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EPIDEMIOLOGICAL

AND

CLINICAL STUDIES

OF

POLYVINYLCHLORIDE

WORKERS

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I N S T I T U T E O F O C C U P A T I O N A L M E D I C I N E

EPIDEMIOLOGICAL AND CLINICAL STUDIES OF POLYVINYLCHLORIDE WORKERS

by

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SUMMARY

We have reported previously an epidemiological survey of 818 present and past workers at a factory making polyvinylchloride (PVC) in which we showed that estimates of exposure to respirable PVC dust were inversely related to lung function after allowing for the effects of age and smoking, and related to prevalence of slight abnormalities of the chest radiograph; one of three experienced readers found that prevalence of small rounded opacities category 0/1 or greater was related to dust exposure after allowing for age.

The present studies extended the sample of the study population to include all other members of the current workforce who had worked at any time in the dustier plants in the factory, in order to examine the prevalence of respiratory abnormality in these men and identify any individuals with clinically important chest illness, and to examine in this extended sample and in the original study group the relationship between dust exposure and radiological appearances based on new readings of the chest radiographs. Also men selected from the first study on the basis of radiological and functional abnormality to which exposure to PVC dust may have made an important contribution have been examined in detailed case/control studies to attempt to identify clinical syndromes associated with PVC dust exposure, and to estimate the clinical severity of the effects of the dust on the lung. Lastly, men working at a second factory manufacturing PVC have been examined to determine the prevalence among them of respiratory symptoms and lung functional and radiological abnormality.

Men were seen by appointment, and questionnaires of respiratory symptoms were administered. A detailed occupational history was recorded, lung function assessed by simple spirometry, and a chest radiograph taken. In the case/control studies, detailed lung function measurements were made, a detailed medical history taken, and a physical examination performed by a physician. An index of exposure to PVC dust was calculated from the detailed occupational history and current measurements of

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airborne levels of respirable PVC dust made in an environmental survey the previous year.

The chest radiographs for the original study population of 818 men were read again according to the ILO U/C Classification (ILO, 1972) by the same three experienced readers who read them previously. The interval between readings was about a year, during which the results of the first reading had been released and discussed. All three readers recorded higher prevalences of small rounded opacities category 0/1 or greater on the second reading compared with the first. For two readers the changes in prevalence were from 2.2% to 3.8%, and 0.5% to 2.6% respectively; the third reader recorded a much higher prevalence on the second reading, a change from about 6% to about 60%. The increase in prevalence for this reader was confined mostly to category 0/1; the increase in category 1/0 or greater was from 10 to 17 radiographs only (1.2% to 2.1%).

Prevalences of small rounded opacities category 0/1 or greater recorded by all three readers were related to age. In the previous readings, the two readers recording lower prevalences of small rounded opacities had not found a relationship with dust exposure. On these second readings one of them did find a relationship between small rounded opacities category 0/1 or greater and dust exposure after allowing for age, prevalence increasing from about 2.5% for men with the lowest PVC dust exposure to about 9% for men with the highest exposure. The reader who had previously detected the relationship with dust exposure (and whose second reading recorded a much higher prevalence of these opacities than the first reading), again found a relationship with dust exposure after allowing for age, but on this reading it was with a higher category of profusion of small rounded opacities, category 1/0 or greater, prevalence increasing from about 1.5% for men with the lowest dust exposure to about 7.5% for men with the highest dust exposure. He did not on this second reading find a relationship between the lower category of opacities and dust exposure.

The chest radiographs for the original study population of 818 men were also read twice within a short time by a panel of five self-trained readers, who had not been informed of the results of other readings. Prevalences of small rounded opacities category 0/1 or greater were found by all readers to be related to age. After allowing for age, prevalences of these small opacities were found to be related to dust exposure by one reader on both readings and another reader on one reading. Another reader found a relationship between small rounded opacities category 1/0 or greater and dust exposure after allowing for age.

We conclude that our previous finding has been confirmed, that estimated PVC dust exposure was related to abnormalities of the lungs demonstrated by the presence of small rounded opacities in the chest radiograph. The slight degree of the radiological abnormalities in most cases, and the difficulty in distinguishing them in an individual radiograph from the effects of age, combined with variations in readers' interpretations of these appearances, have caused some inconsistencies in the detection of the effects of PVC dust.

An additional 229 men at this factory were examined in the present medical survey. There was no evidence of unusual prevalences among them of respiratory symptoms, abnormal lung function or chest radiographic abnormalities. When these groups were combined into one large group of 1,047 men, the relationships of estimates of dust exposure to lung function and radiological abnormality were similar to those found in the original study population.

One hundred and twenty-seven men seen at the second factory manufacturing PVC had a low prevalence of respiratory symptoms and included few men with impaired lung function or clinically important chest radiographic abnormality.

In four case/control studies, men were selected from the original study population on the basis of radiological or lung functional abnormality where PVC dust exposure might have made an important contribution. Men were chosen on the basis of the presence of small rounded opacities, presence of small irregular opacities, or (separately for non-smokers and smokers) low lung function with relatively high estimated PVC dust exposure. These cases, together with suitably matched controls, were given detailed clinical examinations.

Twenty-eight men with small rounded opacities in the chest radiograph had slightly higher prevalences of chronic productive cough and crackles heard through the stethoscope in the mid and end parts of inspiration than controls matched for age, smoking habits and estimated dust exposure, confirming that these opacities were associated with minor functional abnormalities. The lung function of the cases was not significantly different from controls, but an exploratory analysis suggested that within the group of men with small rounded opacities, men with higher dust exposures had an average pattern of lung function abnormality intermediate between an obstructive and a restrictive type, in that the forced expiratory flow rates were reduced in parallel with the FEV_1, but the gas transfer factor was well preserved. This, taken with the findings in the previous study, tends to suggest that the functional effects of PVC dust exposure are caused by disease of the peripheral airways, without airflow obstruction or much alveolar damage.

Clinically important reduction of lung function was found in some of these men, but was not shown to be related to the presence of small rounded opacities or to PVC dust exposure.

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Men with small irregular opacities (not thought to be related to PVC dust exposure) and reduced lung function had an obstructive pattern of lung function abnormality, with relative preservation of gas transfer factor.

For non-smokers and smokers separately, "cases" with lower FEV_1 than other men after allowing for age and height, and with relatively high estimated PVC dust exposure, were compared with controls who had similarly low FEV_1, but had little exposure to PVC dust, so that the effect of dust could be studied. Non-smokers were matched for age, smokers for age and smoking habits.

Among non-smokers, the lung function of the "cases" was within or close to the normal range and no differences were demonstrated between them and the controls. These men were probably in normal respiratory health. Among smokers, both "cases" and controls had a high prevalence of respiratory symptoms and abnormally low lung function of an obstructive pattern. The "cases" had a slightly higher prevalence of crackles heard through the stethoscope than controls, but there were no significant differences between the groups in lung function levels or pattern, and no differences in numbers of men with clinically important reduction of lung function. The respiratory disease evident among smoking "cases" and controls was probably the result of their smoking habit, and there was no evidence to suggest that PVC dust exposure had caused any serious additional damage.

We conclude from the large epidemiological and small case/control studies that exposure to PVC dust in the concentrations experienced in this factory caused a detectable reduction in lung function in the study population, and caused an increase in prevalence of slight abnormalities of the chest radiograph. The clinical features of the non-specific respiratory disease associated with dust exposure additionally included an increase in prevalence of productive cough in those with abnormalities of the chest radiograph, an increase in prevalence of crackles heard through the stethoscope during mid and late inspiration, and a pattern of lung functional abnormality characterised by a uniform reduction of ventilatory capacity, with relative preservation of gas transfer factor. These features suggest that the functional defect is predominantly in peripheral airways in the lung. Important clinical illness could not be shown to be related to PVC dust exposure in spite of careful selection of "cases" and controls, and we conclude that it is unlikely that exposure to PVC dust at these levels has caused serious respiratory disability, though the possibility of a rare idiosyncratic response to the dust cannot be excluded.

1. INTRODUCTION

In a previous epidemiological study (SOUTAR et al., 1980) of 818 men sampled from the workforce of a factory manufacturing polyvinylchloride (PVC), an index of individual cumulative exposure to respirable PVC dust was found to be related to the complaint of mild exertional dyspnoea, reduction of forced vital capacity in one second (FEV_1) and forced vital capacity (FVC), and to prevalence of small rounded opacities in the chest radiographs. Three experienced medical radiographic readers recorded different prevalences of small rounded opacities (category 0/1 or more on the ILO U/C Classification (ILO, 1972)), and the reader recording the greatest prevalence of these opacities found a relationship with dust exposure.

The conclusions reached from this study were that exposure to respirable PVC dust was related to a non-specific disease of the lungs manifested by complaints of slight breathlessness, a functional defect probably of a mixed obstructive and restrictive type, and the presence of slight abnormalities in the chest radiograph.

The present studies were designed to examine the prevalence of respiratory abnormality in all other members of the current workforce who had worked at any time in the dustier plants in the factory and who had not been included in the first survey, to identify any individuals with clinically important chest illness, and to examine in this population and in the original study group the relationship between dust exposure and radiological appearances based on new readings of the chest radiographs.

Men were also selected from the first study on the basis of radiological and functional abnormality to which exposure to PVC dust may have made an important contribution, and have been examined in detailed case/control studies to attempt to identify clinical syndromes associated with PVC dust exposure, and to estimate the clinical severity of the effects of dust on the lung. In these studies, men with small rounded opacities in the chest radiograph were examined and compared with men without opacities matched for age, smoking and dust exposure to study the clinical features associated with these opacities. Men with small irregular opacities (not thought to be related to PVC dust exposure) were also studied in this way. Additionally, for smokers and non-smokers separately, the men with

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the lowest FEV_1 after allowing for age, height, weight and dust exposure among those with higher dust exposures were compared with men similarly selected from those with lower dust exposures. The purpose was to identify clinical features in these men attributable to PVC dust exposure, on the assumption that the higher exposure groups would be likely to include men whose lung function was substantially impaired by PVC dust exposure (if such men existed), while all groups would be likely to include men with impaired lung function from other causes.

Lastly, men working at a second factory manufacturing PVC have been examined to determine the prevalence among them of respiratory symptoms and lung functional abnormality, and identify any men with clinical respiratory illness.

In this report the methods and results of each of these studies are reported separately, and a single discussion covers all three.

2. STUDIES OF DUST-DISEASE RELATIONSHIPS

2.1 Subjects

Men working at the first factory who had worked at any time in those plants where higher PVC dust levels had been found during the environmental survey (plants C1, C4, W1 and W2) but who had not been studied were invited for examination, together with some men seen in the previous survey but who had not been included in the analysis because of incomplete data.

All men currently working at the second factory were invited for examination. This factory was situated in Cheshire, and had been in operation since 1971.

2.2 Methods

A medical survey team visited each factory and men were seen by appointment. At the first factory, medical and occupational data were collected in the same way as in the first survey; that is a detailed occupational history was taken, and a respiratory symptoms questionnaire (MRC, 1976) administered, by trained staff. Simple spirometry was performed using a Gaensler spirometer and a full size chest radiograph was taken. Details of the methods have been described elsewhere (SOUTAR et al., 1980).

At the second factory, a shorter respiratory symptoms questionnaire was administered (RAE et al., 1971), simple spirometry was performed and a chest radiograph taken.

Chest radiographs were read for clinical purposes by a chest physician, and those from the first factory were re-examined under controlled conditions by the three experienced readers who read them previously, and who classified them according to the ILO U/C Classification (ILO, 1972). On this occasion the earlier 818 radiographs were re-read together with the radiographs from the new survey. The interval between first and second readings of these 818 radiographs was approximately one year, during which the results of the first reading were published. A panel of five self-trained readers also read these radiographs. This panel consisted of four non-medically qualified persons, and one medically

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qualified person none of whom had undergone special training in radiology or chest disease; all five had trained themselves independently to read radiographs according to the ILO U/C Classification (COPLAND et al., in press). They had no prior information about the origin of the radiographs, and no knowledge of the results of the first reading at the time of the second. The interval between readings was approximately one month.

An index of dust exposure had been calculated for some of the men at the first factory on the basis of their occupational histories and on measurements of airborne respirable dust made in a detailed environmental survey of the factory carried out the previous year (SOUTAR et al., 1980). (These estimates do not represent actual dust exposure, since only present dust levels were known, but represented an index of relative dust exposure for the purposes of comparison with medical responses.)

Relationships between lung function measurements and dust exposure were studied by multiple regression methods, taking account of age, height, weight and smoking habits. Prevalences of radiographic abnormalities were also examined using linear logistic analysis.

No dust exposure data are available for men surveyed at the second factory. Lung function results were compared with predicted values based on the 135 non-smoking currently employed men and leavers seen in the previous study at the first factory.

2.3 Results for men at first factory

2.3.1 Symptoms and lung function

Two hundred and twenty-nine men attended for examination out of a possible 263. Their mean age, years worked at the factory, mean index of dust exposure and prevalence of chronic cough and sputum were less than those of the 818 men studied in the first survey (Table 1).

The forced expired volume in one second (FEV_1) in relation to predicted values derived from the non-smokers in the first study population are set out in Table 2. Twenty men (9%) had FEV's$_1$ below

80% of predicted, and all but two of these were or had been smokers. These features indicated a lower frequency of respiratory disease than in the original study population.

The lung function results for these 229 men were included with those for the 818 men originally studied, total 1,047 men, and FEV_1 and forced vital capacity (FVC) compared with dust exposure after allowing for age, height, weight, smoking habits, and employment status. The inverse relationships between FEV_1 and FVC and dust exposure were confirmed for this larger population (see Appendix I). The magnitude of the effect of dust on the FEV_1 was of a similar order to that found previously.

2.4 Results for men at second factory

2.4.1 Symptoms and lung function

One hundred and twenty-seven of the male workforce of 134 men were seen. Age distribution and smoking habit are set out in Table 3. Mean age was 39.5 years. Prevalence of lifelong non-smokers was 35%. Prevalences of respiratory symptoms were low. Prevalence of chronic cough and/or sputum was 1%, and of complaints of breathlessness when walking up hill or hurrying on level ground 5%. The distribution of FEV_1 values expressed as percentage of predicted values are set out in Table 4. Six men (4.7%) had FEV_1 values below 80%, and eight (6.3%) above 120%. Clinical details of the six men below 80% are set out in Table 5. The FEV_1/FVC ratios suggest that three may have had airflow obstruction, while three had lung function which was probably normal. These results indicate a low prevalence of respiratory disease.

2.5 Radiological results at first factory

2.5.1 Original study population

The chest radiographs of 818 men examined in 1979 were read twice independently and randomly by three experienced readers. The interval between readings was approximately one year, during which the results of the first reading were released and discussed. These radiographs were also read by a panel of self-trained readers.

Readings by experienced medically qualified readers

All readers recorded higher prevalences of small rounded opacities category 0/1 or more on the second reading than on the first (Table 6). One reader recorded much higher prevalences than the other two on both occasions, and the prevalence on his second reading was strikingly higher than on the first. The increase was found principally among classifications by this reader of category 0/1. The increase in prevalence of category 1/0 or more was from ten to seventeen radiographs only. Tables of consistency are set out in Appendix II. Prevalences of small irregular opacities found by three readers were similar in both readings (Table 7).

The relationships of the results of the first readings with age and index of dust exposure have already been reported (SOUTAR et al., 1980), and these relationships for the second readings are presented here. Prevalences of small rounded opacities category 0/1 or greater recorded by all three readers were related to age (Figure 1). After allowing for age, only reader 03 found a relationship between this category of small opacities and index of dust exposure ($P < 0.05$) (Figure 2). After allowing for dust exposure, these opacities recorded by reader 03 were related to age at the 10% significance level. However, prevalence of small rounded opacities category 1/0 or greater recorded by reader 17 was related both to age and to index of dust exposure ($P < 0.05$ and $P < 0.001$ respectively, each after allowing for the other) (Figures 3 and 4). The other two readers found that this category of small opacities was related to age but not to dust exposure.

Prevalence of small irregular opacities was found by all three readers to be related to age (Figure 5), but not to index of dust exposure.

Readings by self-trained panel of readers

A self-trained panel of five readers read 816 radiographs from the same series (two were unavailable at the time of reading) on two occasions separated by an interval of several weeks, without knowledge of the results of their own first readings or the medical panel's readings. Prevalences of small opacities recorded by these readers are set out in Tables 8 and 9. Differences in prevalences recorded by these readers

on other series of radiographs have been described previously (COPLAND et al., in press).

