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Spirometric studies on the adult general population of Helsinki

- bronchodilation responses, determinants, and intrasession repeatability of FEV_1, FEV_6, FVC, and forced expiratory time

A report from the FinEsS-Helsinki II study

Annette Kainu

ACADEMIC DISSERTATION

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Abstract

Spirometry is the most widely used lung function test in the world. It is fundamental in diagnostic and functional evaluation of various pulmonary diseases. In the studies described in this thesis, the spirometric assessment of reversibility of bronchial obstruction, its determinants, and variation features are described in a general population sample from Helsinki, Finland. This study is a part of the FinEsS study, which is a collaborative study of clinical epidemiology of respiratory health between Finland (Fin), Estonia (Es), and Sweden (S).

Asthma and chronic obstructive pulmonary disease (COPD) constitute the two major obstructive airways diseases. The prevalence of asthma has increased, with around 6% of the population in Helsinki reporting physician-diagnosed asthma. The main cause of COPD is smoking with changes in smoking habits in the population affecting its prevalence with a delay. Whereas airway obstruction in asthma is by definition reversible, COPD is characterized by fixed obstruction. Cough and sputum production, the first symptoms of COPD, are often misinterpreted for “smokers cough” and not recognized as first signs of a chronic illness. Therefore COPD is widely underdiagnosed. More extensive use of spirometry in primary care is advocated to focus smoking cessation interventions on populations at risk. The use of forced expiratory volume in six seconds (FEV_6) instead of forced vital capacity (FVC) has been suggested to enable office spirometry to be used in earlier detection of airflow limitation.

Despite being a widely accepted standard method of assessment of lung function, the methodology and interpretation of spirometry are constantly developing. In 2005, the ATS/ERS Task Force issued a joint statement which endorsed the 12% and 200 ml thresholds for significant change in forced expiratory volume in one second (FEV_1) or FVC during bronchodilation testing, but included the notion that in cases where only FVC improves it should be verified that this is not caused by a longer exhalation time in post-bronchodilator spirometry. This elicited new interest in the assessment of forced expiratory time (FET), a spirometric variable not usually reported or used in assessment.

In this population sample, we examined FET and found it to be on average 10.7 (SD 4.3) s and to increase with ageing and airflow limitation in spirometry. The intrasession repeatability of FET was the poorest of the spirometric variables assessed. Based on the intrasession repeatability, a limit for significant change of 3 s was suggested for FET during bronchodilation testing. FEV_6 was found to perform equally well as FVC in the population and in a subgroup of subjects with airways obstruction.

In the bronchodilation test, decreases were frequently observed in FEV_1 and particularly in FVC. The limit of significant increase based on the 95^{th} percentile of the population sample was 9% for FEV_1 and 6% for FEV_6 and FVC; these are slightly lower than the current limits for single bronchodilation tests (ATS/ERS guidelines). FEV_6 was proven as a valid alternative to FVC also in the bronchodilation test and would remove the need to control duration of exhalation during the spirometric bronchodilation test.

Contents

List of original publications

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

I Kainu A, Lindqvist A, Sarna S, Sovijärvi A. Spirometric and anthropometric determinants of forced expiratory time in a general population. Clinical Physiology and Functional Imaging 2008; 28: 38-42.

II Kainu A, Lindqvist A, Sarna S, Sovijärvi A. Intra-session repeatability of FET and FEV_6 in the general population. Clinical Physiology and Functional Imaging 2008; 28: 196-201.

III Kainu A, Lindqvist A, Sarna S, Lundbäck B, Sovijärvi A. FEV_1 response to bronchodilation in an adult urban population. Chest 2008; 134: 387-393.

IV Kainu A, Lindqvist A, Sarna S, Lundbäck B, Sovijärvi A. Responses of FEV_6, FVC and FET to inhaled bronchodilator in the general adult population (submitted).

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Abbreviations

ACCP	American College of Chest Physicians
AEFV	area of expiratory flow-volume
ANCOVA	analysis of covariance
ATS	American Thoracic Society
BMI	body mass index
BMRC	British Medical Research Council
BTPS	body temperature and pressure saturated
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CoV	coefficient of variation
ECCS	European Community for Coal and Steel
ECRHS	European Community Respiratory Health Survey
ERS	European Respiratory Society
ETS	environmental tobacco smoke
EV	extrapolated volume
FEFx	instantaneous forced expiratory flow when x% of the FVC has been expired
FEF25-75%	mean forced expiratory flow between 25% and 75% of FVC
FET	forced expiratory time
FEV_1	forced expiratory volume in one second
FEV_6	forced expiratory volume in six seconds
FEV_t	forced expiratory volume in t second(s)
FIRS	Forum of International Respiratory Societies
FIV_1	forced inspiratory volume in one second
FIVC	forced inspiratory vital capacity
FRC	functional residual capacity
FVC	forced vital capacity
FVC6	forced vital capacity in six seconds
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRCT	high-resolution computed tomography
IC	inspiratory capacity

ICC	intraclass correlation coefficient
ICS	inhaled corticosteroid
ITS	Intermountain Thoracic Society
IUATLD	International Union Against Tuberculosis and Lung Disease
IVC	inspiratory vital capacity
LLN	lower limit of normal
MEFx	maximal instantaneous forced expiratory flow where x% of the FVC remains to be expired
MEFV	maximum expiratory flow-volume
MMEF	maximum mid-expiratory flow
MS_B	mean squares between groups
MS_W	mean squares within a group
n/a	not applicable
ns	not significant
OAD	obstructive airways disease
OLIN	Obstructive Lung Disease in Northern Sweden
PAR	population attributable risk
PEF	peak expiratory flow
PIF	peak inspiratory flow
PM10	particulate matter under 10 µm in aerodynamic diameter
r	Pearson correlation coefficient
RV	residual volume
SD	standard deviation
sGaw	specific conductance
TLC	total lung capacity
VC	vital capacity
VDGF	vapours, dusts, gases and fumes

1 Introduction

Flow-volume spirometry is a well-established method used in everyday clinical practice to assess ventilatory function in both health and disease. The methodology is continuously under development to better take into consideration accumulating evidence from ongoing research. Since spirometry is widely used in research, the methodology should be the same in different international centers. The most recent standard on spirometry issued in 2005 jointly by the American Thoracic Society (ATS) and European Respiratory Society (ERS) brought small changes and harmonization to the existing methodology (Miller et al., 2005a, 2005b; Pellegrino et al., 2005). In recent years, office spirometry by primary care providers has been debated, as a means of earlier detection of chronic obstructive pulmonary disease (COPD) (Harf, 1992; Ferguson et al., 2000; Enright, 2006a, 2008). In this context, forced expiratory volume in six seconds (FEV_6) has been suggested to replace forced vital capacity (FVC) in assessment of pulmonary function (Ferguson et al., 2000; Vandevoorde et al., 2005a, 2006, 2008; Pedersen, 2006; Lamprecht et al., 2007). Accumulated information on FEV_6 is centered on patient samples from pulmonary function laboratories and less is known about the relationship between FVC, FEV_6, and forced expiratory time (FET) in the general population (Swanney et al., 2000, 2004; Demir et al., 2005; Vandevoorde et al., 2005a, 2006, 2008; Gleeson et al., 2006; Hansen et al., 2006a; Melbye et al., 2006; Lamprecht et al., 2007; Bellia et al., 2008).

The prevalence of obstructive airways diseases (OAD), asthma, and COPD is changing – due to changes in atopic tendency, living standards, and smoking habits. Internationally, a consensus is lacking on what defines COPD, but generally the existing definitions center on the ratio of forced expiratory volume in one second (FEV_1) and FVC. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the ATS/ERS consensus statements advocate the use of postbronchodilator fixed ratio and a limit of 70% to indicate disease (Global Initiative for Chronic Obstructive Lung Disease; Celli et al., 2004; Rabe et al., 2007). The use of a fixed limit of FEV_1/FVC has been criticized and limits based on applicable reference values suggested instead (Aggarwal et al., 2006; Roberts et al., 2006; Hansen et al., 2007; Townsend, 2007). This has also been recommended in the standards for interpretation of spirometry by the ATS and recently also the joint ATS/ERS Task Force in 2005 (ATS, 1991; Pellegrino et al., 2005).

The FinEsS study is a collaborative study of clinical epidemiology of respiratory health between Finland (Fin), Estonia (Es), and Sweden (S). This part of the FinEsS Helsinki study is based on a random general population sample of adults from Helsinki, Finland. All participating subjects underwent flow-volume spirometry with bronchodilation testing. Detailed data were collected to assess variations in FEV_1, FVC, FEV_6, and FET during spirometry.

2 Review of the literature

2.1 Flow-volume spirometry as a lung function measurement

Spirometry has been defined as "a physiological test that measures how an individual inhales or exhales volumes of air as a function of time" (Miller et al., 2005b). It is used to assess pulmonary function in the diagnosis of respiratory disease, in occupational and functional capacity, and in the follow-up of various respiratory diseases. Like blood pressure measurement in hypertension, it is a fundamental tool in the assessment of lung function, especially in obstructive airways diseases (OADs) such as asthma and COPD.

All measurements of lung function should be related to reference values that are representative of the population under investigation (ATS, 1995). In Finland, spirometry reference values developed by Viljanen and coworkers (1982) from an occupational health cohort of subjects aged 18-65 years are used, but new reference values with a wider age range are under way.

2.1.1 Measured variables in flow-volume spirometry

The most important variables from flow-volume spirometry are forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1). FVC is the volume delivered during an expiration made as forcefully and completely as possible, starting from full inspiration. FEVt is the maximal volume exhaled by time t seconds (timed from the time zero defined by back-extrapolation) of a forced expiration from a position of full inspiration, expressed in liters at body temperature and pressure saturated (BTPS) conditions (Miller et al., 2005b; Pellegrino et al., 2005). A model maximum expiratory flow-volume (MEFV) curve is displayed in Figure 1.

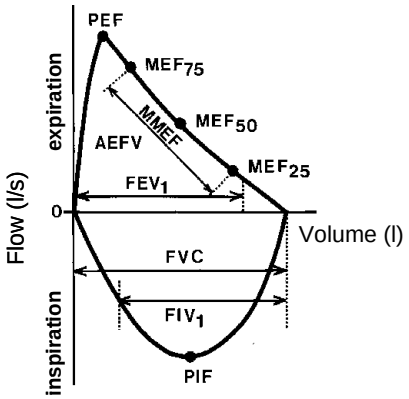

Figure 1 *Maximum expiratory flow-volume curve showing the main variables. For abbreviations, see pages 7-8 (adapted from Sovijärvi et al.,2006).*

Other flow values can also be recorded and used in the assessment. Peak expiratory flow (PEF) is the maximum expiratory flow achieved from a maximum forced expiration starting without hesitation from the point of maximal lung inflation, expressed in l/s. The mean forced expiratory flow between 25% and 75% of the FVC (FEF25-75%) is also known as the maximum mid-expiratory flow (MMEF). Instantaneous forced expiratory flow values at 25%, 50%, and 75% of expired FVC are also being reported (FEF25, FEF50, FEF75), and are of increasing interest in diagnostic evaluation. In the European literature, these values are referred to as maximal instantaneous forced expiratory flow where x% of FVC remains to be expired or MEFx (MEF75, MEF50, MEF25), and hence, MEF75 corresponds to FEF25.

