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Optimum expression of adult lung function based on all-cause mortality: Results from the Reykjavik study

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Summary
A variety of reference curves are used to derive predicted values for adult lung function, even within ethnically similar populations. Alternatives to percentage predicted value are sometimes used to allow for height in research. Strength of association with total mortality can be used to choose the optimal expression, between forced expiratory volume in 1 s (FEV_1) divided by height^2, FEV_1/height^3, FEV_1% predicted and difference from predicted. Data from the Reykjavik Study cohort, 1976–2002, included 5544 men and 8062 women randomly selected from the population. Total mortality was analysed by Cox proportional hazards regression in relation to each height-adjusted measure, allowing for age group, period of recruitment and body mass index, and smoking before or at baseline.
FEV_1/height^2 and FEV_1/height^3 had stronger associations with mortality than FEV_1% predicted and difference from predicted in men and in women. There were similar findings for forced vital capacity (FVC) in non-smokers and in women. FEV_1/height^2 was slightly better predictive than FEV_1/height^3 in men, but distributions of FEV_1/height^3 in men and women were closer than those of FEV_1/height^2.
Clinical practise and epidemiological research would benefit from agreement on how to adjust lung function for height. Replication of these analyses in other cohort studies would inform the choice between FEV_1/height^2 and FEV_1/height^3.

Introduction

Measures of lung function, forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) in particular, are commonly expressed as a percentage of a predicted value for age, height and sex.[1,2] Recent recommendations specify that predicted values should be taken from a population of the same age-range, ethnic group and sex.[3] Some ethnic

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group specific reference curves have been published,[4,5] but there is variation even within those derived from white populations.[6] To avoid choice of reference curves, or selection of inappropriate values, study-specific predicted values are often used in epidemiological studies.[7–14]

Predicted values are usually derived from multiple regression equations of lung function on height and age, for men and women separately.[4–6] In analyses of lung function, a number of methods of adjustment for height are found, in addition to use of % predicted. As an independent variable FEV_1 has been included as FEV_1/height^2,[15] and as FEV_1/height^3.[16] As an outcome variable examples can be found of FEV_1 adjusted for height directly in a multiple regression analysis,[17] and of FEV_1/height^2,[18] as well as of FEV_1 expressed as percentage of predicted value for height, age and gender.[19] Analyses with FEV_1 expressed as FEV_1/height^2 or FEV_1/height^3 normally include age as an independent variable, and also gender if results are combined for men and women. Similar variation exists in analyses of FVC.

Lack of uniformity of expression hampers comparisons of results between studies, and hence of the progression of research. Agreement on the method of adjustment of FEV_1 and FVC for height would be beneficial to all analysing lung function data or using lung function to define patient categories.

A criterion that can be used to choose between the several options is that of best prediction of total mortality. Low lung function is associated with all cause mortality in both men and women.[2,8,9,15,20] Not only is the association present after adjusting for age, smoking, body mass index (BMI), and other risk factors,[2,8,9,20] it has been reported to be similar in magnitude for current, former and never smokers.[2,9] Hole et al.[8] found FEV_1 to be second in importance to cigarette smoking as a predictor of all cause mortality.

It is not possible to deduce from the literature which of the methods of FEV_1 adjusted for height gives the best prediction of total mortality, or whether percentage, rather than absolute, difference from predicted gives the most information, as is often assumed. This paper sets out to answer this question, using a large long-term cohort study carried out in and around Reykjavik, Iceland.[21]

Materials and methods

Study participants

The Reykjavik Study, initiated in 1967 as a prospective study of cardiovascular disease, has been described in detail previously.[21,22] A population register as of 1st December 1966 was used to identify males born 1907–1934 and females born 1908–1935 resident in Reykjavik or adjacent communities, where about half the population of Iceland lived at that time.[21] Men and women were divided into six strata with similar year of birth distribution, with staggered years of first invitation to participate, and up to five follow-up visits.

Spirometry

Spirometry was performed with a Vitalograph (Vitalograph Ltd., Buckingham, UK) at each survey. One machine was used up until 1974, a second until 1983, and a third throughout the study. Each machine was regularly calibrated with a 1 l syringe. Three attempts were recorded for FEV_1 and FVC. Smoking status was recorded at each survey. Participants were divided into never smokers at baseline, current or ex-smokers of only pipe or cigars, ex-cigarette smokers and current cigarette smokers; the small number of women who reported ever smoking only pipe or cigars were excluded. BMI was calculated as weight in kilograms divided by the square of height in metres.

Selection of data

The data were reviewed as longitudinal records for outliers, using a number of criteria. There were a substantial number of outliers in the lung function data in the years up to 1975, but few in the later period, so data were restricted to those collected at or after 1st March 1976. For each participant data from the first survey at or after 1st March 1976, which coincided with the first visit for three strata, were used in the analysis. The sixth stratum, not surveyed until 1991–1996, was omitted. Follow-up for this analysis was until death, or until 1st January 2002 for survivors at that date.

Data analysis

Cox proportional hazards regression was used to relate total mortality to age, BMI, period of survey, baseline smoking groups, and either FEV_1, FEV_1/height^2, FEV_1/height^3, FEV_1% predicted or FEV_1 as difference from predicted value. Three sets of predicted values were calculated, two using published equations,[23,24] the other internally derived values using regression of baseline FEV_1 on age and height for non-smoking men and women separately. Survival from time of lung function measurement was used as the timescale. When non-linearity in the relation of mortality to lung function was detected each measure of lung function was divided into quintile groups so that comparisons could be made. In each of the analyses for each of the nine measures of lung function there were the same number of participants and the same number of fitted parameters, so relative strength of the relation of lung function to mortality was directly measured by the likelihood ratio χ^2 statistic.

Age at baseline was grouped into five categories, <50, 50–<55, 55–<60, 60–<65 and 65 years and over. BMI was divided into underweight (BMI<20), normal weight (BMI 20–<25), overweight (BMI 25–<30) and obese (BMI$\geqslant 30$). Interactions between smoking and measures of FEV_1 were tested. The same analyses were carried out for FVC. All analyses were performed for men and women separately.

Selected height-adjusted predictors of mortality were divided into equal width groups. The effect of adjusting for age, smoking and BMI was assessed by comparing hazard ratios from Cox proportional hazards regression. As all participants were followed up until death or for longer than 10 years, predicted 10 year survival rates were estimated using logistic regression.

The National Bioethics Committee and the Data Protection Authority of Iceland approved the study protocol. All participants provided informed consent.