Prevalence of small rounded opacities category 0/1 or greater was found by all five readers on both readings to be related to age (all relationships were statistically significant at the 5% level except for one which approached this level of significance). Observed data for the second reading are illustrated in Figure 6. After allowing for age, prevalence of this category of small opacity was found to be related to index of dust exposure by reader L5 on both readings and by reader L3 on the second reading. These relationships with dust exposure were statistically significant ($P < 0.01$ and $P < 0.05$ respectively) but in both cases were based on low prevalences of opacities. Some other readings suggested a relationship with dust exposure, but these did not reach statistical significance at the 5% level (Figure 7). Prevalence of small rounded opacities category 1/0 or greater recorded by reader L2 on the first reading was related to age and dust exposure ($P < 0.001$ and $P < 0.05$ respectively, each after allowing for the other).

Magnitude of effects on chest radiographic appearances

The prevalences of small rounded opacities category 0/1 or greater found by individual medical readers on second reading in relation to age ranged from zero for the youngest age group (< 35 yrs) to about 11% for the oldest age group (≥ 60) for reader 15, about 2% and about 6% respectively for reader 03, and about 53% and about 67% for reader 17. The prevalences of these opacities in relation to index of dust exposure ranged from about 2.5% for the lowest two dust categories together (less than 4.5 dust index units) to about 9% for the highest dust category (≥ 30 units) for reader 03 (the other two readers did not find relationships with dust exposure for this category of opacity). The prevalences of small rounded opacities category 1/0 or greater found by reader 17 ranged from zero for the youngest age group to about 6% for the oldest group, and from about 0.5% for the lowest two dust categories to about 7.5% for the highest dust category.

Relationships between small rounded opacities category 0/1 or greater and dust exposure were found by two self-trained readers recording low prevalences of opacities. On the second reading reader L3 recorded a prevalence of about 1% for the lowest two dust categories and about 7.5% for the highest dust category, while for reader L5 the prevalences were 0% and 2.5% respectively on the second reading.

2.5.2 Additional men studied in 1980

The chest radiographs of 229 additional men studied in 1980 were read once by the medically qualified panel of readers, at the same time as the second reading of the 818 radiographs for the original study population. Prevalences of small rounded and small irregular opacities found by each reader are set out in Tables 10 and 11. Prevalences of these opacities tended to be similar to or lower than the prevalences found in the original study population on the second reading.

Within this group, prevalence of small rounded opacities was found by all three readers to be related to age, but not related to index of dust exposure.

When the results from the additional men and the original population were considered together (total 1,047 men), the significances of the relationships of small rounded opacities with dust and age were increased slightly, but the estimates of the size of the effect were not substantially altered.

2.6 Clinical readings of chest radiographs at both factories

Three radiographs at the second factory and eight at the first factory were thought on clinical readings to show clinical abnormalities (pleural thickening or calcification in five, cardiomegaly in three, apical fibrosis in two, and discrete opacities requiring investigation in one).

These men, and those with abnormal lung function, were referred to their general practitioners.

3. CASE/CONTROL STUDIES

3.1 Subjects

For the clinical studies, cases and controls were selected from the 818 men examined at the Hillhouse factory in February 1979 on the basis of chest radiographic abnormality or low FEV_1 after allowing for age and height.

3.1.1 Small rounded opacities

In the previous study, one reader had recorded the presence of small rounded opacities category 0/1 or greater on the ILO U/C scale in the chest radiographs of fifty men (a higher prevalence than the other two readers recorded). Ten of these were of category 1/0 or greater, and all of these were invited to attend for further study, together with a further 20 men randomly selected from the remainder. Reserves were selected in case a man did not attend for examination, and were invited for examination when selected men did not attend.

The controls were men in whose chest radiograph all three readers agreed small opacities were not present, group-matched by three ranges of index of PVC dust exposure, three ranges of age, by smoking category and by employment status (current employment at the factory, pensioner, and those who left for reasons other than retirement). The index of dust exposure was not actual lifetime dust exposure, but was calculated from current personal dust exposure levels and a detailed occupational history for each man (SOUTAR et al., 1980).

3.1.2 Small irregular opacities

In the previous study, 90 men were thought by one or more readers to have small irregular opacities category 0/1 or more. Twenty men, thought by one or more readers to have these opacities and with no small round opacities by any reader, were randomly selected. Twenty controls thought by all three readers not to have opacities of either type, were matched by the same dust and smoking criteria as in the study of men with small rounded opacities, but matched by only two age categories.

3.1.3 Men with low FEV_1

Men with high dust exposure and low FEV_1 after allowing for age, height, weight, employment status and dust exposure were also selected for further study. By "low FEV_1" we mean that the observed FEV_1 was less than that predicted by a multiple regression analysis taking these variables into account (negative residual). The largest negative residual would be associated with the observed FEV_1 which was lowest in comparison with the predicted value. Among non-smokers the sixteen men with largest negative residual FEV_1 among those with an index of dust exposure greater than 10 units were selected together with sixteen controls among those with an index of dust exposure less than 3.5 units, matched by residual FEV_1 and age. Twenty cigarette smoking cases and twenty controls were selected similarly, but the selection criteria for dust exposure were greater than 13.5 or less than 8.5 units respectively (non-smokers tended to have lower dust exposures).

3.2 Methods

A medical team visited the factory and men were seen by appointment. None of the medical team knew to which study group any of the subjects belonged. Some of the cases had received medical reports the previous year informing them of abnormal lung function results, though not of abnormal radiological results (since the presence of low categories of small opacities in the chest radiograph seen in the clinical context had not justified a report of abnormality). One of us (CAS) carried out a clinical examination of the chest, recording physical signs on a questionnaire. Subsequently he recorded a medical history of the subject, reading the questions in standardised format, and recording the answers as given. In case of prolonged hesitation or expressed doubt, individual guidance was given. The questionnaire is appended (Appendix III). The form of the questions on cough, sputum, recent exacerbations of cough and sputum, recent chest illness and smoking history was almost identical to that in the Medical Research Council Questionnaire of Respiratory Symptoms (MRC, 1976). The questionnaire additionally asked about personal history of asthma, hay fever, eczema, perennial rhinitis, pneumonia, acute bronchitis, tuberculosis; childhood history of bronchitis, unduly frequent colds, tonsillitis and ear infections; first degree relative history of chronic bronchitis,

frequent chest colds, asthma, hay fever and eczema, and parental smoking habit.

Skin prick tests to mixed grass pollens, Dermatophagoides pteronyssinus, house dust mix and Aspergillus fumigatus (Bencard) were performed and read at 15 minutes. Weal diameters of 4 mm or more were taken as positive. Men for whom the control solution showed a response of 2 mm or more were excluded from the analysis of skin test results.

Forced expiratory flow/volume curves were recorded on a rolling seal spirometer and X-Y recorder using air and following three vital capacity breaths of 80% helium/20% oxygen. Three technically satisfactory flow/volume curves were recorded on air and two on the helium mixture. The curve selected for analysis was that with the greatest sum of forced vital capacity (FVC) and forced expired volume in one second (FEV_1). Maximum flows at 50% and 25% of vital capacity (i.e. when 25% of the FVC has still to be expired) on air ($\dot{V}\ max_{50}$ and $\dot{V}\ max_{75}$) and helium mixture ($\dot{V}\ max_{50\ He}$ and $\dot{V}\ max_{25\ He}$) and forced expired time were measured on this curve. The peak expiratory flow rate (PEFR) was also recorded, even though the slow response time of the X-Y plotter (relative to the rate of changes in the flow rate measured) could have caused a systematic underestimation of the high flow rates.

Single breath carbon monoxide transfer factor (T_{LCO}) was measured in duplicate using an automated spirometer system (P.K. Morgan Ltd.). Effective alveolar volume ($V_{A_{eff}}$) and T_{LCO} were calculated for each manoeuvre and the means of the readings were analysed.

3.2.1 Methods of analysis

For the four case/control studies the purpose was to compare men in the two groups (cases and controls) on the many measurements taken during clinical examinations. The emphasis was on an exploratory approach to identify suggestive patterns in the data. The scope of the statistical work carried out, and the methods used, are described in Appendix IV. The main results are presented descriptively in this report in terms of average values and variability in each group. Observed average differences in the clinical measurements between cases and controls were tested for statistical significance one at a time, using conventional

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methods (chi-squared tests for binary variables, independent two-sample t-tests for the lung function measurements). In the context of this study these tests are not exact or optimal, but they do give reliable pointers to where real differences exist between the groups studied. Additionally, patterns of abnormality of lung function after taking account of the level of FEV_1 were studied by examining the ratios of the values of other lung function tests to the value of the FEV_1 (for example $\frac{FVC}{FEV_1}$ or $\frac{\dot{V}max_{50}}{FEV_1}$), on the assumption that the FEV_1 expresses an overall level of lung function (of a non-specific type) and the pattern of the lung function ratios reflects type of abnormality, though did not necessarily express adequately its clinical severity. Predicted values for FEV_1 were based on regressions for age, height and weight in 148 non-smokers, excluding pensioners, studied in the previous epidemiological survey.

The accuracy to which the sample of men seen represented the population under study was assessed by examination of their FEV_1 recorded at the previous survey, in 1979.

3.3 Results

3.3.1 Men with small rounded opacities

Twenty-eight men in whose chest radiograph one reader reported small rounded opacities were seen, and 29 controls in whose radiograph all readers agreed no small opacities were present. Characteristics of these groups are set out in Table 12. The majority were smokers.

Sample bias

Possible sample bias was examined by analysis of the FEV_1 values of the year before. Differences of predicted from actual FEV_1 (FEV_1 residuals) were calculated from regressions in the non-smokers studied in the previous survey. The distribution of FEV_1 residuals of cases and controls is set out in Table 13. The mean residual FEV_1 of 28 men with small rounded opacities attending for examination was - 0.29 litres, whereas that for 5 men who were invited but did not attend was - 1.14 litres, suggesting some self-selection of iller men out of the sample ($P < 0.01$). The mean residual FEV_1 of all men invited, whether seen or not, was lower than, but not statistically significantly different from,

those not invited (- 0.42 litres and - 0.72 litres respectively). Thus the bias (mean FEV_1 residual of men seen was - 0.29 litres, and for men not seen was - 0.81 litres, $P < 0.01$) was partly attributable to self-selection for five iller men out of the sample. Amongst the controls, there was no significant difference in mean FEV_1 residual between men seen and men not seen, but the distribution of FEV_1 residuals of men invited but not seen again suggested some self-selection of ill men out of the study.

Examination of the indices of PVC dust exposure available for these men from the previous study (Table 14) shows that men invited but not attending tended to have dust exposures in the lower ranges, suggesting that the absence of these men was unlikely to have seriously affected the results of this study of dust effects on the lung.

The mean residual FEV_1 in 1979 of all men with small rounded opacities invited for examination in 1980, whether seen or not, was - 0.26 litres lower than that for all controls without opacities, a difference which was not statistically significant in these small samples, but which was of the same order as the difference found in the previous analysis of the much larger population.

Comparison of men with small rounded opacities and controls

Men with small rounded opacities in the chest radiograph more often complained of chronic sputum production (9 men, 32%) than the controls (1 man, 3.4%). A first degree relative history of asthma, hay fever or eczema was reported by fewer cases (5 men, 21%) than controls (12 men, 46%), though this was not accompanied by similar differences in prevalences of personal history of allergic symptoms or positive skin tests. No other statistically significant differences in personal or family medical history were demonstrated (Table 15).

Physical signs of gross respiratory dysfunction were rare, and were associated with very low FEV_1 in both cases and controls. Crackles heard through the stethoscope in the middle or late parts of inspiration (heard separately or in combination) were more frequent in cases than controls (Table 15). Wheezes were not audible in these subjects.

Differences between cases and controls in the mean observed results of the lung function measurements were small, and none reached statistical significance at the 5% level (Table 16). Multiple regression analyses, taking account of age, height, weight and dust exposure confirmed the lack of any substantial or statistically significant differences between cases and controls (Appendix IV), nor were any mean differences in pattern of lung function between cases and controls identified.

The FEV_1 of seventeen cases and controls was less than 80% of the predicted value for age and height. Some had substantial impairment of lung function likely to be associated with symptoms, but these men were not significantly over-represented among those with small rounded opacities. The patterns of lung function abnormality in these men, in conventional clinical terms, were obstructive in six men ($\frac{FEV_1}{FVC}$ ratio less than 0.65), restrictive in seven men (ratio greater than 0.75) and intermediate in four men (ratio 0.65 - 0.75). More detailed examination of lung function patterns in these men did not demonstrate any obvious relationships with rounded opacities. Thus although there was in men with small rounded opacities further evidence of abnormalities of the lung, namely increased bronchial mucus secretion and abnormal mechanical functioning of alveolar units (crackles), this lung damage was insufficiently gross to be associated with clinically important loss of lung function in excess of that related to age and smoking habit, and was not associated with a pattern of lung function abnormality which could be distinguished from that found in men without small rounded opacities.

<u>Comparisons of men with low or high dust exposures among those with small rounded opacities and controls without opacities</u>

The men with small rounded opacities were divided into approximately equal groups of those with dust exposures less or greater than 15 dust index units, thus giving a group of men likely to include those whose small rounded opacities were related to dust exposure, and a group in whom they were not likely to be dust-related. The distribution of dust exposures in these men is described in Table 14.

There was no suggestive evidence of differences in prevalences of symptoms and physical signs between those with low or high dust exposure after allowing for age differences. The means for the lung function tests were very similar between the two groups.

Patterns of lung function were analysed by examining the test results divided individually by the FEV_1 to obtain ratios. The $\frac{FVC}{FEV_1}$, $\frac{PEFR}{FEV_1}$, $\frac{\dot{V}max_{50}}{FEV_1}$ and $\frac{\dot{V}max_{25}}{FEV_1}$ ratios (representing airflow during forced expiration) corresponded very closely between the groups but the $\frac{T_{LCO}}{FEV_1}$ ratio was higher in the high dust group (high dust group T_{LCO} ratio 10.28, low dust group 8.56 (Table 17, Figure 8)). After allowing for age and height differences, which were not themselves statistically significantly related to $\frac{T_{LCO}}{FEV_1}$ ratio, in these men, the difference between high and low dust men remained statistically significant only at the 10% level. When the cases with low dust exposure were combined with controls with low dust exposure and compared with cases and controls with high dust exposure, the difference was confirmed. A similar comparison of the effect of dust exposure within controls alone showed similar but slighter trends of those ratios, which could easily have arisen by chance. The forced expiration ratios were similar in all subgroups of men, including that group with no opacities and low dust exposure.

Substantial impairment of lung function (FEV_1 less than 80% of predicted) was not significantly more common in high or low dust groups.

We conclude that there was suggestive evidence that small rounded opacities related to PVC dust exposure were associated with a pattern of lung function abnormality characterised by relatively better preservation of gas transfer factor for the level of FEV_1 than men whose opacities were not related to dust exposure, but no differences in pattern of airflow during forced expiration. Furthermore there were no differences in pattern of airflow between these men and controls without opacities, after allowing for the level of FEV_1.

This suggests that PVC dust-related small rounded opacities were associated with less alveolar damage relative to the level of ventilation than rounded opacities not related to PVC dust, and that reduction of airflow rates during forced expiration tended to be uniform (concentric). These

features taken together suggest a physiological defect intermediate between an obstructive and a restrictive defect, probably the result of disease of very peripheral airways. However, the lung damage indicated by this defect appeared to be slight, for clinically important reductions of lung function were not found more commonly among these men with higher dust exposure than those with lower dust exposure.

3.3.2 Men with small irregular opacities

Eighteen men in whose chest radiograph one or more readers reported small irregular opacities were seen, and 20 controls in whose radiographs all readers agreed no small opacities were present. Characteristics of these groups are set out in Table 18.

Sample bias

Possible sample bias was examined by analysis of the FEV_1 values of the year before, as described for men with small rounded opacities. The mean residual FEV_1 of 18 men with small irregular opacities attending for examination was - 0.50 litres, whereas that for two men who were invited but did not attend was - 0.53 litres. There was no evidence of self-selection of iller men out of the sample of cases, nor among the controls.

Medical histories and lung function

The prevalences of positive answers to selected questions on respiratory symptoms and personal and family medical history are summarised in Table 19. There were no differences in prevalences of chronic respiratory symptoms between cases and controls, but men with irregular opacities more often complained of recent chest illnesses causing time off work or recent increases in cough and phlegm. There were no statistically significant differences in history of allergic symptoms in men seen nor in results of the skin tests. A family history of asthma, hay fever or eczema was more common among the cases, and family history of recurrent bronchitis or chest colds was marginally more common among them than among the controls. There were no important differences in auscultatory signs between the groups; the slightly greater prevalence of mid-inspiratory crackles among the controls seems an isolated finding and is difficult to explain.

