12·5 mm; 4, 12·5–15 mm; 5, >15 mm). Scores for the four allergens were added to a skin test sum score (minimum 0, maximum 20), and defined as positive when this score equalled 3 or more. A histamine biphosphate solution was used as a positive control.[14,21]

Body-mass index was calculated and divided into four classes: underweight (<18·5 kg/m²), normal weight (18·5–25 kg/m²), overweight (25–30 kg/m²), and obese (≥30 kg/m²).[22]

Follow-up surveys

2067 participants had histamine airway responsiveness tested in 1964–72; 59 were excluded because of missing data on peripheral eosinophil count, skin tests, lung function, smoking habits, or respiratory symptoms, resulting in 2008 men and women with complete data for all other covariates. If data on histamine airway responsiveness were not available in the first survey but were available in the first follow-up survey in 1970 in Vlagtwedde or in 1972 in Vlaardingen, data from this first follow-up were used (619 cases). All participants were traced until March 10, 1995, and their vital status (1453 alive, 526 dead) was assessed with 99% success (29 lost to follow-up). Survival time was calculated for each participant from the date of entry until the end of follow-up—March 10, 1995, for individuals registered at the municipalities as being alive; the date of death for individuals identified in the death register of the municipalities; or the last registration of individuals lost to follow-up. Causes of death were obtained from Statistics Netherlands (Voorburg) who coded the primary (maximum 1) and secondary death causes (maximum 3) according to the International Classification of Diseases (panel). The disease groups were classified according to Mackenbach.[23,24]

	All individuals	Individuals without airway hyperresponsiveness	Individuals with airway hyperresponsiveness	p
Number of participants	2008 (100%)	1389 (69%)	619 (31%)	
Sex				
Male	1232 (61%)	834 (60%)	398 (64%)	
Female	776 (39%)	555 (40%)	221 (36%)	0·071
Mean (SD) age (years)	39 (13)	36 (13)	44 (13)	<0·001
Smoking history				
Never	620 (31%)	435 (31%)	185 (30%)	
Ex-smoker	177 (9%)	141 (10%)	36 (6%)	
<15 g/day	752 (38%)	526 (38%)	226 (37%)	
≥15 g/day	459 (23%)	287 (21%)	172 (28%)	0·01
Percentage predicted FEV_1				
Mean (SD)	98% (16)	102% (13)	89% (18)	<0·001
>100%	913 (46%)	750 (54%)	163 (26%)	<0·001
80–100%	857 (43%)	570 (41%)	287 (46%)	
<80%	238 (12%)	69 (5%)	169 (27%)	
Body-mass index				
<18·5 kg/m²	37 (2%)	23 (2%)	14 (2%)	
18·5–25 kg/m²	1013 (50%)	760 (55%)	253 (41%)	
25–30 kg/m²	782 (39%)	504 (36%)	278 (45%)	
>30 kg/m²	176 (9%)	102 (7%)	74 (12%)	<0·001
Residence				
Vlaardingen	848 (42%)	648 (47%)	200 (32%)	<0·001
Vlagtwedde	918 (46%)	583 (42%)	335 (54%)	
Meppel	242 (12%)	158 (11%)	84 (14%)	
Positive skin test	257 (12·8%)	179 (12·9%)	78 (12·6%)	0·859
Eosinophilia	237 (11·8%)	161 (11·6%)	76 (12·3%)	0·660
Respiratory symptoms*				
Cough	275 (13·7%)	142 (10·2%)	133 (21·5%)	<0·001
Pleghm	213 (10·6%)	122 (8·8%)	91 (14·7%)	<0·001
Dyspnoea grade III or more	147 (7·3%)	67 (4·8%)	80 (12·9%)	<0·001
Wheeze	130 (6·5%)	51 (3·7%)	79 (12·8%)	<0·001
Asthma attacks	76 (3·8%)	30 (2·2%)	46 (7·4%)	<0·001

Data are numbers (%) unless otherwise indicated.
*Subgroup percentages are proportions of total in group.

