

# Aetiological factors in persistent sputum production: a case-control study

P Cullinan

## Abstract

**Study objective**—The aim was to explore the aetiological roles of smoking, occupational exposure, childhood respiratory illness, and atopy in persistent sputum production.

**Design**—This was a case-control study. Data were obtained using a questionnaire administered by two observers blind to the subjects' status. Information was sought on lifetime smoking, occupation, hospital admissions due to respiratory disease, and respiratory disease history.

**Setting**—Four general practices in south east England in 1990, with a total population of about 30 000.

**Subjects**—Cases were subjects aged 5 to 54 years with sputum production; one control was selected per case, matched by general practice, age, and sex, forming 210 matched pairs (88% response rate).

**Main results**—Cigarette smoking remains an important cause of persistent sputum production: the odds ratio (95% confidence interval) for current smoking was 7.9 (3.6–20.4). A dose-response relationship was confirmed, with falling risk estimates after stopping smoking. The association of sputum production with occupational exposure to respiratory irritants, which was independent of smoking, was confined to men (odds ratio 2.4, 1.0–6.0) and largely attributable to very heavy exposure. Examination of the relationship with early respiratory disease suggested that much, though not all, was attributable to wheezing illnesses first manifest in childhood.

**Conclusions**—Aetiological fractions derived from the results suggest that in the general population of south east England approximately 68% of all cases of persistent sputum production can be independently attributed to current cigarette smoking, 17% to heavy occupational exposure to respiratory irritants, and 13% to wheezing illnesses first manifest in early childhood.

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In 1983, Cole published the clinical findings of a series of patients referred to the Brompton Hospital with persistent sputum production.<sup>1</sup> Their mean age was 41 years, a high proportion (63%) were female, and two thirds of them had never been cigarette smokers. Many reported serious respiratory disease in childhood. Some of these features were unlike those traditionally associated with chronic bronchitis, and the question arose as

to whether they were representative of contemporary patterns of persistent sputum production or whether they reflected the selective processes that determine referral to a London specialist hospital. In order to answer this question, and to examine some of the current clinical and aetiological features of this disease, a study of persistent sputum production in a general population has been carried out. The findings of the first phase, a cross sectional survey of 30 000 persons registered with four general practices in south east England, have been published previously.<sup>2</sup>

This paper reports the results of the subsequent case-control study designed to assess the aetiological roles of four exposures, specified in prior hypotheses: cigarette smoking, exposure to respiratory irritants at work, early childhood respiratory illness, and atopy. In addition several other potential aetiological factors were examined for descriptive purposes.

## Methods

In the initial cross sectional phase, carried out in 1989, a random sample of 10 000 persons aged five years or over who were registered with four general practices (selected to be geographically representative of south east England) was surveyed.<sup>2</sup> A questionnaire, mailed to all subjects, comprised three questions enquiring into the usual frequencies of cough and sputum; the same questions were asked of all subjects, with guardians being asked to respond when subjects were aged 15 years or less. The response rate was 91% and subsequent telephone interviews showed the reliability of responses to be satisfactory.

The second phase, a case-control study of aetiological factors, was carried out in 1990 and restricted to subjects aged from five to 54 years. Cases were defined as all those persons who had replied "every day" or "half the days of a year" to the closed question concerning the usual frequency of sputum production. These cases were matched one to one by general practice, age, and sex with control subjects chosen at random from those who had reported that they "never or hardly ever" produced sputum.

Information on the exposures of interest was gathered through direct interviews carried out by two trained nurse interviewers who were not informed of the subjects' case/control status. For children under 16 years, guardians were interviewed. Information on the following was sought: lifetime cigarette smoking at five year intervals; all occupations since leaving school; frequent school absence, hospital admission or confinement to bed for respiratory illness up to the age of 10 years; a history of pneumonia, bronchitis, pertussis,

Department of  
Clinical  
Epidemiology,  
National Heart and  
Lung Institute,  
Emmanuel Kaye  
Building, Manresa  
Road, London SW3  
6LR, United Kingdom  
P Cullinan

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asthma, or wheezy bronchitis up to the age of five years.

Independent assessments of occupational exposure to respiratory irritants were made by a panel of three experienced occupational hygienists. The panelists, blinded to the subjects' case/control status, were asked to examine subjects' work histories in their matched pairs and to assess which member of the pair had had the greater respiratory irritant exposure. They were also requested to assess each occupation separately on a four point scale of increasing exposure; from this, a cumulative exposure index was calculated for each adult subject by summing the products of exposure and duration for each occupation. Subjects' recollections of childhood respiratory disease were compared with contemporary records held by their general practitioners. Atopy was assessed by the response to skin prick testing with three common allergens, house dust mite, grass pollen, and cat fur; a positive skin test was defined as one with a mean wheal diameter at least 2 mm greater than from a saline control.