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Differences in mean lung function test results between cases and controls were small and did not approach statistical significance (Table 20). Multiple regression analyses for each lung function measurement, taking account of age, height, weight, and dust index confirmed the lack of any substantial or statistically significant differences between cases and controls (Appendix IV).

Examination of lung function patterns as described for the men with small rounded opacities showed some suggestive but not statistically significant differences between men with irregular opacities and controls. The pattern suggested more airflow obstruction for the level of FEV_1 among cases than controls in that the $\frac{FVC}{FEV_1}$ ratio appeared to be slightly elevated and the $\frac{\dot{V}max}{FEV_1}50$ and $\frac{\dot{V}max}{FEV_1}25$ ratios slightly lower in the cases than controls (Table 21). The patterns were therefore examined among men whose FEV_1 was less than 80% of predicted, and who would therefore be regarded as probably having abnormal lung function. The results indicated that the pattern of lung function associated with small irregular opacities and low FEV_1 was associated with an excessive reduction of relative expiratory flow rates at 50% and 25% of vital capacity and an increase in $\frac{FVC}{FEV_1}$ ratio when compared with men with low FEV_1 but no opacities (Table 22, Figure 9).

We conclude that the presence of small irregular opacities in the chest radiograph was associated with history of recent chest illness, and when these opacities were accompanied by clinically abnormal lung function, the pattern of functional abnormality was of obstructive type. These men were likely to have been suffering from chronic non-specific airflow obstruction, not related to PVC dust exposure.

3.3.3 Non-smokers with low FEV_1

Thirteen non-smokers with large negative residual FEV_1 and high index of dust exposure were seen, and twelve non-smoking controls with large negative residual FEV_1 and low index of dust exposure. Characteristics of these groups are set out in Table 23. Matching was imperfect in that the controls were younger, taller and heavier than the cases. Two invited cases and three controls did not attend for examination, but their FEV_1 residuals calculated from the previous year's measurement, and dust exposures, were similar to those of the men who attended.

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Prevalences of symptoms were low, and there were no significant differences between cases and controls (Table 24). The medical histories did not suggest that these men were suffering from symptoms of any respiratory disease.

There appeared to be substantial differences between cases and controls in some of the lung function results, but this could be attributed to the age and height differences. After allowing for age and height differences, no statistically significant differences in lung function remained (Table 25 and Appendix IV). The pattern of lung function after allowing for level of FEV_1 was also examined, and no distinctive differences in pattern were seen between cases and controls. None of the cases had an FEV_1 of less than 80% of predicted value. Of the controls three were below 80%, none below 75%.

We conclude that among non-smokers selected for large negative residual FEV_1, no detectable differences in symptoms, physical signs or pattern of lung function could be found between men with high estimated dust exposure and those with low exposure. These men were probably all in normal respiratory health.

3.3.4 Smokers with low FEV_1

Eighteen current cigarette smokers with large negative residual FEV_1 and high index of dust exposure were seen, and 18 smoking controls with large negative residual FEV_1 and low index of dust exposure. Five cases and eight controls were invited but not seen. Their FEV_1 residuals calculated from measurements made the previous year were similar to those of the men who attended. Characteristics of these groups are set out in Table 26. Age-matching was close, though controls tended to be taller.

A personal history of hay fever or perennial rhinitis was more common among the controls than the cases. A past history of acute bronchitis, pneumonia or pleurisy and late inspiratory crackles heard on auscultation were slightly commoner among the cases than controls, but these differences did not reach statistical significance at the 5% level (Table 27). Respiratory symptoms were more common in both cases and controls than the non-smokers.

No substantial or statistically significant differences of lung function between cases and controls were apparent (Table 28). A multiple regression analysis for each lung function test allowing for age, height, weight and FEV_1 confirmed that differences in lung function between the groups were small and not statistically significant (Appendix IV). The pattern of lung function after allowing for level of FEV_1 was also examined, and no distinctive differences in pattern were seen between cases and controls. Substantial differences in these patterns between smokers and non-smokers were seen (Figure 10), but these have not been analysed in detail. Seventeen of the smoking cases had an FEV_1 less than 80% of predicted, and six were under 60%. Fifteen of the smoking controls were under 80% and seven under 60%. Thus the selection procedure had selected men with clinically important impairment of lung function equally among both cases and controls.

We conclude that among smokers selected for large negative residual FEV_1 no detectable differences in pattern or level of lung function would be detected between men with high estimated dust exposure and those with low exposure. A higher prevalence of history of asthma or hay fever among the controls probably indicated avoidance of dusty conditions by these men. In view of this the slightly higher prevalences of history of acute bronchitis, pneumonia or pleurisy and of crackles heard through the stethoscope among cases than controls could be related to the differences in prevalence of asthma in these groups rather than to an effect of PVC dust exposure, although the timing of the crackles in late inspiration suggests that they could have been the result of dust exposure, rather than the result of smoking, which tends to be related to mid and late inspiratory crackles. However, there were no other important differences between those men with high or with low dust exposure, and we conclude that these men did not have recognisably different clinical syndromes from those with low exposures.

4. DISCUSSION

Our previous study of 818 present and past workers at a factory making polyvinylchloride (PVC) had shown that estimates of exposure to respirable PVC dust were inversely related to lung function after allowing for the effects of age and smoking, and related to prevalence of slight abnormalities of the chest radiograph; one of three experienced readers found that prevalence of small rounded opacities category 0/1 or greater was related to dust exposure after allowing for age.

The present studies extended the sample of the study population to include all other members of the current workforce who had worked at any time in the dustier plants in the factory, to examine the prevalence of respiratory abnormality in these men, and to examine in this extended population and in the original study group the relationship between dust exposure and radiological appearances. Also men selected from the first study on the basis of radiological and functional abnormality have been examined in detailed case/control studies to attempt to identify clinical syndromes associated with PVC dust exposure, and estimate if possible the clinical severity of the effects of the dust on the lung.

These studies confirm in an extended population at the same factory an inverse relationship of lung function with estimates of exposure to PVC dust, and confirm the relationship between dust exposure and the presence of small rounded opacities in the chest radiograph. The chest radiographs from the original study population were re-read in the present work by the three experienced readers who read them previously, and were also read twice by a self-trained panel of readers. The majority of readers found that the prevalence of small rounded opacities was related to age, and in some readings relationships were found between prevalence of small rounded opacities and estimates of PVC dust exposure, after allowing for age. Not only did readers differ from each other in the detection of the relationship with dust exposure, but also some readers detected this effect on one reading but not on the other. The three experienced readers recorded higher prevalences of small rounded opacities on the second reading than the first, and this is likely to have been the result of a greater awareness of this type of opacity

induced by knowledge and discussion of the results of the first reading. The reader who had first detected the relationship with dust exposure recorded a much greater prevalence of small rounded opacities on the second reading, and in spite of his change in interpretation of small rounded opacities, the relationship of these opacities with dust exposure was again found for his readings, this time between a higher category of profusion and dust exposure.

The reasons for these various differences in detection of these effects are likely to include the slight degree and non-specific nature of the radiographic appearances related to exposure to PVC dust, which are indistinguishable from those related to age, as well as variability in readers' interpretations of the appearances. This helps to explain the differing results reported by other workers (VERTKIN et al., 1970; LILIS et al., 1976; MAPP et al., 1978), and emphasises that in studies of the relationship between non-specific radiological appearances and dust exposure, it is important to take account of the confusing effects of other age-related factors.

In the case/control studies we examined men most likely to have been affected by PVC dust, by selecting men whose radiographs were thought to show small rounded opacities, and also men whose estimated PVC dust exposure was in the higher range and whose FEV_1 was at the lower end of the range after allowing for age, height and weight, together with suitably matched controls. The men with small rounded opacities had slightly increased prevalences of sputum production and of crackles heard through the stethoscope, indicating disturbances of the secretory function of the lung and of the mechanical function of alveolar units, thus confirming that these radiographic abnormalities were associated with minor functional abnormalities. The audible crackles tended to be of the end-inspiratory type, usually associated with diseases in which diffuse fibrosis of the lung occurs (FORGACS, 1978). In spite of this we were unable to show that important clinical illness was related to PVC dust exposure or to the presence of small rounded opacities in the chest radiograph. The previous epidemiological study of 818 men had shown that the presence of small rounded opacities in the chest radiograph was associated with slightly lower lung function than would be expected for age, height, smoking habit and dust exposure. The present

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case/control study has not confirmed this difference, probably because of the smaller numbers of men in this study, and because some iller men did not attend for examination. These missing men, however, tended to have low estimates of PVC dust exposure, so it is unlikely that their omission has caused us to underestimate the seriousness of the effects of PVC dust since their radiological appearances were likely to be related to age rather than PVC dust exposure. We conclude that the presence of small rounded opacities of low categories of profusion in the chest radiograph, while associated with a slight reduction of lung function detectable when these men were studied as part of a large population, does not in an individual worker give cause for concern that exposure to PVC dust has seriously affected his respiratory health.

The case/control studies of men whose lung function was at the lower end of the range did not show any characteristic differences in symptoms or pattern of lung function in men with higher dust exposures compared with men with low dust exposures and similarly low values of lung function. While the non-smokers selected in this way were probably all in normal respiratory health, the substantial amount of clinical illness found among these selected smokers was probably the result of their smoking habit, and showed no characteristic features which would suggest that their illness was the result of exposure to PVC dust. The one exception to this was a slightly greater prevalence of crackles heard through the stethoscope of late inspiratory type. While this could partly be the result of a greater prevalence of men with allergic conditions in the control group (possibly self-selected by their avoidance of dusty conditions), the timing of the crackles in the respiratory cycle suggests that these could have been the result of PVC dust exposure (since smoking tends to cause early and mid-inspiratory crackles), a conclusion consistent with the findings in the men with small rounded opacities. However, there were no other important differences between these men with high or low dust exposure, and we conclude that these men with high exposures did not have recognisably different clinical syndromes from those with low exposures.

These case/control studies, while showing no obvious physiological differences between men with small rounded opacities in the chest

radiograph and controls of similar age and smoking habit but normal radiographs, did suggest among the men with small rounded opacities a difference between men with lower and men with higher estimates of dust exposure, in that the men with higher dust exposures had a pattern of lung function abnormality in which the flow rates during forced expiration were normal after adjusting for the level of FEV_1, but the gas transfer factor appeared to be relatively better preserved than the FEV_1. This form of analysis was an exploratory one, and was based on a convention that the level of FEV_1 represented the overall level of lung function, reasonably sensitive to all types of lung function defect, and that examination of types of lung functional abnormality among other lung function tests should first take account of the level of FEV_1. A simple if crude method of taking account of the level of FEV_1 when considering the value of a second lung function test is to divide the second test result by the value of the FEV_1 to obtain a test:FEV_1 ratio. In this exploratory analysis the ratios of various lung function tests to the FEV_1 have been compared. In the case of the men with small rounded opacities and high dust exposure the values of the ratios of flow rates during forced expiration were very similar to those for men with low dust exposure, whether or not they had small opacities, but there was suggestive evidence that the ratios of gas transfer factor to FEV_1 were higher, implying that the gas transfer factor was relatively better preserved than the FEV_1. This pattern of lung functional abnormality could therefore be considered intermediate between an obstructive type or restrictive type, in that the lung volumes and expiratory flow rates were reduced in a concentric way, a feature of restrictive defects, but the gas transfer factor was not reduced proportionately, even though this would be expected in a classical restrictive defect. The results of the large epidemiological survey had also suggested an intermediate or mixed type of defect, for the FEV_1 and the forced vital capacity were both inversely related to dust exposure, but the ratio between them was not. It is probable that this defect was the result of disease of the peripheral airways, without much accompanying alveolar damage. This is in keeping with what is so far known about the histological appearances of the lungs in exposed animals and man, where fibrosis has not been a prominent feature (FRONGIA et al., 1974; ARNAUD et al., 1978) and in some animal studies an inflammatory reaction has been observed round respiratory and terminal bronchioles (AGARWAL et al., 1978).

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Men with small irregular opacities in the chest radiograph (not thought to be related to PVC dust exposure) and reduced lung function had an obstructive type of functional defect, with relative preservation of the gas transfer factor, demonstrated clearly by the analysis of lung function test:FEV_1 ratios.

We conclude from the large epidemiological and small case/control studies that exposure to PVC dust in the concentrations experienced in this factory caused a small but detectable reduction in lung function in the study population, and caused an increase in prevalence of slight abnormalities of the chest radiograph. The clinical features of the non-specific respiratory disease associated with dust exposure additionally included an increase in prevalence of productive cough in those with abnormalities of the chest radiograph, an increase in prevalence of crackles heard through the stethoscope during mid and late inspiration, and an average pattern of lung functional abnormality characterised by a uniform reduction of ventilatory capacity, with relative preservation of gas transfer factor. Important clinical illness or serious reduction of lung function has not been shown to be related to PVC dust exposure at the levels occurring in this factory, and in view of these case/control studies, we conclude that PVC dust exposure at these levels is unlikely to have caused serious disability.

While differences in PVC formulations or levels of exposure could have accounted for some of the conflicting results reported in the literature, it is probable that differences in study design have been the main cause of these inconsistencies. The high prevalence of abnormalities of lung function occurring as a result of factors other than PVC dust exposure indicates the importance of making comparisons with careful estimates of dust exposure or carefully selected control groups. Where this is not done, the effect of PVC dust exposure may not be detected, especially when the study population has been exposed to other potentially noxious agents (GAMBLE et al., 1976); or effects more properly attributed to other agents including smoking or general atmospheric pollution may be thought to be related to PVC dust exposure (LILIS et al., 1976). In view of the mild degree of the reduction of lung function we found to be related to PVC dust exposure, studies in which defined "abnormal" levels of lung function are compared with exposure would be unlikely to demonstrate effects of PVC dust on the lungs.

The possibility of a rare idiosyncratic disabling response to PVC dust cannot be entirely excluded, and it should be borne in mind that a case of diffuse lung disease in a PVC worker has been reported (ARNAUD et al., 1978), and in our first epidemiological study, one man was found to have clinically obvious lung fibrosis. The relationship of this man's illness to his PVC dust exposure was not clear, though further details of his case will be reported. It is conceivable that different formulations of PVC or exposure to other agents may be related to apparently idiosyncratic reactions in PVC workers. In our studies it has not been possible to take account of the effects of differences in formulations of the PVC, nor of the effects of exposure to vinylchloride monomer, except in a limited examination in the previous study of the effect of probable exposure to monomer on the relationships between PVC dust exposure and disease.

The prevalence of respiratory disease at a second factory manufacturing PVC was low, possibly related to the younger age of the workforce, and a greater proportion of non-smokers among them, and appears to give no cause for concern about an industrial health hazard there.

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	818 men seen in first survey Mean (SD)	229 further men seen in second survey Mean (SD)
Age	46.4 (12.1)	36.5 (13.7)
Years worked at the factory	14.0 (8.6)	9.6 (9.7)
Index of dust exposure	12.9 (12.6)	6.1 (8.3)
Non-smokers	148 (18%)	69 (30%)
Cigarette smokers and other current smokers	436 (53%)	117 (51%)
Ex-smokers	234 (28%)	43 (19%)
Prevalence of chronic cough and/or sputum	192 (23%)	34 (15%)

TABLE 1 Details of populations studied in first and second surveys at first factory.

FEV_1% of predicted value	< 60%	60 - 69%	70 - 79%	80 - 89%	90 - 99%	100 - 109%	110 - 120%	120 - 129%	130%+
Second study (229 men)	2 (0.9%)	7 (3.0%)	11 (4.8%)	26 (11.3%)	36 (15.7%)	72 (31.4%)	50 (21.8%)	22 (9.6%)	3 (1.3%)
First study (818 men)	41 (5.0%)	36 (4.4%)	70 (8.6%)	139 (17.0%)	202 (24.7%)	191 (23.3%)	102 (12.5%)	27 (3.3%)	10 (1.2%)

TABLE 2 Distribution of FEV_1 in relation to predicted values for 229 men in second study at first factory and those for the original study population.

Age range (yr)	Non-Smokers	Current Smokers	Ex-Smokers	All
< 30	15 (47%)	14 (44%)	3 (9%)	32 (100%)
30 - 39	11 (29%)	21 (55%)	6 (16%)	38 "
40 - 49	9 (45%)	5 (25%)	6 (30%)	20 "
50+	10 (27%)	8 (22%)	19 (51%)	37 "
All	45 (35%)	48 (38%)	34 (27%)	127 (100%)

TABLE 3 Ages and smoking habits of 127 men at the second factory.