Slow or relaxed vital capacity is measured as a separate maneuver before the forced expiratory maneuvers. The slow vital capacity (VC) may be larger than FVC, especially in subjects with airflow limitation (Brusasco et al., 1997). Corresponding indices can be measured from inspiratory spirometry, but usually only forced inspiratory vital capacity (FIVC), forced inspiratory volume in one second (FIV_1), and peak inspiratory flow (PIF) are reported.

In 1987, Glindmeyer and coworkers suggested from a purely mathematical model that an end-of-test criterion based on a fixed duration of the FVC maneuver could be applied. Using the standard waveforms presented by Hankinson and Gardner in 1982, which have later been adopted into the ATS 1987 and 1994 standards (ATS, 1987; ATS, 1995), they found that 6.64 s was sufficient to obtain 99% of FVC for spirograms with FEV_1/FVC as low as 50% (Glindmeyer et al., 1987).

FVC is known to be dependent on expiratory time, particularly in obstructive patients and in the elderly (Glindmeyer et al., 1987; Swanney et al., 2000). To overcome problems with FVC, forced expiratory volume in six seconds (FEV_6) has been suggested to be used in lieu of FVC, especially in primary care office spirometry (Ferguson et al., 2000; Derom et al., 2008). FEV_6 is easier for patients to complete and its measurement requires less expensive flow-sensors (Ferguson et al., 2000; Swanney et al., 2000). The use of FEV_6 necessitates applicable reference equations, which have already been calculated at least in the United States (Hankinson et al., 1999, 2003), in New Zealand (Marsh et al., 2006), in elderly South-European adults (Garcia-Rio et al., 2004), and in Brazil (Pereira et al., 2007). Although FVC measurements are recognized to be dependent on total expiratory time, limited data exist on the difference between FVC and FEV_6 in healthy adults or in population samples (Hankinson et al., 2003).

In addition to FEV_6, FVC6 is sometimes used. FVC6 refers to measurement of FEV_6 using a dry-wedge spirometer, still used in field studies but rarely in office spirometry or hospital-based pulmonary function laboratories. In these spirometers, air cooling during the maneuver results in a small dip or reduction of exhaled air volume at the end of MEFV, which means that FVC6< FEV_6, although the difference is usually very small (about 0.050 liters) (Hankinson et al., 2003; Akpinar-Elci et al., 2006; Lamprecht et al., 2007).

Forced expiratory time (FET) has not been traditionally considered a flow-volume spirometry variable, but rather a quality measure signifying satisfactory duration of exhalation. Longer FET during a single pulmonary function testing session has been associated with better spirometric performance in terms of FEV_1+FVC (Tsai et al., 2006). No reference values exist for FET, and it is not usually reported or used in diagnostic evaluation.

FET has originally been investigated as a clinical sign in diseases with chronic obstruction (Rosenblatt & Stein, 1962; Godfrey et al., 1969, 1970; Kern & Patel, 1991, 1994; Holleman et al., 1993; Schapira et al., 1993; Straus et al., 2002), particularly small airways obstruction (Macdonald et al., 1975). In these studies, auscultated FET was usually measured with a stethoscope above the trachea. A normal duration of auscultated forced expiration has been considered to be less than 4 s (Rosenblatt & Stein, 1962; Campbell, 1969), but in some older normal subjects airflow can persist for long periods, although the rates are too low to be detected clinically (Leith & Mead, 1967). Auscultated FET is shorter than spirometric FET since flow at a certain point falls below a limit detectable by auscultation (Lal et al., 1964). The diagnostic accuracy of FET measurements in clinical use has been questioned (Badgett & Tanaka, 1994). In subjects without airflow limitation or restriction in baseline spirometry evaluated for symptoms suggestive of asthma, spirometric FET has been found to generally be under 6 s and shorter in subjects that demonstrated bronchial hyperresponsiveness (Goldstein et al., 2002). However, most studies reporting FET have excluded subjects with FET<6 s, and in these studies mean FET has been around 8-11 s (Hankinson et al., 1977; ATS, 1979; Vandevoorde et al., 2005a, 2006; Gleeson et al., 2006; Jensen et al., 2006).

2.1.2 Determinants of lung function

In childhood and early adulthood, the level of attainable lung function has been shown to be determined by race, genetic predisposition, height, severe or recurrent infections in childhood, respiratory symptoms and disease in childhood, and inhalational exposures, especially to environmental tobacco smoke and air pollution (Lewitter et al., 1984; Woolcock et al., 1984; Lebowitz et al., 1987; Shaheen et al., 1995; Gauderman et al., 2000, 2004, 2007; Sandström & Brunekreef, 2007). Young age at smoking initiation is a risk for both accelerated decline of lung function and failure to reach target growth (Tager et al., 1985, 1988; Lebowitz et al., 1987; Jaakkola et al., 1991).

Of the anthropometric variables, lung function has generally been considered to be a function of race, gender, age, and height, and these variables have most often been included in the reference equations for adults (Morris et al., 1971, 1988; Crapo et al., 1981; Viljanen et al., 1982; Knudson et al., 1983; Quanjer et al., 1983; Miller et al, 1986; Paoletti et al., 1986; Roca et al., 1986, 1988; Hankinson et al., 2003; Marsh et al., 2006; Perez-Padilla et al., 2007).

The strongest determinant of accelerated decrease in FEV_1 is smoking, with a population attributable risk (PAR) for COPD of around 80% (Tashkin et al., 1984, 1994;

Camilli et al., 1987; Peat et al., 1990; Kerstjens et al., 1997; Wilson et al., 2005; Viegi et al., 2007). Women might be more susceptible to the adverse effects of smoking and environmental tobacco smoke (ETS) (Chen et al., 1991; Prescott et al., 1997; Langhammer et al., 2003) or gender might influence disease detection and management (Dales et al., 2006). In addition, inhalation of various other noxious substances, especially vapors, dusts, gases, and fumes (VDGF) has been reported to increase the risk of chronic airflow limitation (van der Lende et al., 1981; Becklake, 1989; Bakke et al., 1991). In a recent Nordic report, Johannessen and coworkers (2005) estimated in a population sample the PAR of smoking-related COPD to be 68%, while occupational exposure to VDGF accounted for about 6% of cases. Long-term exposure to particulate air pollution, namely PM10 particles, has been associated with loss of attainable lung function in children and higher prevalence of airflow limitation and respiratory symptoms in adults (Tashkin et al., 1994; Gauderman et al., 2000, 2004, 2007; Pénard-Morand et al., 2005; Rojas-Martinez et al., 2007).

Moreover, excessive body weight has been described to play a significant role (Chinn et al., 1996), with weight gain influencing decrements in FEV_1 as much as cigarette smoking in subjects aged under 35 years (Morgan & Reger, 2000). Particularly abdominal adiposity seems to play a role (Ochs-Balcom et al., 2006). Physical activity has been demonstrated to slow down the decline of lung function (Pelkonen et al., 2003).

Aging is a problematic aspect in many lung function measures since reference values are often formed from measurements of working age populations and extrapolation of these values to older age cohorts systematically introduces a representation bias to the analysis (Burrows et al., 1986; Janssens et al., 1999; Hardie et al., 2002). However, studying healthy elderly never-smokers may not completely eliminate the representation bias since significant selection will have occurred - those who are “healthy” in the octagenaries probably also represent some genetic predisposition to different body composition among the various acquired traits (Janssens et al., 1999). FEV_1 has also been shown to be a prognostic measure, with lower FEV_1 related to increased morbidity and mortality in the population (Hansen et al., 1999; Knuiman et al., 1999; Anthonisen, 2000; Pelkonen et al., 2000, 2006; Schünemann et al., 2000; Thomason & Strachan, 2000; Mannino et al., 2003, 2006a, 2006b).

2.1.3 Pathological changes in flow-volume spirometry

The pathological changes in flow-volume spirometry can be classified broadly into obstructive, restrictive, and combined (mixed) ventilatory abnormalities. Obstructive airways diseases, mainly asthma and COPD, constitute a major portion of those pulmonary diseases that can be diagnosed with routine flow-volume spirometry.

Asthma is an inflammatory condition of the airways characterized by eosinophilic inflammation that leads to smooth muscle contractility, bronchial hyperresponsiveness, and variable airways obstruction (Global Initiative for Asthma; Bateman et al., 2008). Ongoing eosinophilic inflammation can be detected by exhaled nitric oxide (NO) and

inflammatory substances (e.g. eosinophilic cationic protein) in the sputum and exhaled breath condensate of patients with asthma (Kharitonov & Barnes, 2001; Horvarth et al., 2005; Birrell et al., 2006; Taylor et al., 2006; Bateman et al., 2008). The clinical picture is characterized by recurrent episodes of breathlessness and wheezing, particularly at night. Airways obstruction is reversible in response to bronchodilating medication or spontaneously over time (Bateman et al., 2008).

Chronic obstructive pulmonary disease is caused by inhalation of noxious substances, most commonly tobacco smoke (Global Initiative for Chronic Obstructive Pulmonary Disease; Rabe et al., 2007; Viegi et al., 2007). The inflammation in COPD is mainly neutrophilic and the disease is characterized by a triad of chronic productive cough (chronic bronchitis), emphysema, and airflow limitation. At the early stages of the disease, changes can be seen in small airways but as the disease progresses also larger airways are affected. Disease phenotypes differ with some subjects mainly affected with emphysema whereas others presenting mainly airways obstruction (Global Initiative for Chronic Obstructive Pulmonary Disease). The risk of developing COPD increases with increasing smoking pack-years and ageing. Of older subjects with a smoking history of over 40 pack-years, more than 50% were found to have chronic obstruction in Northern Finland (Kotaniemi et al., 2005).

Obstruction

An obstructive ventilatory defect is defined as a reduction of maximal airflow from the lung disproportionate to the maximal volume (i.e. VC) that can be displaced from the lung (Pellegrino et al., 2005). It implies airway narrowing during exhalation and is characterized by a FEV_1/VC ratio below the 5^{th} percentile of the predicted value. However, at the early stages of airflow limitation, changes are seen in the terminal portion of the spirogram that reflects changes in the small airways. A schematic illustration of the spirograms associated with typical obstructive ventilatory defects are shown in Figure 2. The degree of obstruction is graded based on FEV_1 (Pellegrino et al., 2005).

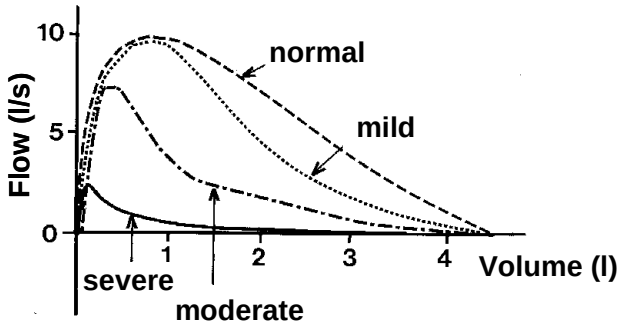

Figure 2 *Flow-volume spirometry curve displaying characteristic obstructive ventilatory defect shown with grading from mild to severe obstructive ventilatory dysfunction (adapted from Sovijärvi et al.,2006).*

A fixed ratio of FEV_1/FVC below 70% for the diagnosis of airflow limitation signifying COPD has been advocated by the international guidelines, namely the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (Global Initiative for Chronic Obstructive Pulmonary Disease; Rabe et al., 2007). The use of a fixed ratio limit has been criticized for underdiagnosing the young and overdiagnosing the elderly (Hardie et al., 2002; Hansen et al., 2006b, 2007; Roberts et al., 2006). Values relative to representative reference values taking into consideration differences in race, gender, age and height are suggested with the applicable lower limit of normal (LLN) used to define abnormal (Pellegrino et al., 2005). The degree of over- and underdiagnosis with the fixed ratio limit is dependent on the reference values used.