Table 1: **Baseline characteristics (1964–72) for all 2008 participants in the general populations of Vlagtwedde, Vlaardingen, and Mepel**

Statistical analyses

The associations of airway responsiveness with all-cause and cause-specific mortality were estimated with Cox's proportional hazards model.[25] Time was defined from initial examination until death. Because of small numbers of deaths due to COPD when restricting to COPD as the primary cause of death, we also included those for whom COPD was a secondary cause of death. Censoring took place when participants were still alive at March 10, 1995, were lost to follow-up (only 1%), or died of a cause other than the one under study in the case of cause-specific mortality.[26] The proportional hazards model accounted for varying durations of follow-up between participants (eg, censoring) and allowed control for potential confounding effects of other risk factors. We controlled for sex, age, percentage predicted

	All individuals	Individuals without airway hyper-responsiveness	Individuals with airway hyper-responsiveness	p
Total	2008	1389	619	
Alive	1453 (72·4%)	1101 (79·3%)	352 (56·9%)	
Lost to follow-up	29 (1·4%)	21 (1·5%)	8 (1·3%)	
Deaths*	526 (26·2%)	267 (19·2%)	259 (41·8%)	<0·001
Cardiovascular	246 (46·8%)	124 (46·4%)	122 (47·1%)	<0·001
Cancers	169 (32·1%)	92 (34·5%)	77 (29·7%)	<0·001
Lung cancer	54 (10·3%)	29 (10·4%)	25 (9·6%)	<0·001
Other	115 (21·9%)	63 (23·6%)	52 (20·1%)	<0·001
COPD†	60 (11·4%)	10 (3·7%)	50 (19·3%)	<0·001
Primary causes	21 (4·0%)	2 (0·7%)	19 (7·3%)	<0·001·
Secondary causes	39 (7·4%)	8 (3·0%)	31 (12·0%)	· ·
Other primary causes	90 (17·1%)	49 (18·4%)	41 (15·8%)	· ·

*Subgroup percentages are proportions of group total. †Primary and secondary causes combined.

Table 2: **Follow-up data and specification of death causes for all participants in 1964–72, during 30 years of follow-up**

FEV_1, smoking habits, body-mass index, and city (as a dichotomous variable: urban area Vlaardingen, rural areas Vlagtwedde and Meppel).[10,27–29] We also adjusted for history of asthma attacks, eosinophilia, and positive skin tests to study whether associations were independent. We then repeated the analyses, excluding participants with a history of asthma attacks. P values were calculated by χ^2 or *t* tests, and significance was defined as $p \leq 0{\cdot}05$ (two-sided).

Results

619 (30·8%) of 2008 participants had histamine airway hyper-responsiveness at the start of the study (table 1). Individuals with airway hyper-responsiveness were older, smoked more heavily, had a lower level of lung function, a higher body-mass index, and significantly more respiratory symptoms, and were less likely to live in Vlaardingen than individuals without hyper-responsiveness.

The mean follow-up time was 23·6 years (SD 6). As of March 10, 1995, 526 individuals had died (table 2). Death was more prevalent in those with airway hyper-responsiveness than in those without. Individuals with airway hyper-responsiveness were more likely to have had COPD either as the primary or a secondary cause of death than those without airway hyper-responsiveness.

Individuals with severe hyper-responsiveness (threshold 1 g/L) had a significantly greater risk of all-cause mortality than those without (threshold >32 g/L, table 3). Figure 1 shows the survival curves for individuals with severe hyper-responsiveness (28 died) compared with those with no threshold (184 died). Airway responsiveness was not associated with mortality from cardiovascular disease or lung cancer, but it was significantly associated with mortality from COPD. The more severe the hyper-responsiveness, the higher the mortality risk of COPD (primary and secondary causes combined). When we excluded COPD as primary, and combined primary and secondary causes of death, the increased risk for all-cause mortality did not disappear. When analyses were repeated with airway responsiveness as a dichotomous variable (threshold ≤16 g/L), hyper-responsive individuals had a 2·49 (95% CI 1·16–5·34) greater risk of mortality from COPD than non-hyper-responsive individuals, but not from all-cause or other cause-specific mortality.