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FEV_1 % of predicted value	60 - 69%	70 - 79%	80 - 89%	90 - 99%	100 - 109%	110 - 119%	120 - 129%	130%+
No. of men in each group	1	5	22	37	39	15	7	1

TABLE 4 Distribution of FEV_1% of predicted value of 127 men at second factory.

	Age (yr)	FEV_1 % predicted FEV_1	FEV_1 % FVC	Cough and/or sputum	Smoking		History of chest illness
					Current	Past	
1	35	75.9	73	No	No	Yes	No
2	29	78.9	77	No	No	No	No
3	27	77.2	78	No	Yes	-	No
4	56	78.8	67	No	No	No	Yes
5	38	74.6	63	Yes	Yes	-	No
6	57	64.0	62	No	No	Yes	Yes

TABLE 5 Details of the six men with FEV_1 below 80% of the predicted value.

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Reader		Category of profusion of small rounded opacities		
		0/0	0/1 or greater	1/0 or greater
03	1st reading	800	18 (2.2%)	2 (0.2%)
	2nd reading	787	31 (3.8%)	7 (0.9%)
15	1st reading	814	4 (0.5%)	2 (0.2%)
	2nd reading	797	21 (2.6%)	18 (2.2%)
17	1st reading	768	50 (6.1%)	10 (1.2%)
	2nd reading	326	492 (60.1%)	17 (2.1%)

TABLE 6 Prevalences of small rounded opacities recorded by three experienced medically qualified readers on first and second readings of 818 chest radiographs.

Reader		Category of profusion of small irregular opacities		
		0/0	0/1 or greater	1/0 or greater
03	1st reading	786	32 (3.9%)	7 (0.9%)
	2nd reading	788	30 (3.7%)	12 (1.5%)
15	1st reading	765	53 (6.5%)	46 (5.6%)
	2nd reading	781	37 (4.5%)	34 (4.2%)
17	1st reading	789	29 (3.5%)	8 (1.0%)
	2nd reading	780	38 (4.6%)	7 (0.9%)

TABLE 7 Prevalences of small irregular opacities recorded by three experienced medically qualified readers on first and second readings of 818 chest radiographs.

Reader		Category of profusion of small rounded opacities		
		0/0	0/1 or greater	1/0 or greater
L1	1st reading	410	406 (49.8%)	363 (44.5%)
	2nd reading	465	351 (43.0%)	328 (40.2%)
L2	1st reading	352	464 (56.9%)	311 (38.1%)
	2nd reading	517	299 (36.6%)	127 (15.6%)
L3	1st reading	760	56 (6.9%)	38 (4.7%)
	2nd reading	781	35 (4.3%)	24 (2.9%)
L4	1st reading	782	34 (4.2%)	34 (4.2%)
	2nd reading	789	27 (3.3%)	27 (3.3%)
L5	1st reading	813	3 (0.4%)	2 (0.2%)
	2nd reading	811	5 (0.6%)	2 (0.2%)

TABLE 8 Prevalences of small rounded opacities recorded by five self-trained readers on first and second readings of 816 chest radiographs.

Reader		Category of profusion of small irregular opacities		
		0/0	0/1 or greater	1/0 or greater
L1	1st reading	778	38 (4.7%)	37 (4.5%)
	2nd reading	791	25 (3.1%)	25 (3.1%)
L2	1st reading	813	3 (0.4%)	3 (0.4%)
	2nd reading	812	4 (0.5%)	2 (0.2%)
L3	1st reading	799	17 (2.1%)	10 (1.2%)
	2nd reading	812	4 (0.5%)	4 (0.5%)
L4	1st reading	809	7 (0.9%)	7 (0.9%)
	2nd reading	810	6 (0.7%)	6 (0.7%)
L5	1st reading	813	3 (0.4%)	2 (0.2%)
	2nd reading	814	2 (0.2%)	2 (0.2%)

TABLE 9 Prevalences of small irregular opacities recorded by five self-trained readers on first and second readings of 816 chest radiographs.

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	Category of profusion of small rounded opacities		
Reader	0/0	0/1 or greater	1/0 or greater
03	223	6 (2.6%)	2 (0.9%)
15	228	1 (0.4%)	1 (0.4%)
17	114	115 (50.2%)	4 (1.7%)

TABLE 10 Prevalences of small rounded opacities recorded by three experienced medically qualified readers in the chest radiographs of 229 additional men.

	Category of profusion of small irregular opacities		
Reader	0/0	0/1 or greater	1/0 or greater
03	224	5 (2.2%)	1 (0.4%)
15	224	5 (2.2%)	5 (2.2%)
17	227	2 (0.9%)	0 (0.0%)

TABLE 11 Prevalences of small irregular opacities recorded by three experienced medically qualified readers in the chest radiographs of 229 additional men.

	Cases Mean (SD)	Controls Mean (SD)
Number of men	28	29
Age (yr)	52.4 (9.1)	51.3 (9.1)
Height (cm)	172.7 (6.2)	174.0 (6.0)
Weight (kg)	80.8 (10.4)	78.1 (12.7)
Dust exposure (yr x mgm^{-3})	24.3 (20.2)	18.6 (14.5)
Non-smokers	1	2
Current smokers	17	20
Ex-smokers	10	7
Currently employed (at time of original survey)	26	26
Pensioners	2	3

TABLE 12 Study of men with radiographic small rounded opacities : characteristics of groups studied.

	1979 FEV_1 residuals (litres)								All
	greater than predicted				less than predicted				
	0.75+	0.5 < 0.75	0.25 < 0.5	< 0.25	< 0.25	0.25 < 0.5	0.5 < 0.75	0.75+	
Cases seen	1	2	1	5	4	4	7	4	28
Cases invited but not seen	0	0	0	0	0	1	1	3	5
Controls seen	1	3	5	6	1	3	5	5	29
Controls invited but not seen	1	0	0	2	2	0	0	3	8

TABLE 13 Distribution of 1979 FEV_1 residuals (actual FEV_1 minus predicted FEV_1 for age and height) of cases with small rounded opacities and controls.

VAB.00011922223

	Index of dust exposure (yr x mgm^{-3})			
	0 - 14.9	15 - 29.9	30 - 44.9	45+
Cases seen	13	6	4	5
Cases invited but not seen	4	1	0	0
Controls seen	16	6	5	2
Controls invited but not seen	2	4	1	1

TABLE 14 Distribution of dust indices among men with small rounded opacities and controls.

VAB.0001192224

A

	Cases	Controls
History of chronic cough	9 (28)	5 (29)
History of chronic sputum	9 (")	1 (")***
Dyspnoea — all grades	13 (")	11 (")
Dyspnoea — grade I	11 (")	7 (")
Dyspnoea — grades II or III	2 (")	4 (")
History of asthma	2 (")	1 (")
History of recent chest illness	15 (")	10 (")
History of acute bronchitis, pneumonia or pleurisy	13 (")	10 (")
History of hay fever or perennial rhinitis	4 (")	7 (")
Childhood history of recurrent bronchitis, asthma, frequent chest colds or eczema	5 (")	4 (")
Family history of recurrent bronchitis or frequent chest colds	13 (23)	12 (28)
Family history of asthma, hay fever or eczema	5 (24)	12 (26)*
Parent(s) smoked	22 (24)	25 (28)
Auscultatory crackles:		
Inspiratory: early	2 (27)	3 (29)
Inspiratory: mid	8 (")	2 (")**
Inspiratory: late	7 (")	2 (")*
Expiratory	0 (")	1 (")
All	9 (")	5 (")
Wheezes present	0 (")	0 (")
Skin prick test(s) positive	5 (")	3 (")

TABLE 15 Men with small rounded opacities : Summary of selected results from medical history questionnaire, physical examination and skin prick tests.
Figures in parentheses are numbers of men for whom the result was recorded.
(Statistical significance of group differences - * $0.1 > P > 0.05$; ** $0.5 > P > 0.01$; *** $P > 0.01$)

VAB.0001192225

	Cases Mean (SD)	Controls Mean (SD)
FEV_1 (litres)	3.0 (0.7)	3.2 (0.8)
FVC (litres)	4.1 (0.9	4.3 (0.9)
PEFR (litres/sec)	7.2 (1.5)	7.4 (1.7)
$\dot{V}max_{50}$ (litres/sec)	3.3 (1.5)	3.4 (1.4)
$\dot{V}max_{25}$ (litres/sec)	0.8 (0.4)	1.0 (0.5)
$\dot{V}max_{50\,Helium}$ (litres/sec) (27 cases) (28 controls)	4.8 (1.9)	4.7 (2.2)
$\dot{V}max_{25\,Helium}$ (litres/sec) (27 cases) (28 controls)	1.1 (0.5)	1.2 (0.6)
T_{Lco} ml/min/mm Hg (27 cases)	27.6 (5.6)	27.8 (7.3)
$V_{A_{eff}}$ (litres) (27 cases)	6.0 (0.9)	6.1 (0.9)

TABLE 16 28 men with small rounded opacities and 29 controls : mean observed values of lung function data. Differences between cases and controls slight and not statistically significant.

	Lower dust exposure Mean (SD)	Higher dust exposure Mean (SD)
Number	13	15
Age (yr)	49	55
Height (cm)	173	172
Dust exposure (yr x mgm^{-3})	7.5	39
Difference of FEV_1 from predicted (litres)	- 0.30 (0.41)	- 0.52 (0.61)
FVC/FEV_1	1.45 (0.06)	1.37 (0.13)
$PEFR/FEV_1$	2.40 (0.24)	2.40 (0.23)
$\dot{V}max_{50}/FEV_1$	1.10 (0.19)	1.30 (0.28)
$\dot{V}max_{25}/FEV_1$	0.29 (0.06)	0.26 (0.09)
T_{LCO}/FEV_1	8.56 (1.63)	10.28 (2.51)**
K_{CO}/FEV_1	1.52 (0.56)	1.85 (0.68)
V_A/FEV_1	1.95 (0.25)	2.19 (0.43)

TABLE 17 Men with small rounded opacities; lung function results divided by FEV_1. (The T_{LCO} and K_{CO} results for the low dust exposure group are based on 12 technically satisfactory readings.)

(Statistical significance of differences between group averages - ** $P < 0.05, > 0.01$)

	Cases Mean (SD)	Controls Mean (SD)
Number of men	18	20
Age (yr)	60.2 (9.2)	59.9 (8.9)
Height (cm)	171.9 (4.4)	171.6 (5.4)
Weight (kg)	75.2 (9.5)	77.9 (9.3)
Dust exposure (yr x mgm^{-3})	15.7 (12.6)	14.4 (9.9)
Non-smokers	2	2
Current smokers	7	9
Ex-smokers	9	9
Currently employed (at time of original epidemiological survey)	9	13
Pensioners	9	7

TABLE 18 Characteristics of men with small irregular opacities, and controls.

A

	Cases	Controls
History of chronic cough	5 (18)	5 (20)
History of chronic sputum	5 (")	5 (")
Dyspnoea — all grades	8 (")	8 (")
Dyspnoea — grade I	4 (")	3 (")
Dyspnoea — grades II or III	4 (")	5 (")
History of asthma	0 (")	2 (")
History of recent chest illness	9 (")	4 (")*
History of acute bronchitis, pneumonia or pleurisy	11 (")	12 (")
History of hay fever or perennial rhinitis	7 (")	6 (")
Childhood history of recurrent bronchitis, frequent chest colds, asthma or eczema	1 (")	5 (")
Family history of recurrent bronchitis or frequent chest colds	15 (")	11 (19)*
Family history of asthma, hay fever or eczema	12 (17)	5 (16)**
Parent(s) smoked	17 (18)	17 (19)
Auscultatory crackles:		
Inspiratory: early	5 (18)	2 (20)
Inspiratory: mid	2 (")	7 (")*
Inspiratory: late	5 (")	9 (")
Expiratory	0 (")	0 (")
All	10 (")	11 (")
Wheezes present	2 (")	0 (")
Skin prick test(s) positive	2 (")	4 (")

TABLE 19 Men with small irregular opacities : Summary of selected results from medical history questionnaire, physical examination and skin prick tests. Figures in parentheses are numbers of men for whom the result was recorded.

(Statistical significance of group differences - * $0.1 > P > 0.05$; ** $0.05 > P > 0.01$)

VAB.0001192229

	Cases Mean (SD)	Controls Mean (SD)
FEV_1 (litres)	2.6 (0.9)	2.6 (0.6)
Difference from predicted FEV_1 (litres)	- 0.61 (0.64)	- 0.48 (0.65)
FVC (litres) (17 cases) (19 controls)	3.9 (1.1)	3.5 (0.8)
PEFR (litres/sec) (19 controls)	6.4 (1.9)	6.5 (1.4)
$\dot{V}max_{50}$ (litres/sec) (17 cases) (19 controls)	2.5 (1.4)	2.7 (1.0)
$\dot{V}max_{25}$ (litres/sec) (17 cases) (19 controls)	0.7 (0.4)	0.8 (0.3)
$\dot{V}max_{50}$ Helium (litres/sec) (17 cases) (16 controls)	3.5 (2.2)	3.8 (2.0)
$\dot{V}max_{25}$ Helium (litres/sec) (17 cases) (16 controls)	0.9 (0.5)	0.9 (0.5)
TLco ml/min/mm Hg (17 cases) (18 controls)	24.6 (6.2)	25.6 (5.4)
VA_{eff} (litres) (17 cases) (18 controls)	5.8 (1.0)	5.7 (1.0)

TABLE 20 18 men with small irregular opacities and 20 controls: mean observed lung function data.
No statistically significant differences between groups.

	Cases Mean (SD)	Controls Mean (SD)
FVC/FEV_1	1.58 (0.42)	1.41 (0.20)
$PEFR/FEV_1$	2.57 (0.43)	2.56 (0.37)
$\dot{V}\ max_{50}/FEV_1$	0.89 (0.34)	1.02 (0.28)
$\dot{V}\ max_{25}/FEV_1$	0.25 (0.07)	0.28 (0.09)
$TLco/FEV_1$	10.8 (4.6)	10.14 (3.4)
Kco/FEV_1	2.0 (1.2)	1.8 (0.8)
VA/FEV_1	2.6 (1.3)	2.2 (0.5)

TABLE 21 Patterns of lung function of all men with irregular opacities and controls. Differences not statistically significant. Numbers of men consistent with those in Table 20.

VAB.0001192231

	Cases Mean (SD)	Controls Mean (SD)
Number	6	8
Age (yr)	68.8	61.1
Height (cm)	167.7	173.6
Dust exposure (yr x mgm^{-3})	15.0	13.7
Difference of FEV_1 from predicted (litres)	- 1.35 (0.46)	- 1.04 (0.34)
FVC/FEV_1	1.99 (0.43)	1.35 (0.39) **
$PEFR/FEV_1$	2.93 (0.44)	2.72 (0.39)
$\dot{V}\ max_{50}/FEV_1$	0.57 (0.27)	1.03 (0.25) **
$\dot{V}\ max_{25}/FEV_1$	0.20 (0.05)	0.26 (0.05) *
T_{tco}/FEV_1	15.2 (5.2)	11.5 (5.2)
K_{co}/FEV_1	3.2 (1.3)	2.3 (1.0)
V_A/FEV_1	3.9 (1.5)	2.3 (0.7) *

TABLE 22 Patterns of lung function among men with and without small irregular opacities and FEV_1 less than 80% of predicted.

(Statistical significance of differences between group averages - * $0.1 > P > 0.05$; ** $P < 0.05$)

	Cases Mean (SD)	Controls Mean (SD)
Number of men	13	12
Age (yr)	46.1 (12.8)	34.3 (8.2)
Height (cm)	172.2 (6.9)	177.1 (8.1)
Weight (kg)	76.4 (10.6)	81.8 (8.0)
Dust exposure (yr x mgm^{-3})	17.2 (8.8)	1.4 (1.2)
Currently employed	11	10
"Leavers"	0	2
Pensioners	2	0

TABLE 23 Characteristics of non-smokers with large negative residual FEV_1, cases with high dust exposure, controls with low dust exposure.

VAB.0001192233

	Cases	Controls
Number of men	13	12
History of chronic cough	1	1
History of chronic sputum	0	1
Dyspnoea (none greater than grade I)	2	0
History of asthma	0	0
History of recent chest illness	3	4
History of acute bronchitis, pneumonia or pleurisy	4	3
History of hay fever or perennial rhinitis	4	3
Childhood history of recurrent bronchitis, frequent chest colds, asthma or eczema	0	1
Family history of recurrent bronchitis or frequent chest colds	9	5
Family history of asthma, hay fever, eczema	7	7
Parent(s) smoked	11	12
Auscultatory crackles:		
Inspiratory (late only)	1	0
Expiratory	1	0
All	2	0
Wheezes	0	0
Skin prick test(s) positive	2	2

TABLE 24 Non-smokers with large negative residual FEV_1, cases with high dust exposure, controls with low exposure: Summary of selected results from medical history questionnaire, physical examination and skin prick tests. None of the differences reached statistical significance at the 10% level.