FET can be measured by auscultation of the chest wall or trachea, or from spirometry. FET is prolonged in subjects with airway obstruction (Hankinson, 1977; ATS, 1979; Vandevoorde et al., 2005a). Auscultated FET had good sensitivity (92%) but poor specificity (43%) for detection of large airways obstruction (Kern & Patel, 1991). Auscultated FET was rejected early on as a screening test for small airways obstruction on the grounds that its intrasubject variability exceeded that of the spirometrically determined FEF25-75% (Macdonald et al., 1975). In their retrospective patient sample, Vandevoorde and coworkers (2005a) reported that spirometric FET was 8.8 (SD 2.6) s in men without airway obstruction and 10.9 (3.7) s in men with airway obstruction. In women the corresponding values were 8.1 (2.1) s and 9.8 (3.1) s, respectively. Unfortunately, in their study subjects with FET<6 s had been excluded before analysis, because shorter exhalations were considered technically unacceptable (Vandevoorde et al., 2005a).

The sensitivity and specificity of the FEV_1/FEV_6 ratio in identifying cases with airflow limitation have been evaluated in various settings and in many cases with varying exclusion criteria. When assessing studies on patient populations, the essential factors to be taken into consideration include the prevalence of disease, the severity of disease found, and the impact of physiologic changes related to increasing age.

FEV_1/FEV_6<LLN has been reported to have 76.7-97% sensitivity and 47.0-98.2% specificity in the diagnosis of obstruction compared with the gold standard of FEV_1/FVC<LLN (Swanney et al., 2000; Vandevoorde et al., 2005a, 2006; Gleeson et al., 2006; Hansen et al., 2006a). The widely differing sensitivity and specificity values have been attributed to differences in the prevalence of obstruction, from 21% (Hansen et al., 2006a) to over 50% (Swanney et al., 2000), the degree of obstruction, the definition of ”abnormal”, and patient selection. A correction of ±5% and LLN±2% for the day-to-day variability of spirometry, improved the specificity of the measurement to 97.4% (Swanney et al., 2000). Besides a high prevalence of obstruction in that study, many of them were severe in degree. On the other hand, Gleeson and coworkers (2006) defined obstruction as FEV_1/FVC or $FEV_1/FEV_6 \leq 100\%$ predicted, resulting in a greater number of borderline cases being labelled as obstructive and a greatly reduced specificity (47%). Most discordant cases between FEV_1/FVC and FEV_1/FEV_6 have had values close to the LLN (Vandevoorde et al., 2005a; Hansen et al., 2006a; Vandevoorde & Swanney, 2006). In most studies, FET<6 s has been an exclusion criterion, which has resulted in omission of 5.4% (Vandevoorde et al., 2005a) to 37% (Gleeson et al., 2006) of subjects and produced

sample selection. The exclusion of FET<6 s spirometries from analysis will reduce the number of normal and restricted ventilatory defects, hence causing oversampling of the obstructive ventilatory defects. It reflects the high quality of spirometric measurements to be expected from tertiary care pulmonary function laboratories and should be taken into consideration when assessing the usability of FEV_6 and FEV_1/FEV_6 in office spirometry and screening. In occupational screening spirometries, a sensitivity of 92% and a specificity of 98% have been reported, with an acceptable rate of misclassification compared with FEV_1/FVC (Akpinar-Elci et al., 2006).

Because of the limited availability of reference values for FEV_6, especially in Europe, and the widespread use of fixed ratio criteria in the diagnosis of COPD, comparable values have been assessed for FEV_1/FEV_6. Using the same cut-off level of 70%, only 86% sensitivity was reported for FEV_1/FEV_6 (Demir et al., 2005). The fixed cut-off of $FEV_1/FEV_6<73\%$ by contrast, is comparable with $FEV_1/FVC<70\%$, with 94.4% sensitivity and 93.3% specificity in a large retrospective patient sample of 11,676 adults with a prevalence of obstruction of 45.9% (Vandevoorde et al., 2006). This same fixed cut-off level has been found applicable in elderly subjects in Norway (Melbye et al., 2006), where the difference between FEV_1/FVC and FEV_1/FEV_6 was shown to increase with advancing age, smoking, and decreasing FEV_1/FVC ratio (Melbye et al., 2006). In the population study by Hansen and coworkers (2006a), substituting FEV_6 for FVC reduced the sensitivity of spirometry to detect airway obstruction, especially in older individuals and those with minor obstruction. FEV_1/FEV_6 values have been found to be useful in following the course of OAD in smokers and for screening smokers for the presence of airway obstruction in the Lung Health Study (Enright et al., 2002). Other indices, e.g. FEV_3/FVC, $1\text{-}FEV_3/FVC$, and FEF25-75/FVC, have been evaluated as measures of bronchodilation, but have yet to demonstrate utility (Hansen et al., 2006b).

With accumulated information on the usability of FEV_1/FEV_6 in detecting obstruction, the gold standard of obstruction has been debated (Vandevoorde et al., 2005b, 2006; Vandevoorde & Swanney, 2006). The reliable measurement of FVC is sometimes challenging. As long as FVC is used as the gold standard, FEV_6 cannot outperform FVC in the spirometric assessment of pulmonary function abnormalities (Vandevoorde et al., 2006). Additionally, most discordant cases are located at the borderline between normal and abnormal. Swanney and coworkers (2000) attempted to compensate for this with their variability correction; however, proper reference values should be developed and used with no additional corrections being necessary (Lamprecht et al., 2007).

Subjects with $FEV_1/FVC<LLN$ and $FEV_1>LLN$ are considered in the GOLD criteria to have stage I COPD (Rabe et al., 2007), but this definition has been questioned and these subjects considered normal variants (Vandevoorde & Swanney, 2006). FEV_1/FVC physiologically diminishes with aging, resulting in potential overdiagnosis (Hardie et al., 2002; Hansen et al., 2006b; Roberts et al., 2006; Medbø & Melbye, 2007). Therefore a limit of 65% has been suggested in subjects aged 70 years or over (Medbø & Melbye, 2007). However, in the elderly, $FEV_1/FVC<70\%$ and $FEV_1/FVC\geq LLN$ have been associated with increased mortality (Mannino & Davis, 2006; Mannino et al., 2006, 2007).

FEV_1 has also been shown to be a measure of overall increased mortality and morbidity (Hansen et al., 1999; Knuisman et al., 1999; Schünemann et al., 2000).

In summary, with the use of appropriate reference equations, FEV_1/FEV_6 has been assessed to be as good as FEV_1/FVC in predicting obstruction (Enright, 2006b; Pedersen, 2006; Lamprecht et al., 2007).

Restriction

A restrictive ventilatory defect is defined as being ”characterized by a reduction in TLC below the 5th percentile of the predicted value and a normal FEV_1/VC” (Pellegrino et al., 2005). Restrictive abnormality can be suspected based on flow-volume spirometry showing reduced VC, high FEV_1/VC (>85-90%), and a flow-volume curve showing a convex pattern. Reduced VC in itself does not prove a restrictive ventilatory defect, being associated with low TLC in no more than half the cases (Aaron et al., 1999; Glady et al., 2003). A schematic illustration of the spirometry curves displaying typical restrictive ventilatory defects are shown in Figure 3. Based on the 2005 ATS/ERS standard, the degree of restriction is also graded based on FEV_1 (Pellegrino et al., 2005).

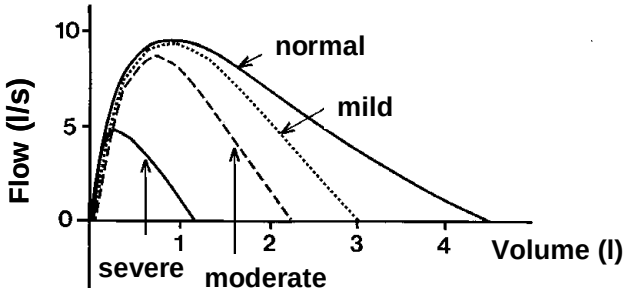

Figure 3 *Flow-volume spirometry curve showing characteristic restrictive ventilatory defect with grading from mild to severe restrictive dysfunction (adapted from Sovijärvi et al., 2006).*

FEV_6 is lower than FVC, especially in individuals with airflow limitation. Demir and coworkers (2005) found in their study of 5,114 patients four subjects with a difference between FVC and FEV_6 that was greater than one liter. Swanney and coworkers (2004) compared three spirometric algorithms against the gold standard of body pletysmographic TLC in the diagnosis of restriction and found that all of the evaluated algorithms had ≥99% accuracy in predicting normal or increased TLC, but that in the prediction of restriction the predictive accuracy was around 50%. However, FEV_6 performed equally well as FVC, and the authors concluded that FEV_6 could be used in lieu of FVC for the spirometric detection of restriction, given that FVC also performs very poorly (Swanney et al., 2004). Glady and coworkers (2003) reported no difference between FVC and slow VC in the prediction of restriction.

Vandevoorde and coworkers (2005a) have first reported in 2005 on a large retrospective patient sample of 11,676 subjects with FET>6 s, with spirometric restriction defined as FVC<LLN in the presence of a normal FEV_1/FVC ratio. Substituting FEV_6 for FVC reduced the sensitivity of detection of restriction to 83.2% and specificity to 99.6%. The prevalence of restrictive pattern (with FVC) was 15.7% (Vandevoorde et al., 2005a). Then, in 2006, the same researchers described based on another large routine pulmonary function test laboratory material the utility of FEV_6 in the diagnosis of restriction combined with FVC (Vandevoorde et al., 2006). FEV_6 in combination with FVC had an improved sensitivity of 95.9% and specificity of 98.6% for the diagnosis of restriction, while the prevalence of spirometric restriction (defined as FVC<LLN) was 14.9% (Vandevoorde et al., 2006).

More recently, Vandevoorde and coworkers (2008) have investigated the ability of FEV_6 and FVC from flow-volume spirometry to predict reduced total lung capacity (restriction) in a patient sample of 12,693 subjects. Obstruction was defined as FEV_1/FVC or FEV_1/FEV_6<LLN. TLC was measured by body plethysmograph and used as the reference standard for restriction. Both FVC and FEV_6 had low positive and high negative predictive values. In nonobstructive subjects, they found that restriction could be positively predicted if FVC or FEV_6 was <55% for males or <40% for females, but that in obstructive patients spirometry could not reliably diagnose a concomitant restrictive defect. However, spirometry can rule out restriction in patients with FVC or FEV_6 >85% predicted in men and >70% predicted in women (Vandevoorde et al., 2008).

In conclusion, FEV_6 has been shown to have lower sensitivity in the detection of restrictive than obstructive disorders, but other flow-volume spirometry variables, namely FVC and VC, perform equally poorly (Pedersen, 2006; Vandevoorde et al., 2008).

Mixed abnormalities

A mixed ventilatory defect is characterized by the coexistence of obstruction and restriction, and is defined physiologically when both FEV_1/VC and TLC are below the 5th percentiles of their relevant predicted values (Pellegrino et al., 2005). During the course of obstructive airways disease, narrowing of the airway lumen causes air trapping, which results in dynamic hyperinflation and the development of a dynamic restriction (Pellegrino & Brusasco, 1997; O'Donnell et al., 2001; Calverley & Koulouris, 2005).