As expected, older age and smoking were associated with increased all-cause and cause-specific mortality, especially mortality from lung cancer and COPD. Furthermore, percentage predicted FEV_1 of less than 80% was significantly associated with increased all-cause mortality, mortality from cardiovascular disease, and from COPD (8·04 [2·79–23·1]). A history of asthma attacks was

	Number of individuals	All deaths (n=526)		Cardiovascular disease (n=246)		Lung cancer (n=54)		COPD, combined primary and secondary (n=60)	
		Relative risk (95% CI)	p	Relative risk (95% CI)	p	Relative risk (95% CI)	p	Relative risk (95% CI)	p
Threshold value of histamin dose									
>32 g/L	998	1·0		1·0		1·0		1·0	
32 g/L	391	0·79 (0·61–1·03)	0·08	0·89 (0·61–1·30)	0·55	0·82 (0·37–1·86)	0·64	3·83 (0·97–15·1)	0·05
16 g/L	286	0·99 (0·76–1·29)	0·93	1·16 (0·80–1·69)	0·43	0·51 (0·20–1·34)	0·17	4·40 (1·16–16·7)	0·03
8 g/L	191	0·96 (0·72–1·28)	0·78	0·90 (0·58–1·38)	0·62	0·92 (0·40–2·15)	0·85	4·78 (1·27–18·0)	0·02
4 g/L	103	1·17 (0·84–1·63)	0·34	1·10 (0·68–1·78)	0·69	1·06 (0·38–2·94)	0·91	6·69 (1·71–26·1)	0·01
1 g/L	39	1·65 (1·05–2·60)	0·03	1·12 (0·54–2·32)	0·76	0·40 (0·05–3·25)	0·39	15·8 (3·72–67·1)	<0·001
Asthma	76	0·80 (0·47–1·34)	0·39	0·73 (0·33–1·63)	0·44	2·30 (0·53–9·97)	0·27	1·47 (0·56–3·90)	0·43
Eosinophilia	237	1·32 (1·04–1·69)	0·02	1·49 (1·05–2·10)	0·02	1·52 (0·75–3·09)	0·24	0·98 (0·46–2·06)	0·95
Positive skin tests	257	0·65 (0·43–0·99)	0·04	0·48 (0·23–0·98)	0·05	0·76 (0·27–2·18)	0·61	0·95 (0·28–3·17)	0·93
Male sex	1232	1·33 (1·00–1·76)	0·05	1·44 (0·95–2·18)	0·09	2·62 (0·70–9·81)	0·15	1·72 (0·55–5·37)	0·35
10-year increase in age		2·92 (2·64–3·22)	<0·001	3·27 (2·80–3·81)	<0·001	2·75 (2·03–3·72)	<0·001	2·90 (2·10–4·00)	<0·001
Smoking									
Never	620	1·0		1·0		1·0		1·0	
Ex-smoker	177	1·36 (0·89–2·08)	0·15	1·38 (0·75–2·55)	0·30	2·67 (0·34–21·1)	0·35	0·90 (0·10–8·42)	0·92
<15 cigarettes/day	752	1·74 (1·32–2·30)	<0·001	1·71 (1·13–2·57)	0·01	4·18 (0·86–20·3)	0·08	4·25 (1·41–12·8)	0·01
≥15 cigarettes/day	459	2·50 (1·82–3·42)	<0·001	2·41 (1·52–3·82)	<0·001	18·0 (3·70–87·9)	<0·001	6·58 (2·03–21·4)	<0·001
Percentage predicted FEV_1									
>100%	913	1·0		1·0		1·0		1·0	
80–100%	857	1·05 (0·85–1·29)	0·65	0·98 (0·72–1·33)	0·88	1·33 (0·68–2·61)	0·40	2·01 (0·71–5·66)	0·19
<80%	238	1·56 (1·20–2·05)	<0·001	1·74 (1·19–2·56)	<0·001	1·79 (0·76–4·23)	0·19	8·04 (2·79–23·1)	<0·001
Body-mass index									
<18·5 kg/m²	37	1·46 (0·74–2·87)	0·28	(0·81 (0·20–3·33)	0·77	1·44 (0·18–11·2)	0·73	2·66 (0·58–12·3)	0·21
18·5–25 kg/m²	1013	1·0		1·0		1·0		1·0	
25–30 kg/m²	782	0·99 (0·82–1·19)	0·89	1·30 (0·98–1·72)	0·07	0·51 (0·28–0·94)	0·03	1·00 (0·57–1·77)	0·99
>30 kg/m²	176	1·18 (0·87–1·62)	0·29	1·41 (0·89–2·23)	0·14	0·21 (0·03–1·57)	0·13	0·43 (0·10–1·93)	0·27
Residence									
Rural	1160	1·0		1·0		1·0		1·0	
Urban	848	0·97 (0·80–1·18)	0·79	1·03 (0·77–1·37)	0·86	1·20 (0·65–2·21)	0·56	0·54 (0·26–1·09)	0·09