	Cases		Controls	
	Mean (SD)	Age and height adjusted residuals (SD)	Mean (SD)	Age and height adjusted residuals (SD)
FEV_1 (litres)	3.3 (0.5)	- 0.05 (0.23)	3.8 (0.5)	0.04 (0.34)
FVC (litres)	4.0 (0.6)	- 0.15 (0.41)	4.9 (0.7)	0.08 (0.55)
PEFR (litres/sec)	7.4 (1.1)	- 0.03 (0.64)	8.1 (0.8)	0.13 (0.79)
$\dot{V}max_{50}$ (" ")	4.2 (1.5)	0.20 (1.20)	4.2 (1.4)	- 0.22 (1.35)
$\dot{V}max_{25}$ (" ")	1.5 (0.7)	0.18 (0.51)	1.6 (0.6)	- 0.01 (0.52)
$\dot{V}max_{50\ Helium}$ (litres/sec) (12 cases)	5.6 (1.3)	0.03 (1.14)	5.8 (1.9)	- 0.05 (1.83)
$\dot{V}max_{25\ Helium}$ (" ") (12 cases)	1.9 (0.7)	0.13 (.51)	2.0 (0.8)	- 0.13 (0.65)
Tlco ml/min/mm Hg (12 cases)	30.7 (5.9)	- 0.09 (4.0)	34.8 (5.4)	0.09 (3.8)
$V_{A_{eff}}$ (litres) (12 cases)	5.7 (0.8)	- 0.14 (0.55)	6.4 (0.9)	0.08 (0.63)

TABLE 25 Non-smokers with large negative residual FEV_1 : Mean lung function results and residuals (difference from predicted values based on regressions for these men) after allowing for age and height. Differences between mean residuals for 13 cases and 12 controls were small and did not approach statistical significance at the 10% level.

VAB.0001192235

	Cases	Controls
No. of men	18	18
Age (yr)	50.8 (7.8)	50.8 (8.8)
Height (cm)	171.9 (5.1)	173.2 (9.1)
Weight (kg)	74.9 (8.8)	74.3 (21.6)
Dust exposure (yr x mgm^{-3})	25.9 (7.7)	4.6 (2.6)
Currently employed	17	16
"Leavers"	1	1
Pensioners	0	1

TABLE 26 Characteristics of smokers with large negative residual FEV_1, cases with high, controls with low index of dust exposure.

VAB.0001192236

A

	Cases	Controls
Number of men	18	18
History of chronic cough	10	11
History of chronic sputum	9	8
Dyspnoea { all grades	10	9
Dyspnoea { grade I	6	6
Dyspnoea { grades II or III	4	3
History of asthma	0	2
History of recent chest illness	11	10
History of acute bronchitis, pneumonia or pleurisy	14	9*
History of hay fever or perennial rhinitis	2	8**
Childhood history of recurrent bronchitis, frequent chest colds, asthma or eczema	5	5
Family history of recurrent bronchitis, frequent chest colds	11	12
Family history of asthma, hay fever, eczema	8	7
Parent(s) smoked	16	18
Auscultatory crackles present:		
Inspiratory : early	3	4
: mid	3	3
: late	7	2*
Expiratory	0	0
All	10	5*
Wheezes present	2	5
Skin prick test(s) positive)	1	4

TABLE 27 Smokers with large negative residual FEV_1, cases with high dust exposure, controls with low exposure.

(Statistical significance of group differences - * $0.1 > P > 0.05$; ** $0.05 > P > 0.01$)

VAB.0001192237

	Cases Mean (SD)	Controls Mean (SD)
FEV_1 (litres)	2.2 (0.6)	2.3 (0.9)
FVC (litres)	3.5 (0.8)	3.6 (0.8)
PEFR (litres/sec)	5.1 (1.3)	5.7 (1.6)
$\dot{V}max_{50}$ (litres/sec)	1.6 (0.8)	1.9 (1.3)
$\dot{V}max_{25}$ (" ")	0.5 (0.2)	0.6 (0.4)
$\dot{V}max_{50}$ Helium (litres/sec) (17 cases)	2.1 (1.1)	2.5 (1.7)
$\dot{V}max_{25}$ Helium (litres/sec) (17 cases)	0.5 (0.2)	0.7 (0.6)
TLco ml/min/mm Hg	24.2 (5.9)	24.6 (7.5)
VA_{eff} (litres)	5.7 (0.8)	5.6 (0.9)

TABLE 28 Mean unadjusted lung function results for smokers with low FEV_1, 18 cases with high dust exposure, 18 controls with low dust exposure. No significant differences in lung function between cases and controls.

A

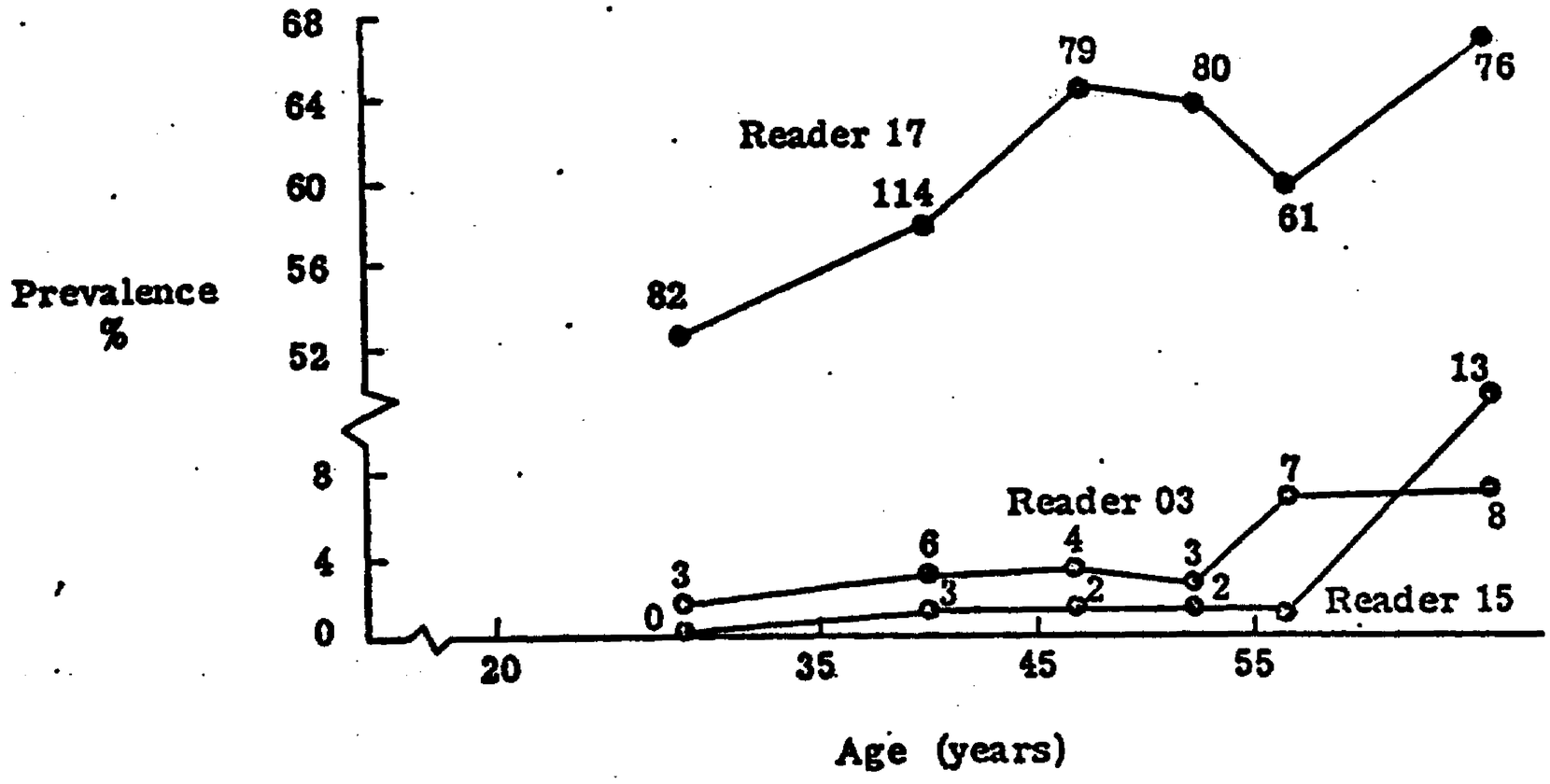

Figure 1 Prevalences of small rounded opacities category 0/1 or greater recorded by three medical readers on second reading, compared with age. Figures on graph are numbers of men.

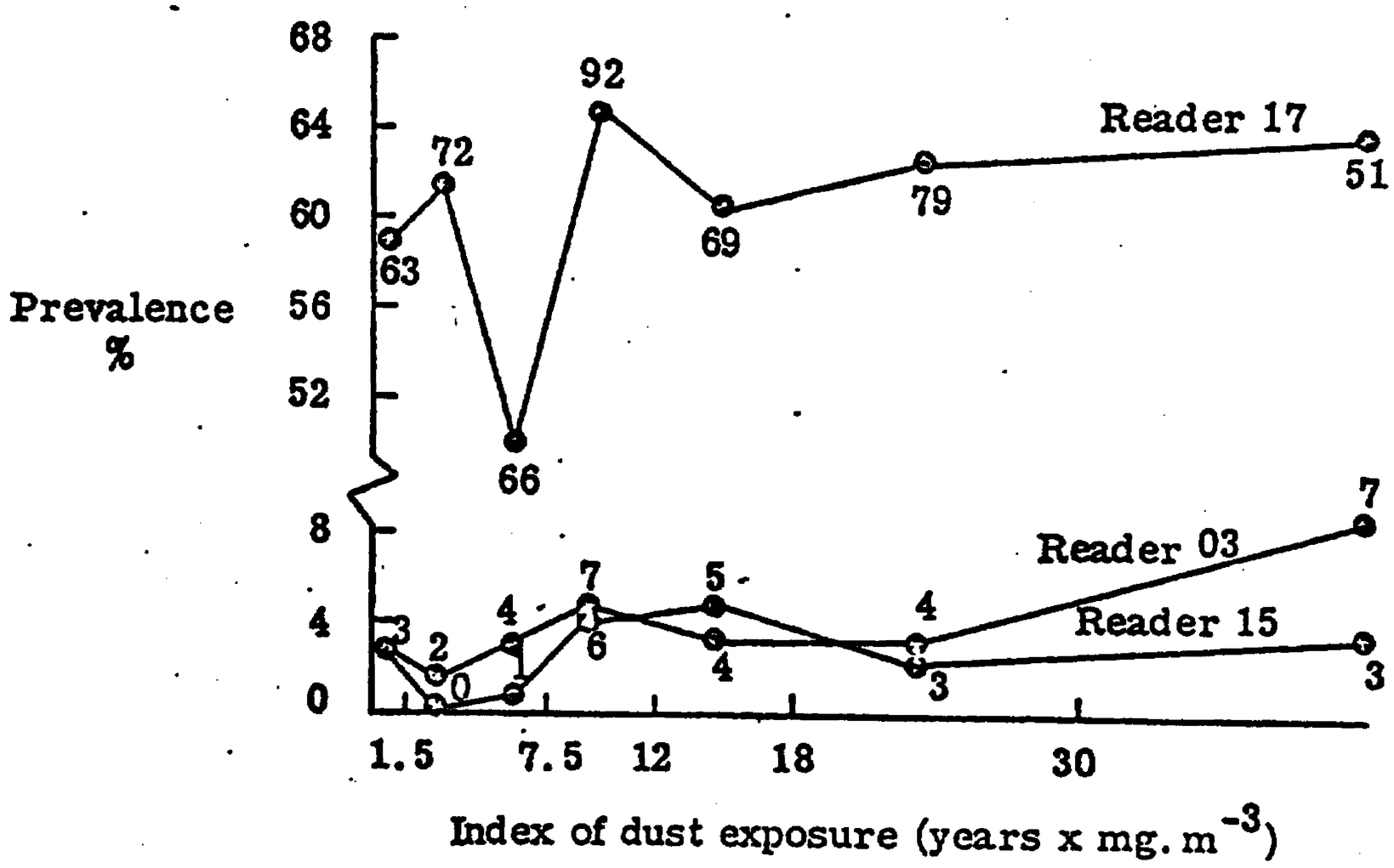

Figure 2 Prevalences of small rounded opacities category 0/1 or greater recorded by three medical readers on second reading, compared with index of dust exposure. Figures on graph are numbers of men.

VAB.0001192239

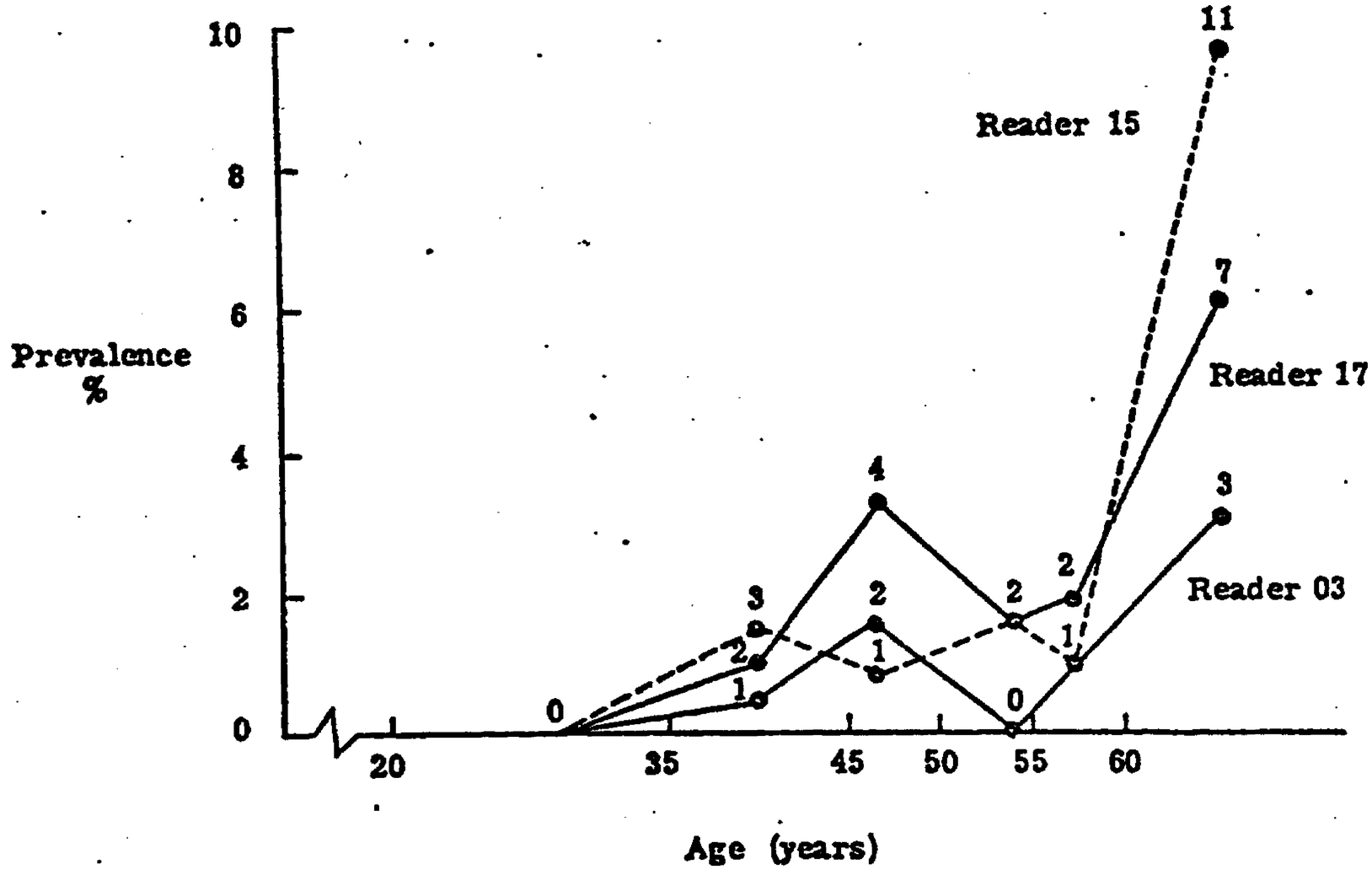

Figure 3 Prevalences of small rounded opacities category 1/0 or greater recorded by three medical readers on second reading, compared with age. Figures on graph are numbers of men.