2.2 Standardization of spirometry

The standardization of spirometry dates back to the 1970s, when both in the United States and in Europe technical development necessitated local agreements on methods to be applied. On both continents, the initial drive to standardization of methods came from occupational interests since legislation was enacted that required medical surveillance of

workers exposed to respiratory hazards (Theodos et al., 1975). Epidemiologic research increased markedly, requiring comparability of data and diagnostic criteria.

2.2.1 The American Thoracic Society

In the United States, the coordination efforts were started slightly earlier, with the first recommendations published in 1975 (Theodos et al., 1975) and the first consensus statement reached in the Snowbird Workshop on standardization of spirometry held in 1977 (ATS, 1979). Thereafter, the American College of Chest Physicians (ACCP) published their own recommendations (in 1983), basically endorsing the Snowbird Workshop results (Zamel et al., 1983).

Standardization work continued on a wider basis driven by both accumulated experience and the advent of computerized spirometers. An update on methodology was published in 1987 (ATS, 1987) and a consensus document on reference values and interpretative principles in 1991 (ATS, 1991). The start-of-test criteria were based on the back-extrapolation method, with a tighter limit for extrapolated volume (EV) at 5% of FVC or 0.100 liters, whichever was greater. This was a significant reduction from the previously accepted upper limit of 10% of FVC (Zamel et al., 1983). The 1987 update also introduced the current form of end-of-test criteria. An end-expiratory pleateau was required for at least 2 s, with an exhalation time of at least 6 s or a forced exhalation of reasonable duration (longer than 15 s was considered not to change clinical judgment) or when for legitimate clinical reasons the subject cannot or should not continue further exhalation. The repeatability criteria became more specific with an upper limit of 5% of the respective volume or 0.100 liters instituted for both FVC and FEV_1. The 1979 document was unclear in the interpretation of which volume 5% was to be calculated, and the new standard resolved this ambiguity. In the 1987 update, the ATS also took a stance to discourage the elimination of subjects from epidemiological studies on the grounds of poor reproducibility since this had been demonstrated to result in a population bias (Eisen et al., 1984, 1985; Kellie et al., 1987). The concept of “best test” defined in terms of largest sum of FEV_1 and FVC was also endorsed.

A separate standard on the interpretation of spirometry was published in 1991. This document introduced the current bronchodilation test limits of 12% of FVC or FEV_1 from baseline with a concurrent absolute change of 200 ml required (ATS, 1991). Previously, the Intermountain Thoracic Society had advocated the use of a 15% change in FVC, a 12% change in FEV_1, or a 45% change in FEF25-75%, and the ACCP a limit of 15-25% for all three variables (Morris et al., 1984; ATS, 1991).

Although workshops were held also on dealing with coordination of measurements of lung volumes, this was not addressed in the published standards. The standardization of spirometry was updated in 1994 to take into account technical developments, most notably driven by the rapid development of computers (ATS, 1995). It included a separate category for monitoring devices, with slightly less stringent measurement quality criteria applied. Instructions for BTPS corrections were more specific and detailed, with

accumulated data on the effects of BTPS corrections on results. The acceptability criteria included EV (<5% FVC and <0.150 liters) and an interim criterion of time-to-PEF<120 ms. The repeatability criteria were changed to equal volume criteria of FVC or FEV_1 ≤0.200 liters, to accommodate the view that relative change values would misclassify subjects with small lung volumes as having poorly repeatable tests (ATS, 1995).

2.2.2 The European Respiratory Society

In Europe, national recommendations prevailed until 1983, when collaborative work within the European Community for Coal and Steel (ECCS) coordinated the first standard (Quanjer et al., 1983). The standardization was driven by needs of occupational health providers for uniform standards to assess potential work-related hazards to respiratory health. Soon thereafter, the European Respiratory Society (ERS) participated in the update, which was then endorsed as an official statement of the ERS (Quanjer et al., 1993).

In the 1993 ERS standard, the main differences in ATS criteria were in the applied curve and variable selection criteria. The ERS standard states that the inspiratory vital capacity (IVC), FVC, FEV_1, and PEF be taken from the largest respective value from the first three technically satisfactory determinations. For IVC, FVC, and FEV_1, the chosen value should not exceed the next highest one by more than 5% or 100 ml, whichever is greater. The start of the forced expiration is obtained by back-extrapolation. EV should not exceed 5% of the FVC or 100 ml, whichever is greater. MMEF is taken as the largest value from the first three technically satisfactory curves provided that the curve has a FVC that differs less than 5% from the largest FVC. MEFx values are taken from an envelope of at least three technically statisfactory MEFV curves, which are superimposed from total lung capacity (TLC). Alternatively, the standard leaves it optional to take the highest value from a set of three curves provided that the FVC of the chosen curves differs less than 5% from the largest FVC. The curves should have comparable form, and the PEF values should differ less than 10% from the largest one (Quanjer et al., 1993). The PEF repeatability criteria advocated in the ERS 1993 standard are therefore quality criteria to ensure other flow values are taken from maneuvers with maximum effort.

The ERS 1993 standard also advocates the use of a uniform set of European reference values based on Quanjer and coworkers (1993), whereas the ATS standard did not take a stance on any one set of reference values, instead focusing on the representativeness of selected reference values at the local level and stressing the need to update reference values regularly (ATS, 1995). The European reference values are based on a collection of earlier studies, and their continuing use has recently been debated (Degens & Merget, 2008).

In bronchodilation testing, the ERS 1993 standard recommends the use of absolute and relative to reference value change in FEV_1 and FVC, setting the limit of significant change at 12% of predicted and 200 ml (Quanjer et al., 1993). Additionally, in adults, an increase in PEF of 60 l/min after administration of a bronchodilator drug was considered to

indicate a clinically significant improvement. The use of MMEF or other instantaneous flows was discouraged.

In 1995, European scientists participated in the ATS updates of standards for spirometry and single-breath carbon monoxide diffusing capacity of the lung, but no joint statement was published by the two societies until 2005 (Brusasco et al., 2005). Although very similar in many aspects, the two major standardization efforts also differed on significant issues, which have had implications for research and development of international guidelines on the diagnosis and treatment of various respiratory conditions, e.g. COPD. The need for harmonization was widely acknowledged already in the mid-1990s and prompted the formation of joint task forces between the ATS and ERS to develop standards in pulmonary function testing, including spirometry.

2.2.3 ATS/ERS Task Force 2005

Internationally, the slightly differing definitions of the ATS and the ERS were recognized to need harmonization to foster research. The joint task force was created to tackle issues of standardization in different lung function measurements – spirometry, diffusion capacity, and body pletysmography. The outcome of this work was published in 2005 as a series in the European Respiratory Journal (Miller et al., 2005a, 2005b; Wanger et al., 2005; MacIntyre et al., 2005; Pellegrino et al., 2005).

The joint ATS/ERS 2005 standard on spirometry (Miller et al., 2005b; Pellegrino et al., 2005) followed the previous ATS 1994 standard on most key issues. This was expected since the ATS standard had been widely adopted in research. The separate category of monitoring devices was discarded with the intention of producing minimum criteria to be fulfilled by all devices used in patient studies. Single curve acceptability criteria included EV being <5% of FVC or 0.150 liters, whichever is greater. On repeatability criteria, the two largest FVC and FEV_1 should be within 0.150 liters, however, when FVC< 1.0 liter, these values are reduced to 0.100 liters. All other flow values should be taken from the “best curve”, which is defined as the curve with the largest sum of FEV_1 and FVC. The endorsement of the “best curve” concept clarified the selection of flow values and left no room for interpretation in curve selection. For lung volume, the largest value of FVC, FIVC, or VC was suggested and especially for the ratio FEV_1/FVC used for the diagnosis of COPD.

FEV_6 was included in the new standard and its better repeatability (compared with FVC) and easier completion were noted, but the statement fell short of recommending its use. It has been speculated that this could be because European reference values for general use are still lacking (Laszlo, 2006).

In bronchodilation testing, the task force endorsed the ATS 1994 criteria, namely the use of change relative to baseline and absolute change, with values exceeding 12% and 200 ml of either FVC or FEV_1 considered significant (Pellegrino et al., 2005). However, the new standard also noted the potential cases where bronchodilation is seen only in FVC and added the requirement that expiratory time not change if an “isolated volume

response" is documented. The term "isolated volume response" was used to describe a situation where only FVC, not FEV_1, increases significantly during the bronchodilation test.

The updated ATS/ERS standards have been adopted in Finland in the national Finnish guidelines that have also been updated in 2006 (Sovijärvi et al., 2006). A new task force on pulmonary function testing, implemented by the Forum of International Respiratory Societies (FIRS) has recently started its work based on the ATS/ERS documents (Brusasco et al., 2005).

2.3 Repeatability of spirometry

The repeatability and variability of spirometry have been extensively investigated during the 1960s and 1970s (Dawson, 1966; Ashrift et al., 1969; McCarthy et al., 1975; Knudson et al., 1976a, 1976b; Cochrane et al., 1977; Nickerson et al., 1980), but since the standardization work had only just started, these studies are not comparable with modern flow-volume spirometry. The measurements and their selection for interpretation differ from the current methods. Repeatability studies among patients with OAD are problematic since variations in spirometry reflect characteristic changes in the disease state in addition to measurement variability. Additionally, assessment of "normal" in these studies has usually been self-reported and is not based on medical evaluation. The method of assessing variability in the studies also varies, with reported percentages not always being directly comparable.

Besides repeatability of the measurement in itself, factors related to instrumentation, technicians, timing of previous medication, and any medication wash-out periods used affect the measurement (Glindmeyer et al., 1982; Demets, 1990; Enright et al., 1995; Künzli et al., 1995; Chinn et al., 2006).

2.3.1 Intrasession repeatability of spirometry

A flow-volume spirometry measurement consists of three acceptable determinations fulfilling repeatability criteria as stated above. Intrasession repeatability refers to the difference between these three determinations.

In healthy adults completing spirometry on multiple occasions, the intrasession repeatability of FVC and FEV_1 in terms of CoV was 2.7% during multiple measurements in one day and 1.8% during weekly measurements; the corresponding figures for FET were 11.8% and 13% (Cochrane et al., 1977). In asymptomatic never-smoking Norwegian men (n=4,989) aged 30-46 years participating in a community survey, the within-subject standard deviation from three recordings of FEV_1 and FVC was on average 102 and 106 ml, respectively, increasing with height and BMI (Humerfelt et al., 1998). Small, but significant, differences were observed between technicians in within-subject repeatability

and levels of FEV_1 and FVC (Künzli et al., 1995; Humerfelt et al., 1998; Chinn et al., 2006).

In patients completing routine spirometry, the coefficient of variation has been reported to be 14.8% for FET and 4.7% for FVC, with longer FET being associated with better performance in spirometry expressed in terms of FEV_1+FVC (Tsai et al., 2006). In a population sample, Hankinson & Bang (1991) found both older and younger subjects to have more difficulty to satisfy ATS acceptability and reproducibility criteria. In addition, the reproducibility criteria relative to FVC and FEV1 seemed to classify a higher percentage of subjects with smaller height and lung volume as having a nonreproducible test (Hankinson & Bang, 1991).

