Bronchial responsiveness and COPD risk; an epidemiological study

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Summary

Chapter 1

Chapter 1 describes the background of the study. The following specific research questions have been formulated:

1. Is the distribution of bronchial responsiveness in a random population sample unimodal? Is this distribution similar for asymptomatic and symptomatic subjects (Chapter 2)?
2. Are the level of bronchial responsiveness and the presence of an increased level of responsiveness associated with factors such as age, gender, skin test positivity, the number of eosinophils in the peripheral blood, area of residence, and cigarette smoking, and are these associations independent of the level of pulmonary function and the presence of respiratory symptoms (Chapter 3)?
3. Is an increased level of bronchial responsiveness associated with manifestations of chronic respiratory disease such as the presence of chronic respiratory symptoms (Chapter 4)?
4. Is an increased level of bronchial responsiveness associated with a low level of pulmonary function, independent of cigarette smoking and the presence of respiratory symptoms (Chapter 5)?
5. Does the level of bronchial responsiveness within individuals vary over an extended period of time, and do factors such as level of FEV_1, age, gender, number of eosinophils in the peripheral blood, cigarette smoking, and the presence of respiratory symptoms affect this variability of bronchial responsiveness (Chapter 6)?
6. Is an increased level of bronchial responsiveness an independent risk factor for accelerated decline of pulmomary function (Chapter 7)?

Chapter 2

Chapter 2 describes the investigation of the distribution of bronchial responsiveness in a population sample of adults, consisting of participants in the 1984 survey in Vlaardingen. Bronchial responsiveness had a unimodal, log-normal distribution for various indices of responsiveness. Although subjects with chronic respiratory symptoms such as chronic cough and phlegm, bronchitis episodes, severe dyspnea, persistent wheeze, and a history of asthmatic attacks tended to be more responsive, it was not possible to distinguish those subjects from subjects without chronic respiratory symptoms by their level of responsiveness alone. The distribution in fact consisted of a series of largely overlapping distributions in asymptomatic and symptomatic groups. A considerable proportion of the subjects without chronic symptoms had levels of responsiveness comparable to those with symptoms.

Chapter 3

Chapter 3 presents the analysis of the association of a variety of factors with the level of bronchial responsiveness in a random sample of 2,216 subjects aged 15-72 years. In 18 years of follow-up, these subjects provided 5,012 observations to the analyses. Because multiple measurements within a subject are correlated, multivariate regression methods for related continuous and binary outcomes were used. Adjustment for FEV_1 was assessed to ensure that the relationship of any particular factor with the level of responsiveness was not confounded by its association with level of pulmonary function. Furthermore, potential effect modification by the presence of respiratory symptoms was assessed.

Older age was associated with higher levels of bronchial responsiveness, and this relationship appeared to be independent of level of FEV_1. For subjects with respiratory symptoms, the increase of level of responsiveness with increase of age was greater than for asymptomatic subjects. Level of bronchial responsiveness did not differ significantly between males and females. Because of the difference in mean level of FEV_1 between males and females, a similar difference in level of responsiveness appeared to be associated with a larger difference in level of FEV_1 for males than for females.

Both skin test positivity and a greater number of eosinophils in the peripheral blood were associated with a higher level of responsiveness, independent of the level of FEV_1 and the presence of chronic respiratory symptoms. Living in the rural area (Vlagtwedde) was associated with increased level of hyperresponsiveness. In the population currently studied, cigarette smoking did not appear to be significantly associated with higher level of responsiveness, if there was adjustment for the level of FEV_1.

Chapter 4

Chapter 4 describes a cross-sectional analysis of the relationship of bronchial responsiveness to the presence of a variety of respiratory symptoms. The analysis was performed in a subpopulation of 1,905 participants of the Vlagtwedde-Vlaardingen study. Respiratory symptom outcomes included chronic cough and phlegm, bronchitis episodes, dyspnea, persistent wheeze, and a history of asthmatic attacks. The association of hyperresponsiveness with symptom prevalence was studied in an analysis stratified by smoking habit. Pooled estimates (Mantel-Haenszel) of the odds ratios for symptom prevalence ranged from 1.7 for chronic phlegm to 4.4 for asthmatic attacks. These results were confirmed in a logistic regression analysis, controlling for potential confounding factors such as age, sex, area of residence, and smoking habits. Bronchial responsiveness was associated with the presence of each of the symptoms, and the odds ratios for symptom prevalence increased with decreasing threshold value. In none of the analyses did this dose-response relationship change significantly after adjustment for level of pulmonary function.

Chapter 5

Chapter 5 discusses the relationship between bronchial responsiveness and level of pulmonary function in a random population sample. The population consisted of 2,156 participants in the Vlagtwedde-Vlaardingen study. Approximately 25% of the subjects responded to a 30 s inhalation challenge (histamine concentration of $\leq$ 16 mg/ml) with a decrease in level of FEV_1 of $\geq$ 10% below their baseline value.

For all smoking subcategories, mean $\%FEV_1$ values were lower in subjects with increased level of bronchial responsiveness. This relationship was confirmed in linear regression analyses with adjustment for age, sex, area of residence, the presence of respiratory symptoms, and smoking habits. Exclusion of subjects with $\%FEV_1 < 80\%$ diminished but did not essentially change the association between FEV_1 and bronchial responsiveness. The magnitude of the effect of responsiveness on level of pulmonary function was considerable and statistically significant. In the subjects $\leq$ 21 yr of age, male responders (PC_{10} at $\leq$ 16 mg/ml) on average had an adjusted FEV_1 of .325 L less than nonresponders and female responders had an adjusted FEV_1 of .305 L less.