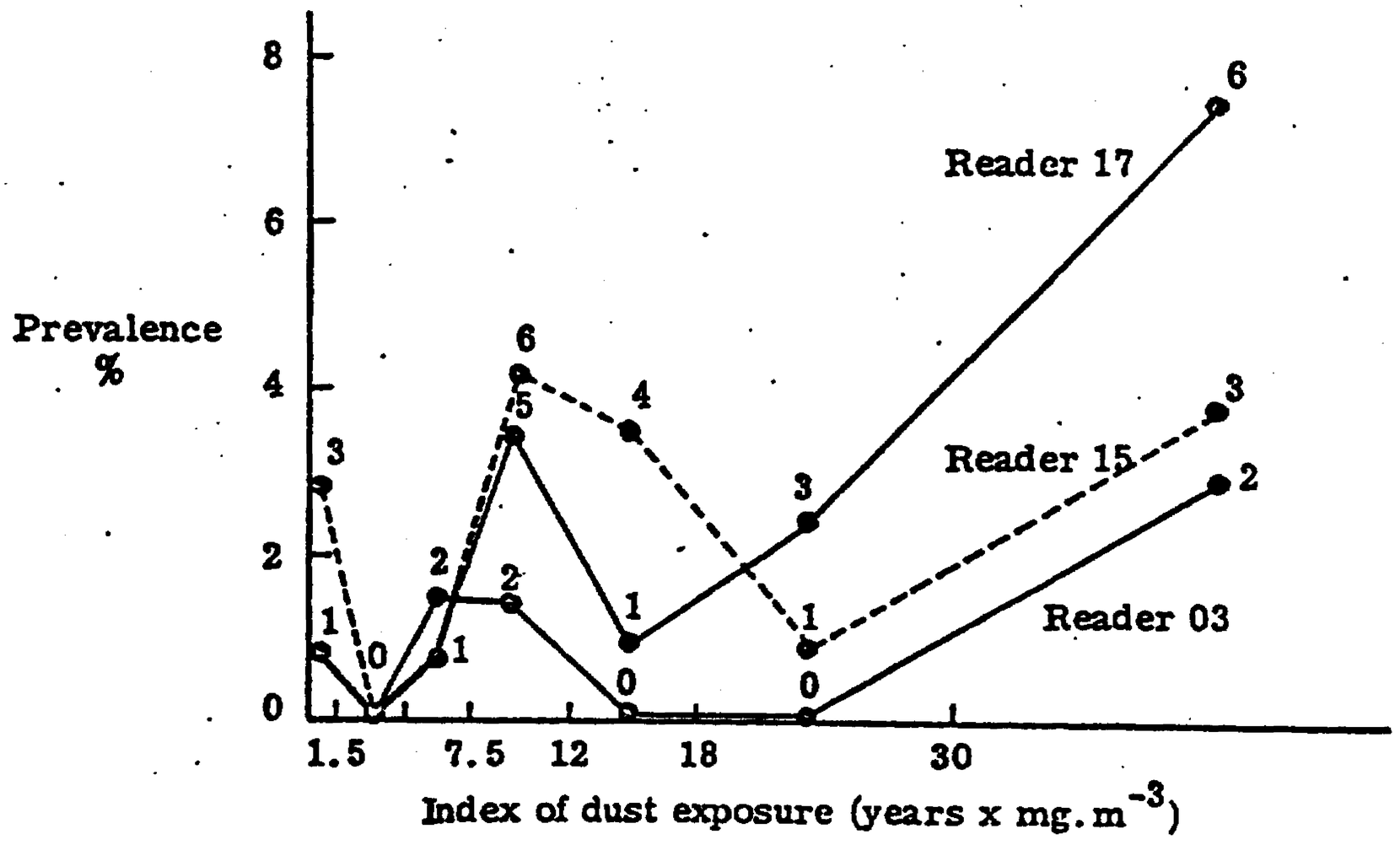

Figure 4 Prevalences of small rounded opacities category 1/0 or greater recorded by three medical readers on second reading, compared with index of dust exposure. Figures on graph are numbers of men.

VAB.0001192240

A

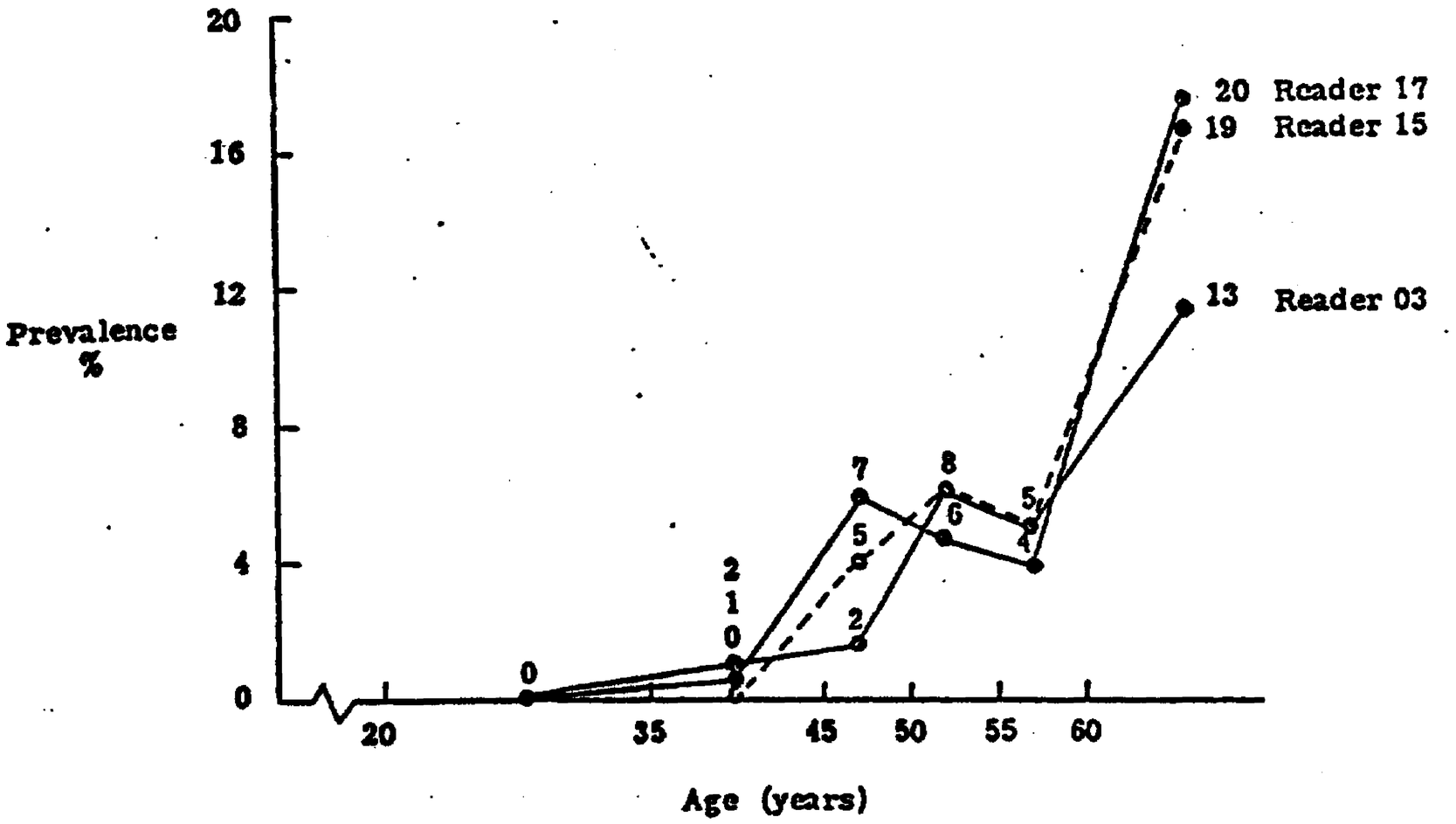

Figure 5 Prevalences of small irregular opacities category 1/0 or greater recorded by three medical readers on second reading, compared with age. Figures on graph are numbers of men.

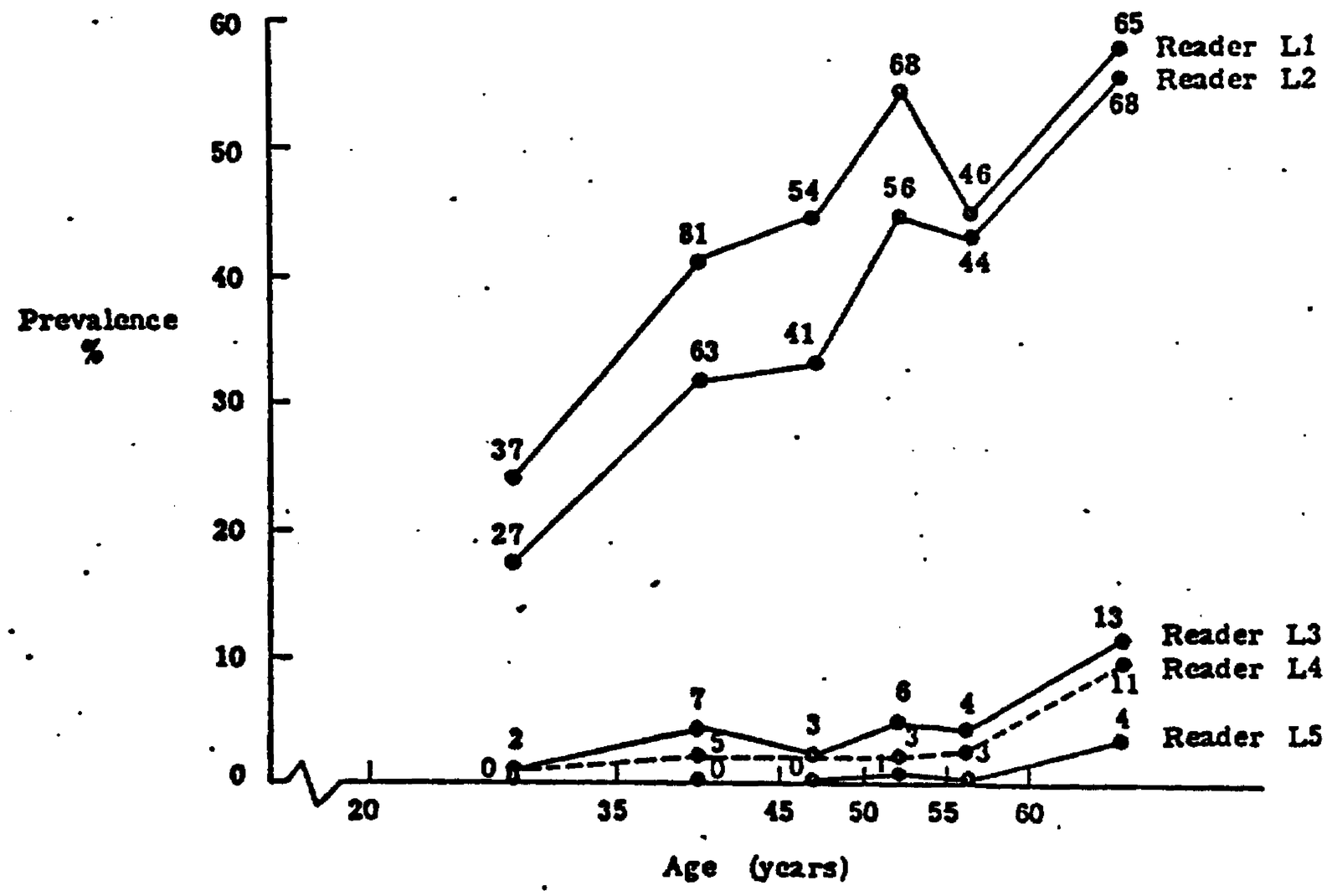

Figure 6 Prevalences of small rounded opacities category 0/1 or greater recorded by five lay panel readers on second reading, compared with age. Figures on graph are numbers of men.

VAB.0001192241

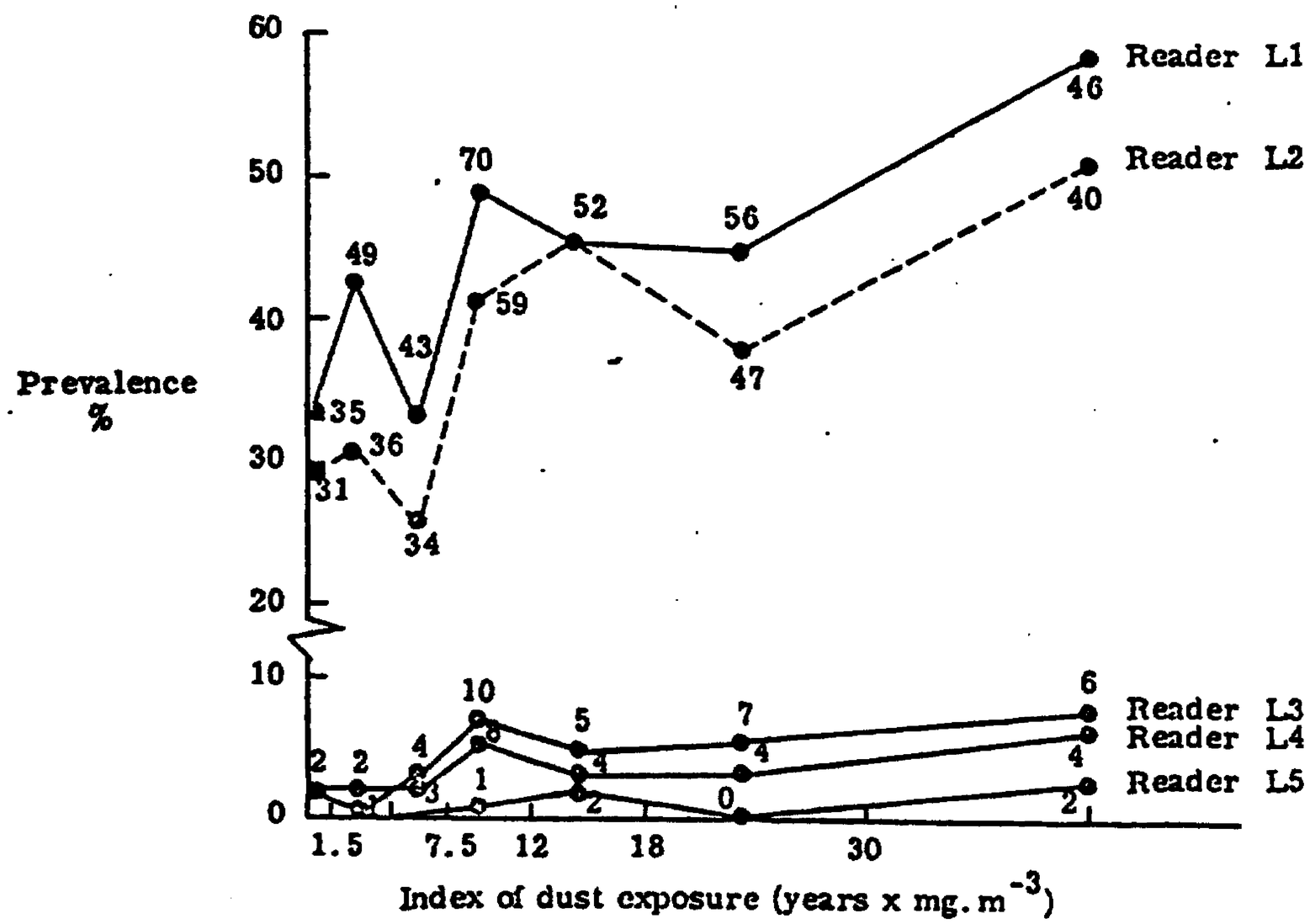

Figure 7 Prevalences of small rounded opacities category 0/1 or greater recorded by five lay panel readers on second reading, compared with index of dust exposure. Figures on graph are numbers of men.