Ninety percent of patients (n=18,000) completing routine flow-volume spirometry in a pulmonary function laboratory were able to reproduce FEV_1 within 120 ml (6.1% of best FEV_1) and FVC within 150 ml (5.3% of best FVC) in a retrospective analysis of patient records (Enright et al., 2004). Older subjects were able to reproduce repeatable spirometries as often as younger patients, but shorter patients and subjects with worse baseline lung function were less able to obtain reproducible maneuvers when expressed as a percentage difference (Enright et al., 2004).

The index of variability of each timed volume (FEV_t) from 1 to 12 s in subjects (n=3,539) participating in screening flow-volume spirometry during an epidemiological survey was calculated, and the least within-test session variability expressed in terms of average range was seen for FEV_6 and FEV_7, both having a mean range of 95 ml (Jensen et al., 2006). FET under 10 s was an exclusion criterion in the study.

Sourk and Nugent (1983) evaluated 79 patients referred to a pulmonary function test and randomized 42 subjects to placebo inhalations and 37 to receive metaproterenol 1,500 µg in a blinded study on variability of spirometry. In response to the placebo inhalations, FVC changed on average 1.3% (SD 6.7%) and had an upper confidence limit of 14.9%. This corresponds to a mean difference of 25 ml (SD 156 ml) and an upper confidence limit of 340 ml. Concurrently, FEV_1 changed on average 0.97% (SD 5.6%) or 11 ml (83 ml), with an upper confidence limit of 12.3% or 178 ml. In this heterogeneous patient material, baseline pulmonary function and clinical factors were reported to have no apparent effect on placebo responses (Sourk & Nugent, 1983).

2.3.2 Circadian variation

In healthy adults pulmonary function, particularly FEV_1, has been shown to follow an endogenous circadian rhythm with minimum values occurring during the usual sleep period during night even in subjects maintaining wakefulness (Spengler & Shea, 2000). On the contrary, FVC remained fairly constant with no circadian variation observed. The ranges (peak to trough) of mean circadian changes in spirometric variables were 2.0-3.2% of average values with individual circadian rhythms (within-subjects) generally larger than the group average changes (between-subjects) (Spengler & Shea, 2000).

Circadian variation in lung function has been studied in a population sample (n=876) with measurements between 09:00 and 21:00 and on four occasions at three-year intervals (Borsboom et al., 1999). Spirometric variables increased from 09:00 until noon, and decreasing thereafter. Average variation in FVC was 4.8% (200 ml) and in FEV_1 2.8% (86 ml) adjusted to average level. In healthy non-asthmatic volunteers, the coefficient of variation was lowest intrasession (1.5% for FEV_1 and 3.1% FVC) and highest over 12 h (3.2% for FEV_1 and 4.1% for FVC) (Randell et al., 1999). In both of these studies, the average diurnal variation was found to be large in relation to longitudinal change, but the authors suggested that longitudinally comparable measurements should be collected after 11:00 to minimize the confounding effect of diurnal changes on judgement of longitudinal changes (Borsboom et al., 1999; Randell et al., 1999). Similar results were earlier reported for 15 subjects (including 5 normal controls) measured five times over two days, with a diurnal variation in FEV_1 found and the highest flows being recorded at midday; the difference was not, however, significant (Hruby & Butler, 1975).

Nineteen stable asthmatics and ten normal controls performed portable spirometry every two hours during the day (from 8:00 until 22:00) and once at night, waking up at different times (02:00, 04:00, and 06:00) in rotation for two weeks in total. Three forced expiratory maneuvers were recorded at each time point. PEF and FEV_1 were found to be equally sensitive to detection of circadian rhythm in stable asthmatics and normal controls, with a significant circadian rhythm detected on 50% of all recorded days. The maximum values of both PEF and FEV_1 coincided at around 14:00 (Troyanov et al., 1994).

2.3.3 Short and long-term repeatability of spirometry

One of the earliest reports on reproducibility of spirometry in an occupational sample examined 38 subjects exposed to small concentrations of beryllium followed for 18-24 months with spirometry completed at 6-month intervals. VC was documented to have the best reproducibility of 0.104 liters or 2.1% and FEV_1 0.113 liters or 3.0%. The relative repeatability of FEV_2 and FEV_3 were better than for FEV_1, although in absolute terms their repeatability was poorer. MMEF values proved to be the least repeatable of the variables evaluated (Dawson, 1966).

In normal adults (n=10) completing spirometry on the same day of the week for six weeks and on three separate days hourly, the variation in any subject for FEV_1 and FVC over the study period was considerably less than for MEF50, MEF75, or FET (Cochrane et al., 1977). FVC varied within subjects 1.8% hourly and 2.9% daily or weekly. FEV_1 varied 2.3% hourly, 2.9% daily, and 3.4% weekly. The corresponding figures for FET were 9.4%, 12.0%, and 13.0% (Cochrane et al., 1977). Correspondingly, McCarthy and coworkers (1976) studied 12 normal subjects ten times each day and found a coefficient of variation for within-day measurements of 3% for both FVC and FEV_1 and 5% for FVC and 7% for FEV_1 for week-to-week measurements.

Based on an analysis of earlier published studies, the upper limit of intraindividual variability in spirometry was assessed to be an increase in excess of 11% in FVC, 13% in

FEV_1, or 25% in FEF25-75%, representing a significant change from baseline, e.g. in bronchodilation testing (Pennock et al., 1981). When following patients over a longer period, the week-to-week change of FVC or FEV_1 must be greater than 20-25% or the change in FEF25-75% greater than 30% to be considered significant (Pennock et al., 1981).

Daily spirometry on five consecutive days in 15 normal subjects yielded mean individual standard deviations of 0.102 liters for FEV_1 and 0.119 liters for FVC. The mean for individual CoV for both FEV_1 and FVC was 2.8% (Rozas & Goldman, 1982). In the same study, patients with airflow obstruction demonstrated significantly higher variability and authors concluded that FEV_1 would need to change 17% and FVC 15% for the change to be considered significant in patients with airflow obstruction, whereas a greater than 5% change in either FEV_1 or FVC would be significant in normal subjects (Rozas & Goldman, 1982).

In two separate studies, Tweeddale and coworkers (1984, 1987) assessed the within-subject variability of FEV_1 in normal and obstructive subjects. In normal subjects and a small group of patients with restrictive ventilatory defects, they demonstrated over a wide range of FEV_1 that its short-term variability was rather constant and suggested a criterion of response of 190 ml or more in normal subjects (Tweedale et al., 1984). In a prospective sample of 150 patients with OAD, the natural variability over a 20-min period when expressed in absolute terms was similar over the entire range of FEV_1 (0.5 – 4.7 liters) and differed insignificantly from that found in normal subjects. The increase in FEV_1 and VC required to exclude natural variability with 95% confidence in these patients was 160 ml and 330 ml, respectively. Natural variability of relative change in FEV_1 was negatively correlated with the level of FEV_1 recorded (Tweeddale et al., 1987).

The long-term variability of flow-volume spirometry is affected by aging and potentially disease-related decreases in measured variables (Glindmeyer et al., 1982; Dirksen et al., 1998; Jensen et al., 2007). Although not directly repeatability issues, two phenomena warrant mentioning in this regard: the horse-racing effect and regression towards the mean (Rijcken et al., 1997). The horse-racing effect refers to subjects observed to have a lower-than-average lung function at one measurement usually having faster decline in lung function in longitudinal follow-up (Burrows et al., 1987). Regression towards the mean is caused by the interaction of change with the initial level of lung function (Rijcken et al., 1997). This means that subjects having below average values at the first measurement, are more likely to have closer to average values in the repeated measurements due to the inherent measurement variability of multiple measurements.

2.4 Assessment of bronchodilation response in flow-volume spirometry

Bronchodilation response refers to the change in airway caliber as a result of inhaled bronchodilating medication that causes improvements in flow or volume variables detectable by pulmonary function tests, e.g. flow-volume spirometry.

Studies on bronchodilation have been conducted on various samples and with differing bronchodilating medications, dosages, and delivery methods, making comparisons difficult. Again, the older studies from 1960s and 1970s are less comparable due to methodological differences (Olsen & Hale, 1968; Boushy, 1972; Skinner & Palmer, 1974; Sobol et al., 1974; Popa & Werner, 1976; Fish & Permutt, 1978; Fairshter & Wilson, 1980).

Standardization of the interpretation of reversibility testing started already in the 1970s (Snider et al., 1974), but wide differences prevailed. Although the 2005 ATS/ERS standard recommended the use of 400 µg of salbutamol aerosol, it still left the choice of medication used open for clinical consideration (Pellegrino et al., 2005).

2.4.1 Selection of variables and indices

A number of possible indices have been evaluated in search of a good measure of bronchodilation, but in reality the clinical question to be answered affects the assessment. Different indices might be appropriate to answer different clinical or research problems. A listing of indices with the formulas used for calculation in the literature is shown in Table 1.

Table 1. *Indices used in the literature for calculation of FEV_1 bronchodilation response*

Index	Abbreviation	Mathematical formula for calculation
absolute change	absolute	FEV1post – FEV1pre
change as a percentage of prebronchodilator value	% initial	$\frac{\text{FEV1post – FEV1pre * 100}}{\text{FEV1pre}}$
change as a percentage of predicted value	% predicted	$\frac{\text{FEV1post-FEV1pre * 100}}{\text{FEV1predicted}}$
change as a percentage of the maximal absolute response ever recorded (during the study period)	% maximal	$\frac{\text{FEV1post – FEV1pre* 100}}{\text{change of FEV1max}}$
change as a percentage of predicted value minus prebronchodilator value	% possible	$\frac{\text{FEV1post – FEV1pre * 100}}{\text{FEV1predicted – FEV1pre}}$
change as a percentage of the highest postbronchodilator value ever recorded during the study period minus prebronchodilator value	% achievable	$\frac{\text{FEV1post-FEV1pre * 100}}{\text{FEV1max-FEV1pre}}$
standardized residuals	sdr	$\frac{\text{[(FEV1post-FEV1predicted) - (FEV1pre - FEV1predicted)]}}{\text{sd of FEV1predicted}}$
percentage with respect to the baseline modified	cf	$\frac{\text{FEV1post-FEV1pre * 100 * 2}}{\text{FEV1pre+FEV1post}}$

FEV1pre= prebronchodilator FEV1; FEV1post=postbronchodilator FEV1; FEV1predicted=reference value for FEV1 for the subject
(Fish & Permutt, 1978; Dompeling et al., 1992; Rodriguez-Carballeira et al., 2007)

In Europe, the 1993 standard (Quanjer et al., 1993) advocated the use of change as a percentage of the predicted value for both FEV_1 and FVC as a measure of significant bronchodilation. It has been debated that the percentage of the predicted value has a lower correlation with predilator values but a high sensitivity and specificity in separating asthma and COPD (Weir & Burge, 1991; Brand et al., 1992). Analysis of variance using change as a percentage of the predicted value and covariance analysis of pre- and postbronchodilator FEV_1 have been demonstrated to offer the best performance, especially in clinical trials (Goedhart & Zanen, 2002).

In fact, most studies have focused on the differential diagnosis of COPD and asthma. COPD is characterized and defined as an "obstruction that is not fully reversible" (Global Initiative for Chronic Obstructive Lung Disease; Rabe et al., 2007). However, many patients with COPD demonstrate partial reversibility, and others have both asthma and COPD (Kesten & Rebuck, 1994; Jeffrey et al., 1999; Ryu & Scanlon, 2001; Mannino, 2008; Shaya et al., 2008). Patient selection in these studies is very difficult since selection fundamentally affects the outcome. The procedure and in particular the inspiratory maneuver preceding forced expiration should be standardized, especially with COPD patients (Eliasson & Degraff, 1985; Reddy et al., 1996; Pellegrino et al., 1998; Santus et al., 2003). Recently, Tashkin and coworkers (2008) found up to 60% of patients with COPD to test reversible following a longer wash-out period of maintenance therapy. Additionally, the choice of bronchodilating medication used in the test might have a greater influence in COPD patients (Dorinsky et al., 1999; Joos et al., 2003; Tashkin et al., 2008).