Table 3: **Relative risks of airway hyper-responsiveness and all-cause and cause-specific mortality after adjustment for major risk factors for mortality during 30 years of follow-up**

	Total	Histamine threshold					
		>32 g/L	32 g/L	16 g/L	8 g/L	4 g/L	1 g/L
Smoking status							
Never	5/620 (1%)	0/307	0/128	1/90 (1%)	1/58 (2%)	1/24 (4%)	2/13 (15%)
Ex-smoker	1/177 (1%)	0/104	0/37	0/14	0/13	1/7 (14%)	0/2
Current smoker	54/1211 (4%)	3/587 (1%)	7/226 (3%)	9/182 (5%)	14/120 (12%)	10/72 (14%)	11/24 (46%)
<15/day	29/752 (4%)	2/390 (1%)	3/136 (2%)	5/109 (5%)	8/64 (13%)	6/38 (16%)	5/15 (33%)
⩾15/day	25/459 (5%)	1/197 (1%)	4/90 (4%)	4/73 (6%)	6/56 (11%)	4/34 (12%)	6/9 (67%)
Total	60/2008 (3%)	3/998 (<1%)	7/391 (2%)	10/286 (8%)	15/191 (8%)	12/103 (12%)	13/39 (33%)

Table 4: **COPD deaths (primary and secondary) according to smoking habits and histamine threshold**

associated with neither all-cause nor cause-specific mortality, whereas eosinophilia and positive skin tests were associated. Male sex, body-mass index (except 25–30 kg/m^2, which was associated with decreased lung cancer), and city were not significantly associated with mortality.

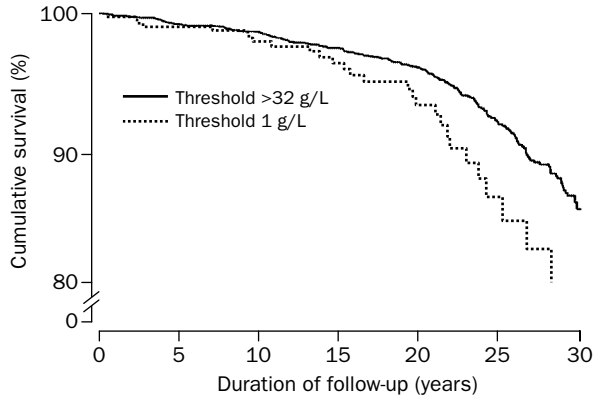
When we repeated analyses restricted to individuals without a history of asthma attacks, the direction and significance of the associations remained unchanged. The relative risk for histamine threshold 1 g/L increased from 16 to 28, and the threshold 32 g/L also became significantly associated with mortality from COPD.