During the interviews other information was gathered for descriptive purposes. Included among this were childhood socioeconomic status (derived from parental occupation), two measures of domestic crowding, and the presence of cigarette smokers in the home during the subject's childhood. In order to examine the relationship between mucus hypersecretion and airflow obstruction, forced expiratory volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC) were measured in adults (16 years or over) by dry wedge spirometry, according to standard guidelines.<sup>3</sup>

Four hundred and eighty subjects (240 matched case/control pairs) were initially selected for the case-control study. Interviews were completed on 448 (93%) of the subjects or 210 (88%) whole pairs. Five subjects refused interview and 27 could not be traced; these were equally cases and controls, but the proportion of men not interviewed was slightly higher than that in the original sample. All children were interviewed.

Analysis was carried out only on the 210 matched and interviewed pairs. Risk estimates are expressed as odds ratios with 95% confidence intervals. The role of confounding and effect modifying variables was assessed by (a) stratification by sex and by four equal age categories, or (b) by conditional logistic regression. Statistical analyses were carried out using EGRET software.

## Results

### CHARACTERISTICS OF SUBJECTS

Of the 420 subjects analysed, 224 (53.3%) were male and 36 (8.6%) aged under 15 years. The mean age of all subjects was 34.4 years, that of females (36.0 years) being a little higher than that of males (32.9 years). Cases and controls were matched exactly on general practice and sex and closely on age (mean age of cases 34.5 years, of controls 34.2 years). Nine cases and six controls were non-white.

The results of spirometry from the adult subjects were fitted to a multiple regression model incorporating the subject's age, sex, and height,

and subsequently case/control status. After controlling for age, sex, and height, case status was significantly and negatively associated with FEV<sub>1</sub> ( $p=0.03$ ) but not with FVC ( $p=0.37$ ). After further controlling for total pack-years of smoking the statistical significance of the relationship between case/control status and FEV<sub>1</sub> was reduced ( $p=0.08$ ).

### CIGARETTE SMOKING

Fifty eight percent of all subjects aged over 15 years had at some time been regular cigarette smokers and 35% were currently smoking: 52% of cases and 18% of controls. The median total pack-years for current or ex-smoking men was 15.8 (range 0.5 to 67.3) compared to 13.6 (range 0.5 to 59.0) for women, a difference which was not statistically significant ( $p=0.32$ , Wilcoxon rank sum test). The odds ratio of persistent sputum production for current smoking was 7.86 (95% confidence interval 3.57–20.45), for ex-smoking 1.91 (0.88–4.38), and for those who had ever smoked 4.22 (2.50–7.50). These ratios were consistently higher for male subjects than for female, even after adjustment for total pack-years smoked. The exposure response relationship between cigarette smoking and sputum production was examined by categorising smokers into equal terciles of total pack-years. A linear increase in the matched odds ratio was found for each categorical increase in total pack-years smoked. The effects of stopping smoking were further examined by categorising ex-smokers according to the length of time for which they had stopped smoking. The results summarised in table I show a falling risk estimate with increasing duration of cessation so that after five years of non-smoking the matched odds ratio was barely above that of those who had never smoked.

Table I Odds ratios associated with ex-smoking: effect of different durations of cessation.

Duration of cessation	Odds ratio (95% CI)
All	1.91 (0.88–4.38)
> 1 year	1.67 (0.68–4.32)
> 2 years	1.44 (0.57–3.83)
> 5 years	1.11 (0.41–3.09)
> 10 years	0.63 (0.16–2.17)

CI = confidence interval.

### OCCUPATIONAL EXPOSURE

A high proportion (48.1%) of subjects aged 15 years or more reported heavy occupational exposure to dusts, gases or fumes, with cases (54.5%) more likely to do so than controls (41.8%). The resultant odds ratio was 1.92 (95% confidence interval 1.17–3.22), and higher among men (2.08, 1.01–4.55) than among women (1.79, 0.89–3.72). There was no significant interaction with age. After adjustment for total pack-years of smoking the overall odds ratio was 2.15 (1.24–3.73), falling in men to 1.81 (0.80–4.10) but rising in women to 2.33 (1.09–4.98).