Meslier and coworkers (1989) investigated 20 subjects with chronic bronchitis and 32 subjects with stable airways obstruction and measured forced expiratory flows before and after increasing doses of salbutamol to differentiate asthma from chronic bronchitis. Using discriminant analysis, FEV_1 was found to be the most effective index of forced expiration to discriminate among the mechanisms of airflow obstruction in asthma and chronic bronchitis (Meslier et al., 1989).

Earlier, Light and coworkers (1977) evaluated 20 adults with reversible airways obstruction defined as 15% improvement in FEV_1 following 150 µg isoproterenol and found FEV_1 to be the best test for evaluating the response to bronchodilators and that the use of MMEF or body pletysmography did not allow more conclusions than the use of FVC and FEV_1 alone. On the other hand, body pletysmography was observed to result in a greatest number of significant responses in patients with OAD (COPD or asthma), when compared with spirometry (FVC and FEV_1) and impulse oscillometry (van Noord et al., 1994). The study did not, however, take into consideration the natural variability of the measurements compared. Oscillometry was insensitive in subjects with severe baseline obstruction, who were more likely to respond in improvements in FVC (van Noord et al., 1994; Zerah et al., 1995; Houghton et al., 2004a, 2004b; Rodriquez-Carballeira et al., 2007; Schermer et al., 2007), but results from other modalities have lacked general usability (Hadcroft & Calverley, 2001).

Dompeling and coworkers (1992) examined 72 asthmatics and 111 subjects with COPD on six test occasions over two years and compared the bronchodilation response

achieved at each visit using 400 µg of salbutamol and 80 µg of ipratropium bromide. They compared six different indices for their ability to differentiate between asthma and COPD, for the reproducibility of the bronchodilation response, and dependence on prebronchodilator FEV_1. Dependence on prebronchodilator FEV_1 implies that responses are not directly comparable between subjects. The reproducibility of bronchodilation response is a more complex issue since reversibility of obstruction is asthma is characteristically fluctuating, hence changes in measurements day-to-day or week-to-week can change as disease state changes without any changes in measurement accuracy. They found the "% possible" or change as a percentage of the predicted minus prebronchodilator value and "% achievable" or change as a percentage of the maximal postbronchodilator minus prebronchodilator value to depend least on prebronchodilator FEV_1 and to have the highest reproducibility, whereas "% initial" or change as a percentage of the prebronchodilator value was the most dependent on the prebronchodilator lung function and had the worst reproducibility. One of the inclusion criteria of the study was that subjects could not use any corticosteroids or cromoglycate during the study, which would quite fundamentally affect bronchodilation responses during the two years of the study, at least in the participating asthmatics (Dompeling et al., 1992).

The use of the ratio of change in FEV_1 to change in FVC to differentiate between flow responders and volume responders has been suggested, with a ratio over one signifying predominantly flow response (Paré et al., 1983; de la Hoz, 2002). The use of partial expiratory flow-volume curves has been evaluated in the assessment of bronchodilation response, with potentially promising results in early studies (Barnes et al., 1981), but ultimately found not to bring any additional benefit in differentiating between healthy and asthmatic responses (Berry & Fairshter, 1985).

2.4.2 FEV_1 response to bronchodilation

Studies on healthy adults

Watanabe and coworkers (1974) investigated 75 subjects aged 20-81 years who were classified as "normal" based on subjects' self-reported status. Of these, 12 men and 4 women were current smokers with a smoking history of under 10 pack-years. All of the subjects denied having "smoker's cough". Bronchodilation testing was undertaken with 3 or 4 deep inhalations of an aerosol mist from a Bronkometer pocket nebulizer, with each dose containing isoetharine 350 µg, phenyl ephrine 70 µg and thenyldiamine 30 µg. Average FEV_1 changed from 3.610 liters to 3.692 liters, which is +2.5% (SD 3.9%). Twelve of the subjects showed a decrease in FEV_1 despite a concomitant increase in specific conductance (sGaw). FVC remained virtually unchanged in light of the mean value of 0.2% (SD 2.5%)(Watanabe et al., 1974). From this data, Sourk and Nugent (1983) have since recalculated 95% confidence intervals, finding changes in excess of 5.2%, 10.5%, and 49% in the FVC, FEV_1, and FEF25-75%, respectively, occurring in

only 5% of normal subjects. Watanabe and coworkers (1974) also showed that bronchodilation response tended to decrease with aging and suggested that this could be due to the decreasing sensitivity of bronchial smooth muscle β-adrenergic receptors as subjects age. The larger the bronchodilation response, the greater its variation in long-term follow-up (Watanabe et al., 1974).

In a small group of normal controls (n=5), FEV_1 increased on average 4.0% with 200 µg salbutamol (Holmes et al., 1978). A similar magnitude of change was reported in a dose-response study, where responses to 100 µg, 200 µg and 800 µg of salbutamol were 4.1%, 3.8%, and 4.7% from baseline, respectively (Houghton et al., 2004a).

Population studies

Lorber and coworkers (1978) reported one of the first population studies on bronchodilation response in 1063 subjects from the general population. However, since no physician was in attendance during spirometry, the study protocol limited bronchodilation testing completed in subjects without tachycardia, any history suggesting cardiac disease, hypertension, diabetes mellitus, hyperthyroidism, pregnancy, lactation, or regular use of bronchodilator medications. Subjects with lower baseline FEV_1 tended to have larger bronchodilating responses to isoproterenol. Subjects with better-than-average lung function initially showed no systematic improvement after isoproterenol, and the authors identified a level of lung function above which a ”zero mean change group” was formed. They defined significant bronchodilator response as a degree of improvement greater than that observed in 95% of the ”zero mean change group”, being 0.315 liters or 7.7% change in FEV_1 and 0.403 liters or 10.7% change in FVC (Lorber et al., 1978).

Dales and coworkers (1988) studied a population sample of 2,609 subjects (1,982 adults) with spirometry and bronchodilation testing using 500 µg of terbutaline sulfate. The population mean for change in FEV_1 was 68 (SD 129) ml or 2.1% (4.3%) from the baseline. In the healthy subgroup, change in FEV_1 was 57 (128) ml or 1.8% (4.0%). The 95th percentile of change in FEV_1 in the healthy subgroup was 291 ml or 9%. In absolute change of FEV_1, bronchodilation response and the corresponding 95th percentile were higher in men, and within age groups it was greater in taller than in shorter participants. A negative association between predicted FEV_1 and bronchodilation response was observed with higher response detected in subjects with reduced FEV_1 (Dales et al., 1988).

Lehmann and coworkers (2007) investigated a general population sample, inviting all adults aged 47-48 and 71-73 years in Bergen, Norway. Subjects without anti-asthmatic medication and completing acceptable flow-volume spirometry with salbutamol reversibility testing (n=3,088) were included in a study analyzing the role of symptoms in prediction of bronchodilation response. FEV_1 reversibility ≥12% and ≥200 ml was obtained in 2% of middle-aged and 4% of elderly subjects. Wheezing without cold, dyspnea climbing two flights of stairs, and morning cough predicted an increased FEV_1 bronchodilator response, whereas chronic cough had an inverse relationship (Lehmann et al., 2007). In a separate report, the importance of anthropometric variables and smoking

history in the response to salbutamol found change in FEV_1 in the middle-aged of 0.071 (SD 0.122) liters or 2.4% (4.1%) baseline and in the elderly 0.064 (0.113) liters or 3.3% (5.9%) from baseline (Lehmann et al., 2006). Female gender, old age, and BMI were positively correlated with the relative change measures. In linear regression analysis, smoking was found to be the strongest determinant of bronchodilation response, but all of the variables together explained only 7-16% of measurement variability, and hence, are of minor importance in the interpretation of the test (Lehmann et al., 2006).

Johannessen and coworkers (2005, 2006) studied a sample (n=2,235) of the general population in two reports on prevalence and risk factors of COPD and on postbronchodilator reference values for flow-volume spirometry. In men, the mean change in FEV_1 was 0.145 (SD 0.134) liters in 27- to 39-year-olds, 0.078 (0.120) liters in 40- to 59-year-olds, and 0.034 (0.178) liters in 60- to 82-year-olds. For women, the corresponding values were 0.115 (0.101) liters, 0.056 (0.095) liters, and 0.046 (0.081) liters. Bronchodilation response decreased with aging, with no gender difference (Johannessen et al., 2006).

Studies on patient groups

Bronchodilation response has been extensively investigated in different patient groups, especially in various clinical trials. The design of studies varies greatly, with varying numbers of subjects with asthma and/or COPD, diagnostic criteria, degrees of obstruction, and different baseline treatment allowed. In this summary, only studies focusing on bronchodilation response and its determinants are considered.

Reversibility testing conducted with 250 µg of isoproterenol in 985 subjects with COPD who were evaluated and followed for three years in a trial of intermittent positive pressure breathing was reported to be on average 15% relative to baseline or 5% relative to predicted normal for subjects who were able to abstain from bronchodilators for 6 h previously (Anthonisen et al., 1986). All subjects had baseline FEV_1<60% predicted, FEV_1/FVC<60%, and TLC ≥80% predicted.

Guyatt and coworkers (1988) studied 24 subjects (one woman) with chronic airflow limitation and tested the ability of acute change in FEV_1 to predict long-term symptomatic response to albuterol and theophylline. They found reproducibility of acute change in FEV_1 to be poor (ICC 0.17), and the change in FEV_1 was not associated with symptomatic response to either albuterol or theophylline (Guyatt et al., 1988). Their study was likely to also include asthmatics based on current criteria since changes in FEV_1 were on average 0.150 (0.09) liters or 19.7% (11.2%) from baseline. Initial FEV_1 reversibility was under 25% in 19 and between 25-35% in 5 subjects (Guyatt et al., 1988). Additionally, other studies have shown that variability of spirometry is greater in subjects with low baseline FEV_1, and the subjects evaluated by Guyatt and coworkers had on average a baseline FEV_1 of 0.93 (0.34) liters. They concluded that acute response to inhaled β2-agonist is not useful for identifying patients with chronic airflow limitation likely to benefit from bronchodilator treatment (Guyatt et al., 1988).

In a population sample of 123 volunteers (90 men, 33 women) consisting of current or ex-smokers experiencing breathlessness who responded to an advertisement for lung function testing had a median FEV_1 response to 400 µg salbutamol from the baseline of 10.4% or 165 ml in current smokers and 9.8% or 140 ml in ex-smokers (Reid et al., 2003). A significant inverse relationship between prebronchodilator FEV_1 and change in FEV_1 expressed as a percentage increase was found, but also a positive relationship between absolute change and prebronchodilator FEV_1. Median change in FVC was 9.3% or 275 ml in current smokers and 7.0% or 220 ml in ex-smokers. Inhaled corticosteroid (ICS) use was reported by 58% of study subjects, and the use of ICS was weakly correlated with lower prebronchodilator FEV_1 (r=-0.2) and greater change in FEV_1 (r=0.3) in bronchodilation testing (Reid et al., 2003).