Table 4 shows the proportions of COPD deaths for increasing thresholds stratified for smoking habits. Although increasing trend was more pronounced in smokers with 46% of COPD deaths in the group with severe hyper-responsiveness (threshold 1 g/L), an increasing proportion of COPD deaths with increasing hyper-responsiveness was also present among never smokers. Although the absolute rate of death in the 1 g/L threshold group was substantially higher in heavy smokers (six of nine) than in light smokers (five of 15), the rates in the other histamine threshold groups were similar in these smoking groups.

Participants in Meppel were selected for challenge testing on the basis of respiratory symptoms. Therefore, we repeated the analyses with additional adjustment for the other respiratory symptoms—cough, phlegm, dyspnoea grade III or more, and wheeze—and found that results remained unchanged.

Discussion

Smoking is one of the most important risk factors for COPD.[30] In our population, nearly 61% of individuals smoked, and 23% of these were heavy smokers. In addition to smoking, airway hyper-responsiveness contributes to mortality from COPD, and individuals with airway hyper-responsiveness who smoke have an increased mortality risk from COPD since both characteristics contribute to mortality. We could not analyse whether these people have an extra risk of mortality, because of limited numbers of COPD deaths. We showed in table 4 that the increasing trend was more pronounced in smokers with 46% COPD deaths in the group with severe hyper-responsiveness (1 g/L).



Number at risk

>32 g/L	998	973	957	930	900	585	48
1 g/L	39	35	31	27	21	11	1

Survival curve for individuals with severe histamine airway hyper-responsiveness and individuals with no histamine threshold, 1964–72

Adjusted for sex, age, smoking, lung function, eosinophilia, postive skin tests, asthma, and city (Vlagtwedde, Vlaardingen, Meppel).

Low lung function is a risk factor for mortality.[31] Low lung function and airway hyper-responsiveness can be indicators of the presence of chronic airway inflammation in the lungs, and low lung function is associated with more severe airway hyper-responsiveness.[30] Thus, the increased risk of airway hyper-responsiveness to mortality from COPD might simply have been due to low lung function. This was, however, not the case since both factors independently predicted mortality from COPD with high relative risks. Moreover, when we repeated analyses without lung function, the relative risks associated with decreasing histamine thresholds of 32, 16, 8, 4, and 1 g/L increased substantially with relative risks of 4, 7, 10, 19, and 57, respectively, whereas relative risks associated with smoking remained unchanged.

In previous analyses, peripheral blood eosinophilia was associated with increased mortality from cardiovascular disease, whereas positive skin tests were associated with decreased mortality from cardiovascular disease.[32] Although allergy influences the degree of airway responsiveness,[30] we found that its association with mortality from COPD was independent of eosinophilia and positive skin tests.

Almost all individuals with asthma have airway hyper-responsiveness.[30] We found that airway hyper-responsiveness and not a history of asthma attacks was associated with an increased mortality risk of COPD. In addition, the association between airway hyper-responsiveness and mortality from COPD remained after exclusion of individuals with a history of asthma attacks. Many people with airway hyper-responsiveness in the general population are symptom-free,[1] and we also found that many hyper-responsive individuals (31%) had no history of asthma attacks (only 8%). Airway hyper-responsiveness was strongly associated with the presence of all respiratory symptoms.[33] Our data show that airway hyper-responsiveness was associated with mortality from COPD independent of these symptoms.