Agreement between the occupational hygienists for the matched pair analysis was high; they were unanimous in 58% of the pairs and in a further 28% one or more considered that there had been no difference in exposure between the two pair members when the other(s) reported a difference. In the remaining 14% of pairs one panellist assessed the opposite member of the pair

to have been more heavily exposed than the other two panellists. Using the majority verdict of the panel, the overall odds ratio was 1.20 (95% confidence interval 0.77–1.87), higher in men (1.74, 0.96–3.23) than in women (0.71, 0.34–1.45). After adjustment for total pack-years of smoking, the odds ratios were 1.04 (0.64–1.69) overall, 2.39 (0.96–5.99) in men, and 0.60 (0.28–1.25) in women.

The existence of an exposure-response relationship was examined by calculating the mean cumulative exposure measures of the three panelists and dividing the results into equal terciles. A trend of increasing matched odds ratio with increasing cumulative exposure was found for all subjects; after stratification by sex this was found to be confined to men, with risk estimates of 1.05 (0.36–3.07), 1.66 (0.67–4.22), and 2.65 (1.13–6.44) in the first, second, and third categories of cumulative exposure respectively.

#### CHILDHOOD RESPIRATORY DISEASE

Fifty two subjects (12.4%) reported frequent school absence, 27 (6.4%) reported hospital admissions in early life, and 16 (3.8%) reported confinement to bed during childhood for respiratory disease. Reported school absence was most common (17.0%) among subjects in the youngest age category, aged from five to 24 years. One hundred and thirty three (31.7%) subjects reported a specific respiratory disease before the age of five years, with pertussis (19.5%) being the most frequent. Childhood pertussis was most commonly reported by those in the oldest age category (over 44 years, 34.2%) whereas a history of asthma or wheezy bronchitis was most common among the youngest subjects (11.3%). There was no statistically significant relationship between cigarette smoking and any of the measures of early respiratory disease.

Risk estimates associated with the various measures of early respiratory disease are displayed in table II. The odds ratios for frequent school absence, for hospital admissions in childhood, and for asthma and wheezy bronchitis before the age of five years were all raised, with confidence intervals exclusive of 1.00. Odds ratios for pneumonia and for bronchitis were over 1.00 but not significantly so; the odds ratio for pertussis was 0.94 (0.56–1.57). Stratification by age group revealed that the odds ratio for frequent school absence in the youngest group (15.00) was much higher than those in the older groups (1.25 to 1.67) and a similar pattern was found for the specific

wheezing diseases. For the infective diseases, odds ratios tended to be higher in the youngest and the oldest age categories than in the two intermediate categories.

In order to examine further the effect of early wheezing, subjects considered to have "persistent" asthma were excluded. These were those who reported a history of asthma or wheezy bronchitis before the age of five years and who also replied positively to three or more of seven questions concerning current wheeze on exercise, at night, or on waking. Table II shows that after exclusion of these 15 subjects the various risk estimates fell consistently but that the estimate for hospital admission in childhood remained significantly raised.

Medical details for the relevant age period were recorded in general practice records for 198 (47.1%) of the subjects; cases were slightly more likely (49.5%) than controls (45.7%) to have available records. The proportions of subjects' reports of specific childhood disease that were also recorded contemporaneously by their general practitioners ranged from 2% (pertussis) to 24% (bronchitis and asthma). For all diseases, with the exception of wheezy bronchitis, case subjects' reports of childhood respiratory disease were more likely than controls' to be recorded in the available general practice records (table III); however, none of the differences was statistically significant (Fisher's exact test).

Table III Number of subjects reporting respiratory disease in childhood. Figures in brackets are proportions also recorded in general practitioner records.

	Cases	Controls
Pneumonia	13 (39%)	9 (11%)
Bronchitis	24 (25%)	17 (24%)
Pneumonia or bronchitis	32 (31%)	25 (20%)
Pertussis	40 (3%)	42 (2%)
Pertussis or pneumonia	50 (14%)	45 (4%)
Asthma	13 (23%)	4 (25%)
Wheezy bronchitis	14 (7%)	4 (50%)
Asthma or wheezy bronchitis	21 (19%)	7 (29%)

#### ATOPY

Eleven subjects declined skin prick testing; they were slightly younger (mean age 30.9 years) than those tested (34.4 years) but did not differ in terms of sex or case/control status. One hundred and fifty subjects (36.7%) had at least one positive skin prick test, with the proportion higher among males (43.6%) than among females (29.8%), and lowest in the oldest age category (over 44 years, 26.5%). Of the individual allergens, house dust mite produced the highest proportion (26.9%) of positive results. Atopy (a positive result to one or more allergens) was strongly associated with a childhood history of asthma or wheezy bronchitis; 74.2% of those with such a history were atopic compared to 36.5% of those without such a history ( $p < 0.001$ ). There were no significant differences in rates of atopy between those who had ever smoked, were currently smoking, or had never smoked.