Since measurement repeatability and disease state can fluctuate within a subject between measurements, the significance of each patient's response to inhaled albuterol has been assessed with a statistical model taking into consideration five measurements at baseline, following inhaled saline solution (acting as a placebo control) and albuterol (5 mg/ml four breaths from nebulizer) in this order (Hansen et al., 1993). In very severe to severe obstruction, relative change of FEV_1 was found to identify significantly more "significant" responders, when saline was used as the comparison, which was suggested as one potential explanation for the discrepancy between symptom relief and demonstrated reversibility in spirometry. Bronchodilation response has been reported to be dependent on baseline values, especially in newly referred patients with asthma, but this dependency was less strong in bronchitis and even weaker in subjects with emphysema (Goedhart et al., 2004).

Schermer and coworkers (2007) studied 2,210 patients with varying degrees of COPD and assessed the relative role of flow and volume responses after salbutamol. Average change in FEV_1 was 0.180 (SD 0.150) liters or 6.3% (5.1%) of predicted. In their patient sample, subjects with mild COPD had greater flow responses (change in FEV_1), whereas in subjects with severe COPD the bronchodilation response was greater in volume (change in FVC). Changes in expiratory time were not registered in their study. The authors hypothesize that the difference could be explained by the higher degree of loss of lung elastic recoil and/or compression of the smaller airways due to enlarged air spaces associated with progression of COPD to more severe stages (Schermer et al., 2007).

2.4.3 FVC response to bronchodilation

Assessment of changes in lung volumes during the bronchodilation test with flow-volume spirometry is demanding. Bronchodilation may induce changes in lung volume compartments, such as residual volume (RV) related to TLC, and changes in nonventilated lung compartments (Gimeno et al., 1993; Pellegrino & Brusasco, 1997; O'Donnell, 2000; O'Donnell et al., 2001). Flow-volume spirometry can only give suggestive evidence of these changes.

Girard and Light (1983) demonstrated that FVC responders in spirometry could be divided into two major categories: true volume responders and those with prolonged FET in postbronchodilator spirometry. Individuals with prolonged FET did not demonstrate any significant change in FEV_3 or FEV_6 in postbronchodilator spirometry (Girard & Light, 1983). Prolongation of FET in bronchodilation testing has been suggested to also be due to actual bronchodilation, but this has not been confirmed (de la Hoz, 2002; Tsai et al., 2006).

Ramsdell and Tisi (1979) studied retrospectively all patients referred to the pulmonary function laboratory for spirometry and bronchodilation testing over a one-year period. Isoproterenol 2.25 mg was used as the bronchodilator. Four types of response were identified: no response, isolated volume, isolated flow, and dual response. These groups were evaluated based on FEV_1/FVC% or FEF25-75%, but because the groups were defined by these two variables, even the isolated volume response group showed a mean FEV_1 response of +150 ml or 13%. However, the isolated volume responders had significantly more severe airways obstruction than did the isolated flow responders (Ramsdell & Tisi, 1979).

In the United States, the Intermountain Thoracic Society issued its own guidelines and criteria for significant bronchodilation response. These criteria were more specific and detailed and included also the assessment of FET in FVC bronchodilation, stating that for a change in FVC to be significant, FET should not increase by >10% (Morris et al., 1984).

Smith and coworkers (1992) evaluated 100 subjects with suspected reversible airways obstruction with the intent of elucidating mechanisms to explain the occasional discrepancy between symptom improvement following bronchodilator therapy not detectable in spirometry. Subjects received differing bronchodilating medication (metaproterenol, isoproterenol, albuterol, or atropine in combination with β-agonist) at doses that were increased until subjects experienced side-effects of tremor or tachycardia. They concluded that improvements in volume-related parameters may explain the discrepancy in some patients and that FEF25-75% at baseline was higher in patients who required pletysmography to identify response (Smith et al., 1992). However, in some studies, body pletysmography was unable to identify more significant responses than flow-volume spirometry (Light et al., 1977; Berger & Smith, 1988). This can be explained by varying consideration of measurement repeatability in these studies.

Pellegrino and Brusasco (1997) have suggested that in some subjects with dynamic hyperinflation in severe COPD bronchodilation could decrease functional residual capacity and reduce the elastic work of breathing. The relationship between hyperinflation and bronchodilation response to 200 µg of salbutamol was retrospectively studied in 281 subjects with severe hyperinflation (TLC>133%) and in 676 subjects with moderate hyperinflation (115%<TLC<133%) (Newton et al., 2002). FEV_1 improved in 26-33% of patients, but VC increased in up to 76%. In the severely hyperinflated group, change in FEV_1 was on average 0.16 (SD 0.01) liters or 14.9% (SD 0.9%), the corresponding figures for moderately hyperinflated individuals were 0.15 (0.01) liters and 11.0% (0.7%). Both groups showed stronger FVC responses, with a mean increase of 0.34 (0.02) liters or

15.6% (0.9%) in the severely hyperinflated group and 0.20 (0.01) liters or 9.1% (0.6%) in the moderately hyperinflated group (Newton et al., 2002).

In subjects with emphysema and without reversibility in terms of change in FEV_1 during the bronchodilation test (n=88), significant reductions in lung hyperinflation (decrease in RV) were detected in 83%, with the greatest changes observed in those with the most severe disease (O'Donnell et al., 2001). Similarly, subjects with expiratory flow limitation showed significant decreases in functional residual capacity (FRC), associated with increase in inspiratory capacity (IC). Thus, subjects with dynamic hyperinflation despite having no improvement in expiratory flow, benefited through reduction of hyperinflation that permitted them to breathe at a lower lung volume (Tantucci et al., 1998).

Change in FEV_3 has been shown to correlate well with change in FVC, although the method used included a shorter MEFV maneuver, where subjects were not encouraged to continue after 4 s (Hansen et al., 1993). Paré and coworkers (1983) studied 15 subjects with asthma and used a change ratio of change in FEV_1 divided by change in FVC of under one to signify volume response correlating with the presence of a marker of small airways dysfunction, and they suggested a postbronchodilator recruitment of peripheral airways as a possible explanation.

Of ten patients with COPD, five had "isolated volume response to bronchodilators", i.e. improvement in only FVC, whereas five responded in both FEV_1 and FVC. Small airway caliber was measured by high-resolution computed tomography (HRCT). In subjects with FEV_1 and FVC response, the airway caliber increased with the cube root of increase in lung volume, but it was unchanged or even decreased in all but one of the FVC responders. The authors suggested longitudinal traction or space competition as potential underlying mechanisms. Subjects with only FVC response were reported to have more severe emphysema (Cerveri et al., 2000).

In a Norwegian population material studied for postbronchodilator reference values in flow-volume spirometry, the mean changes in FVC for men following 0.3 mg of salbutamol were reported as 0.010 (SD 0.137) liters in 27- to 39-year-olds, -0.022 (0.131) liters in 40- to 59-year-olds, and -0.026 (0.132) liters in 60- to 82-year-olds. The corresponding mean values for women were -0.009 (0.110) liters, -0.021 (0.111) liters, and -0.001 (0.103) liters (Johannessen et al., 2006).

In conclusion, bronchodilator reversibility is a fundamental feature of asthma, which also reflects treatment response. Interpretation of studies conducted with patients with OAD should take into consideration the proportion of asthmatics included. COPD is characterized by airflow limitation that is not fully reversible. However, with longer wash-out periods of previous medication and combined use of β-sympatomimetic and anticholinergic bronchodilating medication, Tashkin and coworkers (2008) have recently found up to 60% of COPD patients reversible on ATS/ERS criteria. Also in patients with COPD, bronchodilator reversibility varies with time (Vestbo & Hansen, 2001; Calverley et al., 2003; Anthonisen et al., 2005; Hansen & Vestbo, 2005). Earlier, reversibility was

associated with poor outcome and disease progression (Kanner, 1984; Postma et al., 1985, 1986), and in other studies with potential treatment response to inhaled corticosteroids (Nisar et al., 1990, 1992; Kerstjens et al., 1993). Airway hyperresponsiveness in asymptomatic subjects has been associated with increased risk of developing both asthma and COPD, and an increased COPD mortality (Hospers et al., 2000; Vestbo & Hansen, 2001; Brutsche et al., 2006). Hansen and coworkers (1999) have shown that treatment response has an effect on mortality of COPD as far as the level of FEV_1 is concerned, but that this effect seems to be due to the role of FEV_1 as a variable associated with mortality and morbidity and not due to other treatment effects of the medications under assessment.

2.5 Prevalence of obstructive airways disease in adults in Finland

Prevalence of a disease in a population is defined as the total number of cases in the population at a given time divided by the number of individuals in the population. Conversely, incidence is defined as the number of new cases of a disease within a given time period. Hence, prevalence is a measurement of all individuals affected by the disease at a given point in time, regardless of the date of contraction; whereas incidence is a measurement of individuals who contract the disease during a specified time interval.

The earliest population studies on the prevalence of obstructive airways disease in Finland date back to the 1960s and 1970s. Järvinen and coworkers (1960a, 1960b) found a prevalence of obstructive pulmonary emphysema of 8.7% and 3.7% for men and women, respectively. Huhti (1965) reported for a small rural community prevalence rates for asthma of 0.5% and 1.6%, emphysema 10.0% and 2.3%, and chronic bronchitis 28.2% and 5.8% for men and women, respectively. These initial studies included chest x-rays and clinical examination in addition to questionnaire information. In 1970, Alanko published a questionnaire study for the same rural community studied earlier by Huhti (1965). The prevalence of asthma was lower in young adults (0.2%) than in the middle-aged (3.3%), with a population prevalence of 1.2% (Alanko, 1970).

Since these early studies, increasing rates of asthma prevalence were reported during the 1980s and 1990s. The prevalence of asthma in young conscripts has been followed from 1926, with the prevalence remaining under 0.1% until the 1960s. The prevalence of asthma started rising from 0.29% in 1966 to 1.79% in 1989 and 3.45% in 2003 (Haahtela et al., 1990; Latvala et al., 2005). However, between 1989 and 2003 the asthma-cases seemed to have become milder and better controlled (Latvala et al., 2005). This has been attributed to the nationwide asthma-programme 1994-2004 (Haahtela et al., 2006). In a nationally representative sample, the prevalence of asthma was reported as 4% in 1988 (Vesterinen et al., 1988).

In a study analyzing the role of atopy and smoking in the development of chronic bronchitis, the prevalence was lowest in nonatopic nonsmokers (4.1%), increasing to 10.1% in atopic nonsmokers, 10.6% in nonatopic smokers, and 25.7% in atopic smokers (Terho et al., 1987). Atopy was found to predispose to chronic bronchitis (Terho et al.,

1995). In a large twin study of 13,888 subjects, the age-adjusted cumulative incidence of asthma was between 1.7% and 2.2%, and the heritability was estimated at 35.6% (Nieminen et al., 1991).

Isoaho and coworkers (1994a, 1994b) reported on a rural community sample aged 64 years or over and defined obstruction as $FEV_1/FVC<0.66$. The prevalence of COPD was 12.5% for men and 3.0% for women. Among current smokers, the prevalence of COPD was 35% for men and 13% for women, whereas never-smokers had a prevalence of 2%. The prevalence of current asthma was 2.9% in men and 3.8% in women.