Airway hyper-responsiveness is a risk factor for the development of respiratory symptoms[2] and decline of FEV_1.[5–8] Airway hyper-responsiveness is not only important in the development of asthma and COPD, but also predicts mortality from COPD after 30 years of follow-up, independent of other traditional risk factors such as smoking or low lung function. This association is supported by the fact that not only was the association independent of major traditional risk factors as smoking and reduced lung function but it was a dose-dependent relation.

We probably underestimated the association between airway hyper-responsiveness and mortality from COPD. We investigated COPD as combined primary and

secondary causes of death because only 21 individuals had COPD as the primary cause of death. Since airway responsiveness was not associated with mortality from cardiovascular disease, the main primary cause of death for those who died with COPD as a secondary cause, this is likely to result in an underestimation of the risk associated with COPD mortality.

Since airway responsiveness is an integrated physiological response to pharmacological and physical stimuli involving, for example, airway epithelium, inflammatory cells, chemical mediators, and the autonomic nervous system, it is difficult in epidemiological research to separate the type and nature of the observed increase in airway responsiveness. The same level of response can be achieved from different pathophysiological mechanisms—eg, in a young person with asthma the response might indicate increased airway inflammation, and in an older smoker it can indicate heightened vagal tone.[30] If hyper-responsiveness signifies susceptibility of the lung to inhaled particles and subsequent lung inflammation with chronic sequelae, this may have important implications for further research. Future studies should establish the factors that determine histamine airway hyper-responsiveness and its prevention.

Airway hyper-responsiveness plays an important part not just in development of COPD but also in its mortality. The relative risks for mortality from COPD associated with airway hyper-responsiveness were roughly equivalent to the relative risks associated with cigarette smoking and low lung function and were present in individuals without asthma. Although this trend was more pronounced in smokers, an increasing percentage of COPD deaths with increasing hyper-responsiveness was also present among never smokers.

We conclude that airway responsiveness predicts mortality of COPD, especially among smokers, and that the high prevalence of airway hyper-responsiveness in the population (6–35%) has particular implications for mortality from COPD.

Contributors

Jeannette Hospers collected and analysed the data and wrote the paper. Dirkje Postma designed and supervised the study, analysed and interpreted the data, and wrote the paper. Bert Rijcken designed the initial protocol, carried out the study, and interpreted the data. Scott Weiss designed the initial protocol, interpreted the data, and wrote the paper. Jan Schouten designed the initial protocol, supervised the analysis, interpreted the data, and wrote the paper.

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References

1 Jansen DF, Timens W, Kraan J, Rijcken B, Postma DS. (A)symptomatic bronchial hyperresponsiveness and asthma. *Respir Med* 1997; **91:** 121–34.

2 Xu X, Rijcken B, Schouten JP, Weiss ST. Airway responsiveness and development and remission of chronic respiratory symptoms in adults. *Lancet* 1997; **350:** 1431–34.

3 Hopp RJ, Townley RG, Biven RE, Bewtra AK, Nair NM. The presence of airway reactivity before the development of asthma. *Am Rev Respir Dis* 1990; **141:** 2–8.

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

5 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 longitudinal study in the elderly. *Am J Respir Crit Care Med* 1995; **151:** 656–62.

6 Annesi I, Neukirch F, Orvoen-Frija E, 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.

7 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.

8 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.

9 Postma DS, Wempe JB, Renkema TEJ, Van der Mark TW, Koëter GH. Hyperresponsiveness as a determinant of the outcome in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991; **143:** 1458–62.

10 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; the Normative Aging Study. *Am Rev Respir Dis* 1987; **135:** 1255–60.

11 Beaty TH, Newill CA, Cohen BH, Tockman MS, Bryant SH, Spurgeon HA. Effects of pulmonary function on mortality. *J Chron Dis* 1985; **38:** 703–10.

12 Freund KM, Belanger AJ, D'Agostino RB, Kannel WB. The health risks of smoking. The Framingham Study: 34 years of follow-up. *Ann Epidemiol* 1993; **3:** 417–24.