Matched analyses of the 199 pairs who were tested revealed a risk estimate for one or more positive skin tests of 1.04 (95% confidence interval 0.69–1.57). Stratification by sex did not alter this result materially. There was a trend of falling risk estimates with increasing age, from 1.67 (0.68–4.32) in the youngest age category to 0.36

Table II Prevalence of childhood respiratory disease in control subjects, and associated odds ratios: all subjects, and after exclusion of those with persistent asthma.

Exposure	Prevalence in control subjects	Odds ratio (95% CI)	
		All subjects	Excluding persistent asthma
<i>Age &lt; 10 years</i>			
Hospital admission	2.9%	3.50 (1.37–10.60)	2.83 (1.07–8.78)
School absence	8.1%	2.64 (1.28–5.85)	2.10 (0.95–4.99)
Two or more weeks in bed	1.9%	3.00 (0.91–12.76)	2.75 (0.81–11.84)
<i>Age &lt; 5 years</i>			
Pneumonia	4.3%	1.50 (0.56–4.23)	1.57 (0.56–4.78)
Bronchitis	8.1%	1.47 (0.73–3.04)	1.14 (0.52–2.53)
Pertussis	20.0%	0.94 (0.56–1.57)	0.88 (0.52–1.49)
Asthma	1.9%	4.00 (1.08–22.09)	3.00 (0.24–15.80)
Wheezy bronchitis	1.9%	4.33 (1.19–23.71)	3.00 (0.54–30.39)
Asthma or wheezy bronchitis	3.3%	3.80 (1.37–13.02)	2.00 (0.43–12.36)

CI = confidence interval

(0.10–1.05) in the oldest. No significant changes to any of these estimates were found after adjustment for a childhood history of asthma or wheezy bronchitis.

#### OTHER EXPOSURES

The effects of childhood socioeconomic group were examined by classifying all subjects according to their parents' occupation. Of 393 subjects for whom full information was available, 117 (29.8%) were classified in non-manual childhood socioeconomic groups (I, II, IIIa) and 276 (70.2%) in manual groups (IIIb, IV, V). There were strongly significant ( $p < 0.005$ ) associations between childhood socioeconomic group and the number of persons in the household, the number of persons per bedroom, and the presence of a parent who smoked, all of which were more common among the children of manual workers. There were no significant differences in the frequencies of any of the measures of childhood respiratory disease except reported pertussis, which was more common ( $p = 0.004$ ) among the children of manual workers. These associations persisted after stratification by subject's age. In addition, subjects classified in manual groups were more likely ( $p = 0.002$ ) to be current smokers as adults.

**Table IV** Risk estimates associated with domestic exposures during childhood.

	Odds ratio (95% CI)	
	All subjects	Excluding current smokers
Manual childhood socioeconomic group	2.03 (1.30–3.23)	1.75 (1.13–2.72)
> 2 persons per bedroom	1.70 (0.95–3.12)	1.52 (0.89–2.59)
> 3 siblings	1.74 (1.02–3.04)	1.82 (1.04–3.23)
Parental smoking <sup>a</sup>	2.82 (1.59–5.24)	1.77 (1.00–3.21)
Intensity of parental smoking		
1	1.00	1.00
2	1.13 (0.59–2.17)	1.07 (0.49–2.27)
3	1.85 (1.06–3.28)	1.41 (0.71–2.82)
4	2.64 (1.28–5.52)	3.78 (2.06–7.07)

<sup>a</sup> see text

CI = confidence interval

The odds ratios associated with these exposures are summarised in table IV. The risk of persistent sputum production was raised in children of manual workers, in those with more than three siblings, and in those of whom one or more parents were cigarette smokers. There were no significant interactions between these effects and the subject's current age. After exclusion of subjects who were current cigarette smokers the risk estimate for manual socioeconomic group fell but remained significantly greater than unity. In the same way and after adjustment for a history of childhood respiratory disease, the risk estimate for parental smoking remained significantly raised. In addition, after categorisation of level of parental smoking into equal quartiles, a trend of increasing risk with increasing exposure was found.