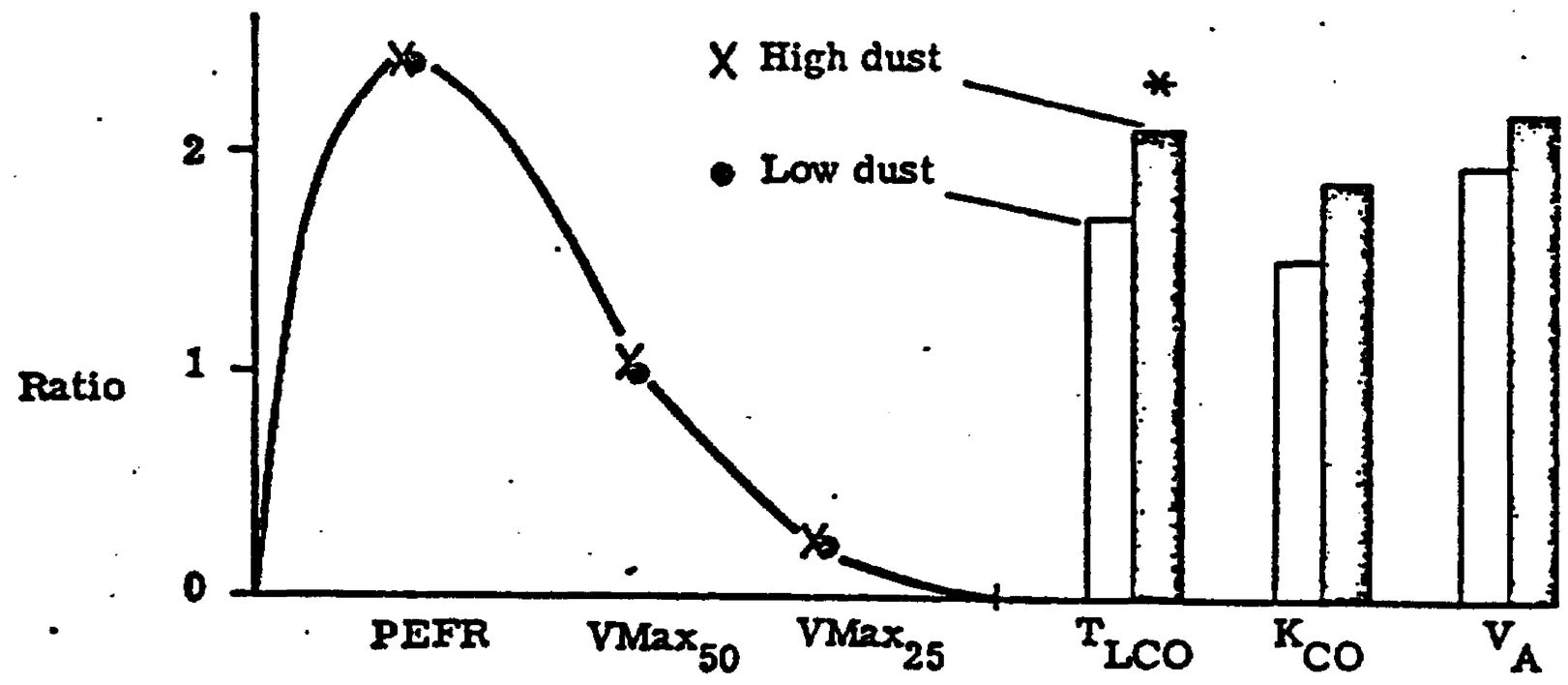

Figure 8 Lung function values relative to FEV_1 in men with rounded opacities (* $P < 0.05$)

A

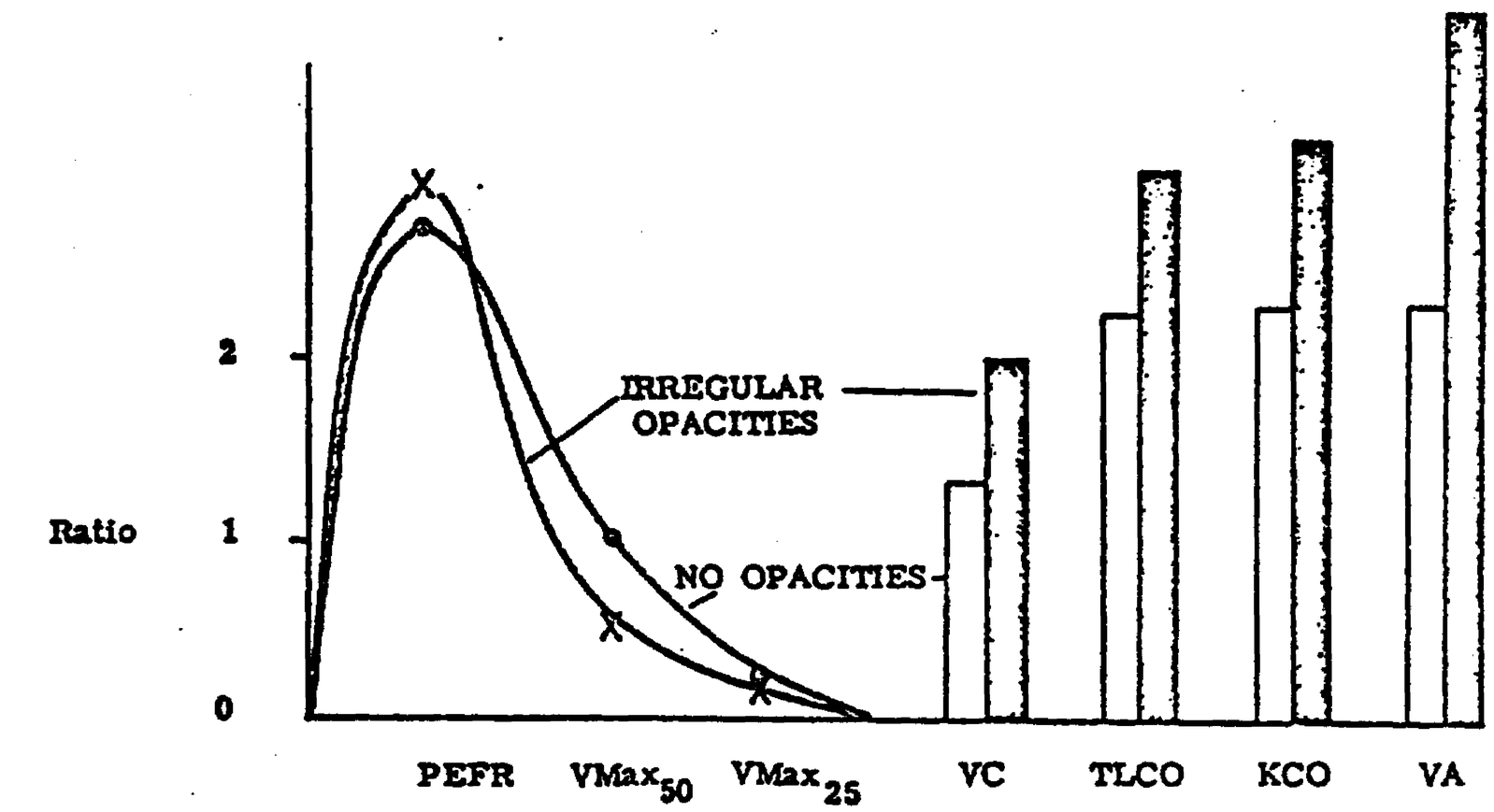

Figure 9

Lung function values relative to FEV_1 in men with irregular opacities and FEV_1 less than 80% predicted.

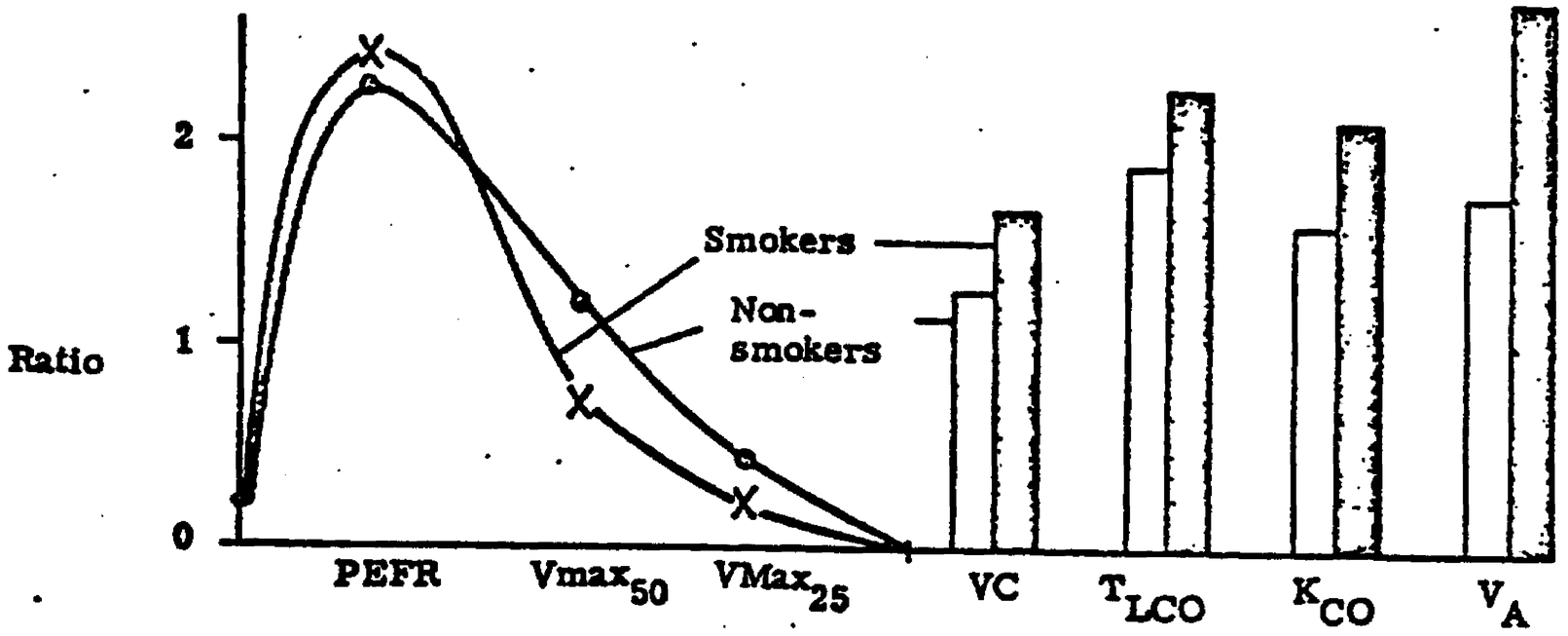

Figure 10

Lung function values relative to FEV_1 in men with low FEV_1

A

APPENDIX I

REGRESSIONS FOR LUNG FUNCTION FOR 1,047 MEN

Variable		Regression Coefficient	P-value
Height		0.0426	< 0.0001
Weight		- 0.0014	n.s.
Age	Non-Smokers	- 0.0285	< 0.0001
	Ex-Smokers	- 0.0370	< 0.0001
	Other Smokers	- 0.0483	< 0.0001
	Cigarette Smokers	- 0.0397	< 0.0001
Lifetime Cigarette Consumption (1,000 packs)		- 0.0143	< 0.0001
Dust Index (yr x mg/m^3)		- 0.0033	< 0.05

TABLE 1 Regression of FEV_1 - different intercepts for employment and smoking categories allowed but not shown.

Status	Smoking Category			
	Cigarette Smoker	Other Smokers	Ex-Smokers	Non-Smokers
Current Workers	- 0.0041	- 0.0037	- 0.0022	- 0.0050
Number	418	58	228	188
	< 0.1	n.s.	n.s.	n.s.
Leavers	- 0.0266	0.0466	0.0227	0.0086
Number	25	3	13	16
	< 0.1	n.s.	n.s.	n.s.
Pensioners	- 0.0018	- 0.0159	- 0.0011	0.0182
Number	41	8	36	13
	n.s.	n.s.	n.s.	n.s.

TABLE 2 Regression coefficients for dust index against FEV_1.

VAB.0001192244

APPENDIX I Contd.

Variable		Regression Coefficient	P-value
Height		0.0645	< 0.0001
Weight		- 0.0067	< 0.002
Age	Non-Smokers	- 0.0236	< 0.0001
	Ex-smokers	- 0.0307	< 0.0001
	Other Smokers	- 0.0414	< 0.0001
	Cigarette Smokers	- 0.0319	< 0.0001
Lifetime Cigarette Consumption (1,000 packs)		- 0.0136	< 0.0001
Dust Index (yr x mg/m^3)		- 0.0035	< 0.05

TABLE 3 Regression of FVC - different intercepts for employment and smoking categories allowed but not shown.

Status	Smoking Category			
	Cigarette Smoker	Other Smokers	Ex-Smokers	Non-Smokers
Current workers	- 0.0049	- 0.0029	- 0.0024	- 0.0084
Number	418	58	228	188
	P < 0.1	n.s.	n.s.	n.s.
Leavers	- 0.0197	0.0359	0.0402	0.0080
Number	25	3	13	16
	n.s.	n.s.	P < 0.05	n.s.
Pensioners	0.0002	0.0029	0.0015	0.0148
Number	41	8	36	13
	n.s.	n.s.	n.s.	n.s.

TABLE 4 Regression coefficients for dust index against FVC. Expansion of model of regression for FVC illustrated in Table 3.

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APPENDIX II

AGREEMENT BETWEEN FIRST AND SECOND READINGS OVER PRESENCE OF SMALL ROUNDED OPACITIES CATEGORY 0/1 OR MORE FOR THREE MEDICALLY QUALIFIED READERS

Reader 03

1st reading \ 2nd reading	Small rounded opacities: Absent	Small rounded opacities: Present	Total
Absent	778	22	800
Present	9	9	18
Total	787	31	818

Reader 15

1st reading \ 2nd reading	Small rounded opacities: Absent	Small rounded opacities: Present	Total
Absent	794	20	814
Present	3	1	4
Total	797	21	818

Reader 17

1st reading \ 2nd reading	Small rounded opacities: Absent	Small rounded opacities: Present	Total
Absent	318	450	768
Present	8	42	50
Total	326	492	818

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APPENDIX II Contd.

AGREEMENT BETWEEN FIRST AND SECOND READINGS OVER PRESENCE OF SMALL ROUNDED OPACITIES CATEGORY 0/1, AND CATEGORY 1/0 OR MORE FOR READER 17

2nd Reading

1st Reading	Category of small rounded opacities			All
	0/0	0/1	1/0+	
0/0	318	444	6	768
0/1	7	27	6	40
1/0+	1	4	5	10
All	326	475	17	818

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APPENDIX III

I N S T I T U T E O F O C C U P A T I O N A L M E D I C I N E

PERSONAL DETAILS

Surname:

Initials:

Date of Birth:

Reference No.:

PLACE OF EXAMINATION:

DATE OF EXAMINATION:

INSTRUCTIONS FOR COMPLETING QUESTIONNAIRE:

For "Y : N" answers: Mark answer which does apply.

For "numeric" answers: Fill in appropriate numbers right justified, i.e. using the right-most boxes.

APPENDIX III Contd.

QUESTIONNAIRE

Reference No. | | | | | | | |

COUGH		
1	Do you usually cough first thing in the morning in the winter?	Y : N
2	Do you usually cough during the day - or at night - in the winter?	Y : N
If YES to 1 or 2		
3	Do you cough like this on most days for as much as three months each year?	Y : N
PHLEGM		
4	Do you usually bring up any phlegm from your chest first thing in the morning in winter?	Y : N
5	Do you usually bring up any phlegm from your chest during the day - or at night - in the winter?	Y : N
If YES to 4 or 5		
6	Do you bring up phlegm like this on most days for as much as three months each year?	Y : N
PERIODS OF COUGH AND PHLEGM		
7a	In the past three years have you had a period of (increased) cough and phlegm lasting for three weeks or more?	Y : N
If YES		
7b	Have you had more than one such period?	Y : N
CHEST ILLNESSES		
8a	During the past three years have you had any chest illness which has kept you from your usual activities for as much as a week?	Y : N
If YES		
8b	Did you bring up more phlegm than usual in any of these illnesses?	Y : N
If YES		
8c	Have you had more than one illness like this in the past three years?	Y : N

APPENDIX III Contd.

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BREATHLESSNESS

If the subject is disabled from walking by any condition other than heart or lung disease, omit question 9 and enter 1 here ☐

9a	Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?	Y : N
If YES		
9b	Do you get short of breath walking with other people of your own age on level ground?	Y : N
If YES		
9c	Do you have to stop for breath when walking at your own pace on level ground?	Y : N

ASTHMA

10a	Have you ever had asthma?	Y : N
If YES		
10b	Have you had an attack of asthma in the past 5 years?	Y : N
If YES		
10c	When you have an attack, are you aware of a whistling noise in your chest?	Y : N

CHILDHOOD ILLNESSES

When you were a child (before 15 years old) did you suffer from:

11a	Catarrh?	Y : N
If YES		
11b	Nose? or	Y : N
11c	Chest?	Y : N
11d	Discharging ears?	Y : N
11e	Bronchitis more than other children?	Y : N
11f	Head colds more than other children? or	Y : N
11g	Chest colds more than other children?	Y : N
11h	Asthma?	Y : N
11i	Whooping cough?	Y : N
11j	Eczema of the skin when you were an infant?	Y : N

APPENDIX III Contd.