Chapter 6

Chapter 6 presents the results of an analysis of long-term variability of bronchial responsiveness, which has been studied in a random population sample of participants in the Vlagtwedde-Vlaardingen study. Over a follow-up period of 18 years 2,216 subjects contributed 5,012 observations to the analysis. A regression method for related continuous data provided an estimate of the intraclass correlation coefficient of bronchial responsiveness. Variability of responsiveness as a binary variable was investigated with use of regression methods for binary data that provided odds ratios as an index of variability. This method permits the inclusion of the various values of the independent variables at every point in time. In this way changes, e.g. of smoking habits, could be included in the model. Hyperresponsiveness was defined as a threshold value of $\leq$ 16 mg/ml. The variability of responsiveness, expressed as the intraclass correlation coefficient for the continuous measurement and as an odds ratio for the binary measurement, appeared to be considerable. Adjustment of the analyses for level of FEV_1 and other covariables resulted in slightly lower intraclass correlation coefficients and lower odds ratios. These results indicate that in longitudinal epidemiologic research of population samples, a single measurement of responsiveness will not be sufficient to characterize a subject. Therefore, methods for longitudinal analyses should be applied that allow for adjustment of changes in level of responsiveness during the follow-up.

Chapter 7

Chapter 7 describes results of longitudinal analyses of the relationship of bronchial hyperresponsiveness (defined as a PC_{10} at $\leq$ 16 mg/ml) with decline of FEV_1. This relationship was studied prospectively in 1,509 subjects, 840 males and 669 females, who participated

in the longitudinal Vlagtwedde-Vlaardingen study from 1965 to 1985. The study population was seen at 3-yr intervals, and thus, measurements of pulmonary function and bronchial responsiveness were made at consecutive occasions 3, or a multiple of 3, years apart. A total of 3,197 paired observations were included in the analyses, 1,798 for males, and 1,399 for females. The mean age of the study population was 39 yr (range 25 to 76 yr). Bronchial responsiveness and several additional independent variables were assessed before the change in FEV_1 was measured. All values of FEV_1 were adjusted for standing height. The mean annual change in height-adjusted FEV_1 was greater for males than for females and greater for smokers than for nonsmokers.

In multiple linear regression analyses in males and females separately, there was no significant association between hyperresponsiveness and annual change of FEV_1. In the analyses stratified by gender and responder status, ex-smoking and current smoking females had a significantly greater decline of FEV_1 compared to hyperresponsive never-smoking females. This potential effect modification was tested by including an interaction term of hyperresponsiveness and smoking in the regression model. This interaction term appeared to be statistically significant. In addition, this association could be demonstrated for subgroups of females ≤ 40 yr of age and > 40 yr. These results suggest that there is an accelerated decline of FEV_1 in hyperresponsive former or current smoking females and this interactive effect of smoking and hyperresponsiveness on decline tends to occur early in adult life. No such relationships could be demonstrated for males.

Because bronchial responsiveness was measured before the change in FEV_1, it is unlikely that bronchial responsiveness developed concurrently with accelerated decline. We conclude that bronchial hyperresponsiveness is associated with steeper decline of FEV_1 for ever-smoking females, whereas, for the age range under study, no significant relationship could be demonstrated for males. As in the average Dutch adult population, approximately 25% of the female smokers will be hyperresponsive, we recommend that females should be strongly discouraged from starting to smoke cigarette and, if they have started, be advised to quit.

Chapter 8

Chapter 8 summarizes evidence for the conclusion that increased bronchial hyperresponsiveness should be considered as an important risk factor of COPD. Increased bronchial responsiveness was significantly associated with an increased risk for a variety of expressions of obstructive lung disease: increased level of responsiveness was associated with lower level of FEV_1, presence of respiratory symptoms, decreased maximal lung growth, early onset of accelerated decline of FEV_1 for smoking females, specifically for older females.

The relationship of bronchial hyperresponsiveness to pulmonary function was clarified with use of a conceptual model of growth and decline of FEV_1 with time. In a discussion of limitations of the study we suggested that the efficiency of the analyses might be improved by ascertainment of cases lost to follow-up, by a quantitative estimate of life time tobobacco consumption (packyears), and possibly by a more specific index (PC_{20}) or a continuous index of responsiveness (dose-response slope). Possible additional anal-

yses in data of the Vlagtwedde-Vlaardingen study are proposed, including analyses of factors influencing the maximal attained level of pulmonary function in early adulthood, the prolongation of a possible plateau phase, and the onset of decline in pulmonary function, with special attention for the male-female differences. Further issues to be studied include the meaning of the presence of hyperresponsiveness in the absence of chronic respiratory symptoms. So far level and decline of FEV_1 have been analyzed as continuous outcome variables. Other continuous outcomes might be studied, such as changes in VC and FEV_1/VC%. It might also be interesting to study dichotomous outcome variables for COPD, such as the incidence of respiratory symptoms or a certain degree of airflow limitation (e.g., %FEV_1 of <65%).