13 Van der Lende R, Kok TJ, Peset Reig R, Quanjer PH, Schouten JP, Orie NGM. Decreases in VC and FEV_1 with time: indicators for effects of smoking and air pollution. *Bull Eur Physiopathol Respir* 1981; **17:** 775–92.

14 Van der Lende R. Epidemiology of chronic non-specific lung disease (chronic bronchitis). Assen: Van Gorcum, 1969.

15 Van der Lende R, Orie NGM. The MRC-ECCS questionnaire on respiratory symptoms (use in epidemiology). *Scand J Respir Dis* 1972; **53:** 218–26.

16 British Medical Research Council's Committee on Research into Chronic Bronchitis. Instructions for the use of the questionnaire on respiratory symptoms. London: Medical Research Council, 1966.

17 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.

18 De Vries K, Goei JT, Booy-Noord H, Orie NMG. Changes during 24 hours in the lung function and histamine hyperreactivity of the bronchial tree in asthmatic and bronchitic patients. *Int Arch Allergy* 1962; **20:** 93–101.

19 Eiser NM, Kerrebijn KF, Quanjer PH. Guidelines for standardization of bronchial challenges with (nonspecific) bronchoconstricting agents. *Bull Eur Physiopathol Respir* 1983; **19:** 495–514.

20 Mensinga TT, Schouten JP, Rijcken B, Weiss ST, Speizer FE, Van der Lende R. The relationship of eosinophilia and positive skin test reactivity to respiratory symptom prevalence in a community-based population study. *J Allergy Clin Immunol* 1990; **86:** 99–107.

21 Mensinga TT, Schouten JP, Rijcken B, Weiss ST, Van der Lende R. Host factors and environmental determinants associated with skin test reactivity and eosinophilia in a community-based population study. *Ann Epidemiol* 1994; **4:** 382–92.

22 Bailey KV, Ferro-Luzzi A. Use of body mass index of adults in assessing individual and community nutritional status. *Bull World Health Organ* 1995; **73:** 673–80.

23 Mackenbach JP, Kunst AE, Looman CWN, Habbema JDF, Van der Maas PJ. Gezondheidszorg en 'vermijdbare' sterfte. Rotterdam: Erasmus Universiteit, 1988: 329–40.

24 Mackenbach JP. Mortality and medical care. Rotterdam: Erasmus University, 1988.

25 Cox DR. Regression models and life tables. *J R Stat Soc* 1972; **34:** 187–220.

26 Prentice RL, Kalbfleisch JD, Peterson AV, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. *Biometrics* 1978; **34:** 541–54.

27 Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. *BMJ* 1994; **309:** 901–11.

28 Burchfiel CM, Enright PL, Sharp DS, Po-Huang Chyou, Rodriguez BL, Curb JD. Factors associated with variations in pulmonary function among elderly Japanese-American men. *Chest* 1997; **112:** 87–97.

29 Chailleux E, Binet F, Sadoul P. Facteurs prognostiques de la survie des insuffisants respiratoires obstructifs traites par oxygenotherapie a long terme. Donnees de l'observatoire de l'ANTADIR. *Rev Mal Respir* 1992; **9:** 603–11.

30 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.

31 Weiss ST, Segal MR, Sparrow D, Wager C. Relation of FEV_1 and peripheral blood leukocyte count to total mortality. The Normative Aging Study. *Am J Epidemiol* 1995; **142:** 493–98.

32 Hospers JJ, Rijcken B, Schouten JP, Postma DS, Weiss ST. Eosinophilia and positive skin tests predict cardiovascular mortality in a general population sample followed for 30 years. *Am J Epidemiol* 1999; **150:** 482–91.

33 Rijcken B, Schouten JP, Weiss ST, Speizer FE, Van der Lende R. The relationship of nonspecific bronchial responsiveness to respiratory symptoms in a random populaton sample. *Am Rev Respir Dis* 1987; **136:** 62–68.