PAST ILLNESSES

Have you ever had (in adult or childhood life):

12a	An injury or operation affecting your chest?	Y : N
12b	Heart trouble?	Y : N
12c	Bronchitis?	Y : N
12d	Do colds usually go to your chest?	Y : N
12e	Pneumonia?	Y : N
12f	Pleurisy?	Y : N
12g	Tuberculosis (T.B.)?	Y : N
12h	Other chest trouble?	Y : N
12i	Eczema of the skin in front of your elbows or behind your knees?	Y : N
12j	Hay fever (itching, sneezing or a running or stuffy nose, in the summer months)?	Y : N
12k	Apart from colds, itching of your nose, sneezing, or a running or stuffy nose, at other times of the year?	Y : N
12l	Simusitis?	Y : N

If YES

12m	One attack? or	Y : N
12n	Recurrent attacks?	Y : N

FAMILY HISTORY

Is your father alive? Y : N

Does/Did your father suffer from:

13a	Frequent colds on the chest/or recurrent chestiness?	Y : N
13b	Chronic bronchitis?	Y : N
13c	Asthma?	Y : N
13d	Eczema of the skin?	Y : N
13e	Hay fever?	Y : N

APPENDIX III Contd.

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Is your mother alive?		Y : N
Does/Did your mother suffer from:		
13f	Frequent colds on the chest/or recurrent chestiness?	Y : N
13g	Chronic bronchitis?	Y : N
13h	Asthma?	Y : N
13i	Eczema of the skin?	Y : N
13j	Hay fever?	Y : N
If you have brothers and sisters, has any one of them suffered from:		
13k	Frequent colds on the chest/or recurrent chestiness?	Y : N
13l	Chronic bronchitis?	Y : N
13m	Asthma?	Y : N
13n	Eczema of the skin?	Y : N
13o	Hay fever?	Y : N
If you have children, has any one of them suffered from:		
13p	Frequent colds in the chest/or recurrent chestiness?	Y : N
13q	Bronchitis?	Y : N
13r	Asthma?	Y : N
13s	Eczema of the skin in front of the elbows or behind the knees?	Y : N
If YES		
13t	As an infant? or	Y : N
13u	In later life?	Y : N
13v	Hay fever?	Y : N

21a Do or did you smoke other cigars?	Y : N
If YES	
21b How many of these do or did you usually smoke per week?	☐☐
For present smokers:	
22a Have you been cutting down your smoking over the past year?	Y : N
If YES	
22b How many cigarettes did you usually smoke per day before you cut down?	☐☐
For ex-smokers:	Month ☐☐ Year ☐☐
22c When did you last give up smoking?	
Family history of smoking	
23a Does or did your father smoke?	Y : N
If NO omit 23b, c and d.	
23b Cigarettes?	Y : N
23c Pipe?	Y : N
23d Cigar?	Y : N
23e Does or did your mother smoke?	Y : N
If NO omit 23f, g and h.	
23f Cigarettes?	Y : N
23g Pipe?	Y : N
23h Cigar?	Y : N

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APPENDIX IV

Case/control studies : statistical approach

Each case/control study provided data for two groups of men. Multiple measurements were available for each man. Most were measurements of lung function or presence/absence of symptoms; the studies were designed to compare men in the two groups in these respects. The remainder (age, height, weight, smoking status) were characteristics which, if ignored, might have obscured real comparisons between the groups. The men studied were selected to be broadly comparable in terms of these characteristics. It had been hoped that pair-matched studies would be possible. This, however, would have led to unmatched cases and so a less stringent objective of group comparability was set. This was achieved in three of the studies, but not in the fourth - non-response was an added complication. In all studies there were some differences between cases and controls in how these "nuisance" characteristics were inter-related.

The studies were not designed to test specific hypotheses about particular lung function values or about particular clinical signs. Rather they were carried out to identify suggestive patterns of differences, if any, between the groups over a wide range of clinical measurements. The data were considered from several viewpoints to draw out what patterns existed. In this way the emphasis was on exploratory analysis rather than on formal statistical testing. Such tests were carried out, but interpreted as a check on subjective assessments of differences rather than as the main focus of the analysis. The exploratory nature of the work also influenced the other main emphasis of the analysis, i.e. a study of variables one-at-a-time based on clinical significance, and subsequent teasing out of patterns, rather than a formal multivariate exercise without full regard for the meaning of the measurements.

In testing for statistical significance, the binary variables (i.e. responses to the medical questionnaire) were examined using (Pearson, not log-likelihood) chi-squared tests, without continuity correction. The continuous variables (lung function measurements) were tested using

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independent two sample t-tests assuming equality of variances. The Tables show that in general this assumption was realistic. Significance levels reported were not adjusted in any way to take account of the multiplicity of tests carried out on each group, or of the inter-relationship of the many response variables. Additionally, covariance analyses (using multiple linear regression programs) were carried out for the lung function measurements. These analyses were designed to eliminate bias, insofar as the matching had been imperfect, and also to reduce unexplained within-group variability and to obtain better tests of group differences. The detailed results are shown in the accompanying Tables. Plots of residuals were examined to see if the summary statistics (mean, residual s.d.) used in tests of group comparisons represented the data adequately. The identification of outliers (i.e. men with unusually low values) was indeed of some intrinsic interest also, though again this was not considered the main focus of the work - it was considered a priori likely that some ill men would be found among both cases and controls, and this in fact happened. Finally, the pattern of lung function measurements was studied by standardising for FEV_1 level, as outlined in the report.

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REGRESSION ANALYSIS FOR LUNG FUNCTION VARIABLES

SUMMARY OF RESULTS FROM REGRESSIONS FOR MEN WITH SMALL ROUNDED OPACITIES

Dependent variables		Intercept	Independent variables: Age (years)	Height (cms)	Weight (kg)	Dust exposure (years x mg/m³)	Effect on intercept of presence of opacities	Multiple R	No. of men
FEV_1 litres	(a)	-1.988	-0.037	0.041	-0.0001	-0.002	-0.027	0.6482	57
	(b)		-4.126	2.796	-0.017	-0.500	-0.168		
	(c)		***	**	NS	NS	NS		
FVC litres	(a)	-3.915	-0.035	0.060	-0.005	-0.002	-0.051	0.6166	57
	(b)		-3.207	3.393	-0.597	-0.329	-0.265		
	(c)		**	**	NS	NS	NS		
$\dot{V}max_{50}$ litres/sec	(a)	0.191	-0.051	0.030	0.007	-0.001	-0.021	0.4211	57
	(b)		-2.600	0.952	0.446	-0.062	-0.060		
	(c)		*	NS	NS	NS	NS		
$\dot{V}max_{25}$ litres/sec	(a)	0.535	-0.024	0.009	0.002	-0.002	-0.075	0.5960	57
	(b)		-4.288	0.986	0.388	-0.648	-0.767		
	(c)		***	NS	NS	NS	NS		
$\dot{V}max_{50}$ H litres/sec	(a)	0.878	-0.065	0.034	0.017	-0.007	0.277	0.3834	55
	(b)		-2.122	0.674	0.651	-0.448	0.508		
	(c)		*	NS	NS	NS	NS		
$\dot{V}max_{25}$ H litres/sec	(a)	2.281	-0.030	0.001	0.003	-0.0002	-0.092	0.4991	55
	(b)		-3.702	0.101	0.416	-0.053	-0.640		
	(c)		**	NS	NS	NS	NS		
T_{Lco} ml/min/mm Hg	(a)	6.796	-0.315	0.083	0.264	0.104	-1.370	0.684	56
	(b)		-3.946	0.657	4.096	2.607	-0.843		
	(c)		***	NS	***	*	NS		
PEFR litres/sec	(a)	-0.297	-0.063	0.056	0.017	-0.011	0.032	0.5675	57
	(b)		-3.038	1.667	1.007	-1.016	0.087		
	(c)		**	NS	NS	NS	NS		
V_A litres	(a)	-4.018	-0.023	0.067	-0.005	0.002	0.086	0.5250	56
	(b)		-1.810	3.285	-0.506	0.275	0.383		
	(c)		NS	**	NS	NS	NS		

(a) Regression coefficient
(b) t-Value
(c) Significance of P-Value

Key to significance levels

$P \geq 0.05$	not significant	NS
$P < 0.05$	significant	*
$P < 0.01$	very significant	**
$P < 0.001$	highly significant	***

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REGRESSION ANALYSIS FOR LUNG FUNCTION VARIABLES

SUMMARY OF RESULTS FROM REGRESSIONS FOR MEN WITH SMALL IRREGULAR OPACITIES

Dependent variables		Intercept	Independent variables: Age (years)	Height (cms)	Weight (kg)	Dust exposure (years x mg/m³)	Effect on intercept of presence of opacities	Multiple R	No. of men
FEV_1 litres	(a)	-3.046	-0.047	0.056	-0.013	-0.007	-0.059	0.6871	37
	(b)		-4.034	2.363	-1.029	-0.823	-0.294		
	(c)		***	*	NS	NS	NS		
FVC litres	(a)	-8.683	-0.037	0.096	-0.024	-0.009	0.226	0.6365	36
	(b)		-2.348	2.925	-1.419	-0.747	0.823		
	(c)		*	**	NS	NS	NS		
$\dot{V}max_{50}$ litres/sec	(a)	7.941	-0.066	-0.007	0.0005	-0.011	-0.142	0.5021	36
	(b)		-3.089	-0.151	0.021	-0.684	-0.378		
	(c)		**	NS	NS	NS	NS		
$\dot{V}max_{25}$ litres/sec	(a)	3.016	-0.019	-0.008	0.004	-0.006	-0.057	0.5199	36
	(b)		-3.105	-0.588	0.597	-1.352	-0.521		
	(c)		**	NS	NS	NS	NS		
$\dot{V}max_{50\ H}$ litres/sec	(a)	7.594	-0.134	0.017	0.023	-0.014	-0.376	0.5686	33
	(b)		-3.502	0.210	0.599	-0.506	-0.575		
	(c)		**	NS	NS	NS	NS		
$\dot{V}max_{25\ H}$ litres/sec	(a)	1.935	-0.027	0.001	0.007	-0.006	-0.026	0.4745	33
	(b)		-2.705	0.045	0.663	-0.791	-0.155		
	(c)		*	NS	NS	NS	NS		
T_LCO ml/min/mm Hg	(a)	34.814	-0.378	0.008	0.166	-0.060	-0.253	0.6363	35
	(b)		-4.053	0.043	1.435	-0.833	-0.147		
	(c)		***	NS	NS	NS	NS		
PEFR litres/sec	(a)	9.985	-0.113	0.027	-0.011	-0.023	-0.156	0.6479	37
	(b)		-4.411	0.511	-0.396	-1.169	-0.353		
	(c)		***	NS	NS	NS	NS		
V_A litres	(a)	-12.648	-0.021	0.114	0.002	-0.003	0.121	0.6324	35
	(b)		-1.280	3.339	0.092	-0.251	0.398		
	(c)		NS	**	NS	NS	NS		

(a) Regression coefficient
(b) t-Value
(c) Significance of P-Value

Key to significance levels

$P \geq 0.05$	not significant	NS
$P < 0.05$	significant	*
$P < 0.01$	very significant	**
$P < 0.001$	highly significant	***

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REGRESSION ANALYSIS FOR LUNG FUNCTION VARIABLES

SUMMARY OF RESULTS FROM REGRESSIONS FOR NON-SMOKERS WITH LOW FEV_1

Dependent variables		Intercept	Independent variables: Age (years)	Height (cms)	Weight (kg)	FEV_1	Effect on intercept of high dust exposure	Multiple R	No. of men
FVC litres	(a)	-1.952	-0.004	0.029	-0.012	0.759	-0.354	0.8823	25
	(b)		-0.340	1.195	-0.855	2.425	-1.822		
	(c)		NS	NS	NS	*	NS		
$\dot{V}max_{50}$ litres/sec	(a)	3.622	0.003	-0.051	0.054	1.344	0.673	0.5066	25
	(b)		0.080	-0.637	1.126	1.307	1.053		
	(c)		NS	NS	NS	NS	NS		
$\dot{V}max_{25}$ litres/sec	(a)	2.573	-0.008	-0.027	0.008	0.915	0.377	0.6951	25
	(b)		-0.562	-0.899	0.424	2.348	1.559		
	(c)		NS	NS	NS	*	NS		
$\dot{V}max_{50}$ H litres/sec	(a)	8.197	0.065	-0.131	0.085	3.105	0.366	0.6298	24
	(b)		1.407	-1.584	1.605	2.869	0.543		
	(c)		NS	NS	NS	*	NS		
$\dot{V}max_{25}$ H litres/sec	(a)	3.624	-0.018	-0.041	0.030	1.015	0.420	0.7378	24
	(b)		-0.992	-1.224	1.399	2.337	1.555		
	(c)		NS	NS	NS	*	NS		
T_{LCO} ml/min/mm Hg	(a)	-23.710	-0.065	0.294	-0.054	3.454	-0.204	0.7597	24
	(b)		-0.537	1.180	-0.354	1.060	-0.099		
	(c)		NS	NS	NS	NS	NS		
PEFR litres/sec	(a)	5.130	-0.005	-0.022	0.035	1.091	0.021	0.7610	25
	(b)		-0.248	-0.511	1.375	1.970	0.061		
	(c)		NS	NS	NS	NS	NS		
V_A litres	(a)	-8.367	0.017	0.076	-0.020	0.624	-0.302	0.8014	24
	(b)		0.986	2.136	-0.941	1.336	-1.020		
	(c)		NS	*	NS	NS	NS		

(a) Regression coefficient
(b) t-Value
(c) Significance of P-Value

Key to significance levels

$P \geq 0.05$	not significant	NS
$P < 0.05$	significant	*
$P < 0.01$	very significant	**
$P < 0.001$	highly significant	***

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REGRESSION ANALYSIS FOR LUNG FUNCTION VARIABLES

SUMMARY OF RESULTS FROM REGRESSIONS FOR SMOKERS WITH LOW FEV_1

Dependent variables		Intercept	Independent variables: Age (years)	Height (cms)	Weight (kg)	FEV_1	Effect on intercept of high dust exposure	Multiple R	No. of men
FVC litres	(a)	-2.041	-0.003	0.022	0.0001	0.845	0.029	0.9116	36
	(b)		-0.303	2.034	0.031	7.106	0.250		
	(c)		NS	NS	NS	***	NS		
$\dot{V}max_{50}$ litres/sec	(a)	1.619	0.007	-0.020	-0.002	1.478	-0.089	0.8762	36
	(b)		0.510	-1.113	-0.261	7.705	-0.474		
	(c)		NS	NS	NS	***	NS		
$\dot{V}max_{25}$ litres/sec	(a)	-0.084	0.001	-0.001	-0.001	0.382	-0.061	0.8703	36
	(b)		0.199	-0.243	-0.455	6.909	-1.123		
	(c)		NS	NS	NS	***	NS		
$\dot{V}max_{50}$ H litres/sec	(a)	4.150	0.013	-0.040	-0.001	1.993	-0.249	0.8647	35
	(b)		0.689	-1.607	-0.127	7.445	-0.932		
	(c)		NS	NS	NS	***	NS		
$\dot{V}max_{25}$ H litres/sec	(a)	-1.591	0.008	0.003	0.001	0.550	-0.158	0.8092	35
	(b)		1.054	0.321	0.244	5.040	-1.452		
	(c)		NS	NS	NS	***	NS		
T_{LCO} ml/min/mm Hg	(a)	3.807	-0.222	0.114	0.069	3.162	0.073	0.6412	36
	(b)		-1.683	0.658	1.097	1.678	0.040		
	(c)		NS	NS	NS	NS	NS		
PEFR litres/sec	(a)	7.295	-0.004	-0.033	0.001	1.868	-0.356	0.8324	36
	(b)		-0.204	-1.196	0.090	6.115	-1.186		
	(c)		NS	NS	NS	***	NS		
V_A litres	(a)	-3.871	0.007	0.042	0.006	0.555	0.189	0.7467	36
	(b)		0.490	2.168	0.836	2.595	0.900		
	(c)		NS	*	NS	*	NS		

(a) Regression coefficient
(b) t-Value
(c) Significance of P-Value

Key to significance levels

$P \geq 0.05$	not significant	NS
$P < 0.05$	significant	*
$P < 0.01$	very significant	**
$P < 0.001$	highly significant	***

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