#### Discussion

This study examined the role of four factors in the aetiology of persistent sputum production in the general population of south east England. The case-control method used here has seldom been

employed in aetiological studies of chronic obstructive respiratory disease. The results confirm that cigarette smoking continues to be strongly associated with persistent sputum production and the magnitude of its effect makes the assessment of other aetiological factors difficult. That its role is causal is suggested here by the findings of a dose-response relationship and by the evidence that cessation of smoking leads to a reduction in risk. The fall in risk with duration of cessation is similar to that reported by Brown *et al* in their analysis of recent data from the Scottish Heart Study<sup>4</sup>; both in their survey and in the current study, after between two and five years without smoking the risk of persistent sputum production had returned almost to that found in persons who have never smoked. The results reported here also suggest a stronger association between cigarette smoking and sputum production in males than females, independent of the total number of pack-years of cigarettes smoked. Anderson and Ferris<sup>5</sup> have reported a higher prevalence of chronic bronchitis among US males, also independent of smoking history. The explanation for such a difference is unknown; it may reflect an interaction with other aetiologically important exposures (such as occupational dust exposure) or a difference in the way in which men smoke, such as their preference for stronger cigarettes. Spirometry from the current study showed an independent relationship between mucus hypersecretion and reduced FEV<sub>1</sub> which was accounted for, at least in part, by cigarette smoking, a common aetiological factor.

A strong relationship was also identified for two non-specific measures of childhood respiratory disease: stratification by age and examination of specific respiratory diseases suggested that much, though not all, of this relationship may be attributable to asthma first manifest during early childhood. Strachan *et al*,<sup>6</sup> in a study of children born in 1958, showed that among persons aged 23 years much of the association between sputum production and a history of respiratory illness before the age of seven years was accounted for by a history of recent wheeze; support for their conclusion that this represents persistent asthma is provided above by the fall in odds ratios after the exclusion of subjects with both childhood and current wheezing. Like other studies of the relationship between childhood and adult respiratory diseases,<sup>7</sup> this study was unable to show an association between childhood pertussis and long term respiratory symptoms.

The issue of preferential recall, whereby symptomatic subjects are more likely to remember potentially significant past events, has frequently been cited as a reason why results based on such evidence (particularly from case-control studies) should be viewed with caution.<sup>8</sup> Our study suggests that in this population there was no evidence of differential recall—the proportion of childhood diseases recalled which were also recorded by the general practitioner was no different between cases and controls. Records, inevitably, were incomplete and frequently missing but there was no evidence that this was related to the case/control status of the subject.

No association between atopy and persistent sputum production was found. Other studies of

this area have produced conflicting results; in their survey of the residents of Tucson for example, Burrows *et al*<sup>9</sup> found no difference in the prevalences of chronic sputum production between adults with different degrees of reactivity to skin prick testing. In a small sample of Finnish farmers, however, chronic bronchitis was more common among those with positive skin tests.<sup>10</sup> The mechanism of any association between atopy and sputum production is likely to reflect the association of the former with asthma, possibly influenced by the effects of cigarette smoking.<sup>11</sup>

The high proportion of subjects reporting heavy exposure to respiratory irritants at work suggests that this question was interpreted loosely and the risk estimates based on these responses should be viewed cautiously. The results from assessments made by the occupational hygienists, however, point towards a weak relationship in men between occupational exposure and persistent sputum production, independent of smoking. Further evidence is provided by the finding of a dose-response relationship, again confined to men. Some of the difficulties encountered in demonstrating such a relationship in a general population are due to the wide range of exposures encountered and, particularly in a population such as this, to the fact that relatively few subjects will have received heavy exposures. Korn *et al*,<sup>12</sup> in a large cross sectional survey of adults living in six US cities, described a relationship, independent of smoking, between occupational dust exposure and chronic phlegm, with "odds ratios" similar to those reported here; they too were able to demonstrate a weak exposure-response effect with increasing risk with increasing duration of exposure.

The remaining aetiological factors examined were included for descriptive purposes only. A strong relationship between sputum production and childhood socioeconomic group was found which was not wholly explained by current cigarette smoking, by parental smoking, or by an index of domestic crowding. This may reflect inadequate measurement of such confounding factors or a more complex relationship between early social circumstances and subsequent respiratory disease. The effect of parental smoking during early childhood was only partially confounded by active smoking and displayed an exposure-response relationship, suggesting a causal role. If the mechanism of this association

was simply a direct irritant effect, then one would expect the strength of the association to diminish with increasing age (similar to the effects of stopping active smoking); we found no evidence for any such interaction, lending support to the hypothesis that the lung in early childhood may be especially susceptible to damage.

The individual effects of some of these exposures may be expressed as aetiological fractions<sup>13</sup> using the odds ratios obtained above. The results suggest that in this population approximately 68% of all cases of persistent sputum production can be independently attributed to current cigarette smoking, 17% to heavy occupational exposure to respiratory irritants, and 13% to asthma or wheezy bronchitis first manifest before the age of six years. If these estimates are accurate then it would suggest that the process of referral to hospital of persons with chronic sputum production tends to exclude those who are current smokers, presumably because this is seen to be sufficient cause for their symptoms.

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