Hedman and coworkers (1999) reported for a postal questionnaire study population a nonresponse-adjusted prevalence of doctor-diagnosed asthma of 4.4% and COPD of 3.7%, with the definition of asthma or COPD varying slightly from current practice. In a nation-wide study (n=7,217), von Hertzen and coworkers (2000) found an age-adjusted prevalence of chronic bronchitis and/or emphysema of 22% among men and 7% among women, and clinically relevant airways obstruction in 11% of men and 5% of women.

Karjalainen and coworkers (2001) reported that 29% of male asthma cases and 17% of female asthma cases were associated with occupation, with the risk being highest in agricultural, manufacturing, and service occupations. In another study on occupational influences, Jaakkola and coworkers (2003) reported increased asthma risks in traditional industries, in forestry, and in several nonindustrial occupations, such as female wait-staff, cleaners, and dental workers.

Pelkonen and coworkers (2006) reported a 30-year cumulative incidence of chronic bronchitis and COPD of 42% and 32%, respectively, in continuous smokers, compared with 26% and 14% in ex-smokers and 22% and 12% in never-smokers. Subjects with chronic bronchitis had on average 252 ml lower FEV_1 than those without chronic bronchitis, the change being most prominent in symptomatic subjects and smokers. In subjects with chronic bronchitis, the hazard ratio for all-cause mortality was increased to 1.30 (95% CI 1.02-1.65) in the 40-year mortality follow-up between 1960 and 2000 (Pelkonen et al., 2006).

In the FinEsS studies, Kotaniemi observed from Finnish Lapland a self-reported physician-diagnosed asthma prevalence of 6.0% (Kotaniemi et al., 2001, 2002; Lindström et al., 2001). Based on spirometry, 9.4% of the population sample had COPD using GOLD criteria, with the risk of COPD increasing significantly with age, smoking pack-years, and family history of OAD. Among subjects with over 40 smoking pack-years, the prevalence of COPD was over 50%, and, furthermore, early start of smoking was identified as a strong risk factor for the disease (Kotaniemi et al., 2005). In Helsinki, the prevalence of physician-diagnosed asthma was 6.6% based on the 1996 postal questionnaire study (phase I) (Pallasaho et al., 1999, 2002; Pallasaho, 2006).

In summary, the population prevalence of asthma has increased in Finland, as in most Western countries, with physician-diagnosed asthma reported in 6% of subjects, and fixed obstruction fulfilling COPD diagnostic criteria (GOLD) in approximately 9% of subjects. In addition to the nationwide asthma programme (Haahtela et al., 2006), Finland also has an ongoing Action Programme on chronic bronchitis and COPD (Pietinalho et al., 2007).

3 Aims of the study

1. To evaluate FET and its spirometric and anthropometric determinants in a nonselected adult population sample and in healthy nonsmokers (I)

2. To evaluate the intrasession repeatability of FET and FEV_6 and the determinants of variability in the general adult population (II)

3. To determine the distribution and range of bronchodilation response in terms of changes in FEV_1 in a general adult urban population and in a subgroup of healthy asymptomatic nonsmokers to identify normal response and its anthropometric and spirometric determinants (III)

4. To assess concurrent variations in FEV_6, FVC, and FET in the bronchodilation test in a general population sample of adults using flow-volume spirometry and to evaluate FVC and FEV_6 response to bronchodilator (IV)

4 Materials and methods

4.1 The FinEsS study design and study subjects

The FinEsS study is a collaborative study of clinical epidemiology of respiratory health between Finland (Fin), Estonia (Es), and Sweden (S). In Finland, research has been conducted in Helsinki, Southern Finland, and in Kemi, Northern Finland. In Estonia, study centers are located in Tallinn, Narva, and Saaremaa. In Sweden, studies have been conducted in Norrbotten, Stockholm, and Örebro. Figure 4 presents the study areas.

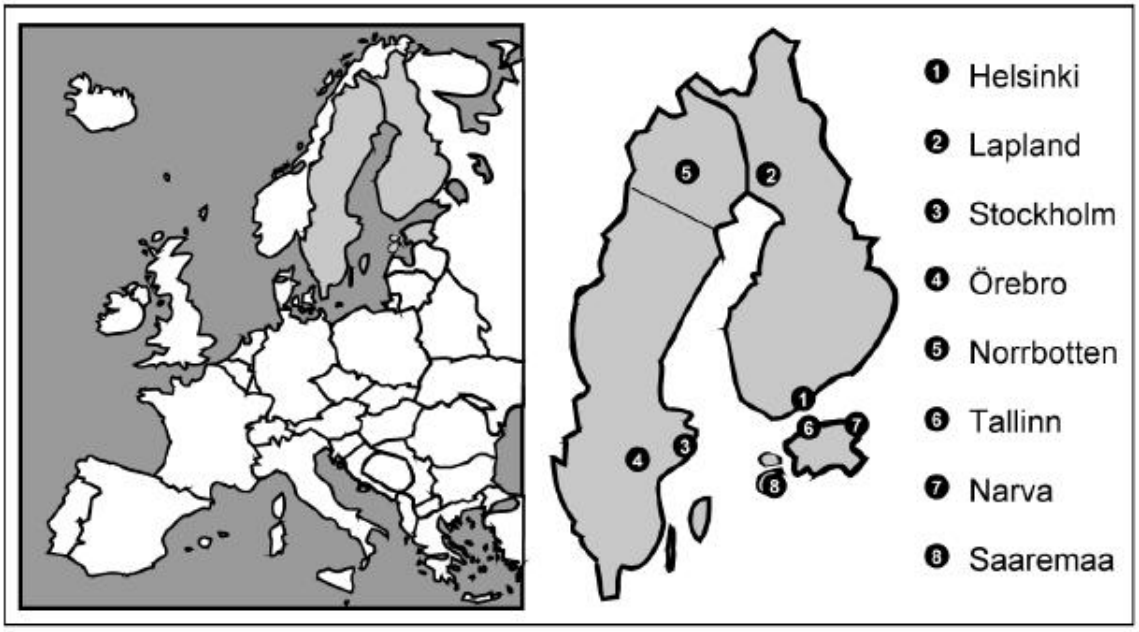

Figure 4 *Map showing FinEsS study areas (Pallasaho, 2006)*

In 1995, a random sample of 8,000 individuals from the Finnish Population Registre Center stratified by gender and 10-year age cohorts was selected to represent the adult population aged 24-69 years in Helsinki. In the first phase, a postal questionnaire (Pallasaho, 2006) that included questions about respiratory health was sent to subjects. Altogether 6,062 individuals, 2,600 men and 3,462 women, responded. Eighty-eight individuals were not reached (mail returned repeatedly), and 4 individuals had died. The response rate corrected to the reachable portion was 76.8%. Young men and individuals of foreign descent, as judged by a non-Scandinavian name, were more likely not to respond to the postal survey. Response rate by gender and age cohort is shown in Figure 5.

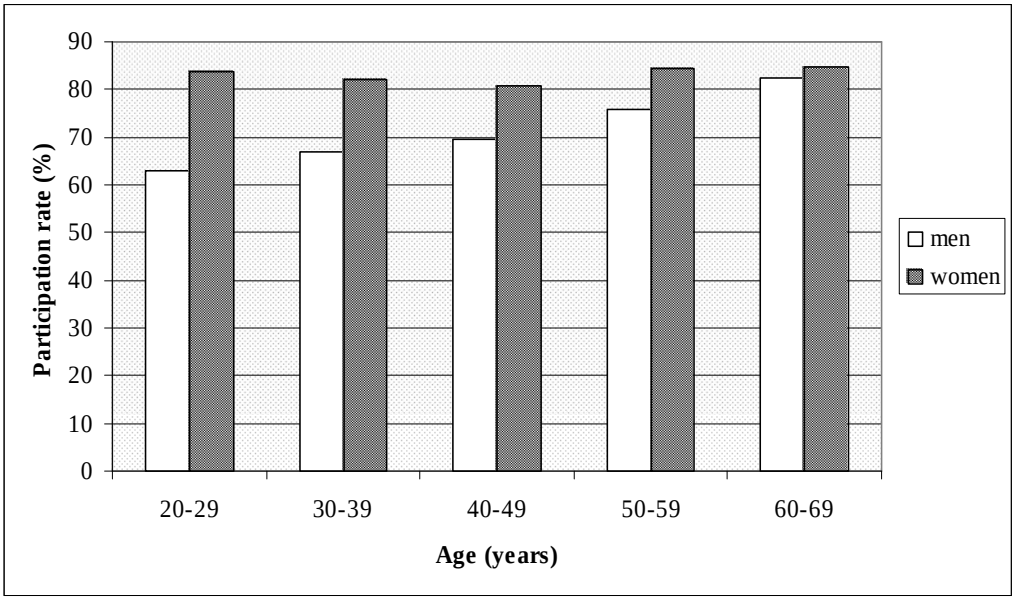

Figure 5 *Response rate in FinEsS-Helsinki phase I stratified by gender and age*

In 2000, a further random sample of 1,200 subjects stratified by age and gender was selected from the original postal questionnaire responders to participate in the subsequent clinical phase of the study. Since the original mailing of the postal questionnaire, 34 subjects had died and 27 subjects had no current mailing address in the Population Register. Four subjects were reached but deemed unable to participate due to severe illness, e.g. terminal cancer and previous severe stroke. In total, 643 individuals participated from 2001 – 2003 in the clinical studies. The response rate in phase II corrected with the nonreachable individuals was 56.7%.

A nonresponder analysis was conducted to assess the postal questionnaire information for responders and nonresponders in phase II. Nonresponders were more often young male smokers. Responders did not significantly differ from nonresponders in terms of symptoms or previous diagnoses of OAD when assessed with the Chi-squared test. The study sample consisted of the 643 individuals participating in phase II of the FinEsS-Helsinki study. Figure 6 shows the age and gender distribution of the study subjects.

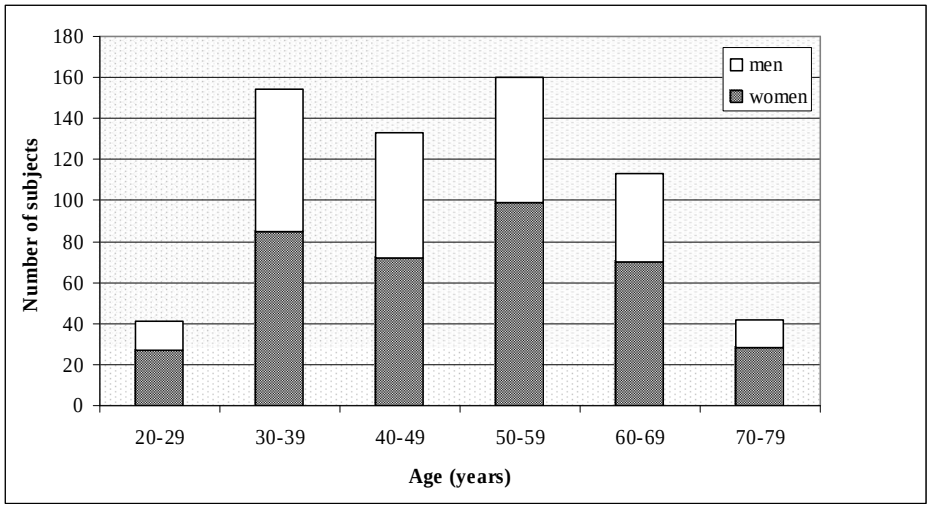

Figure 6 *Age and gender distribution of FinEsS-Helsinki phase II participants*

Of the 643 subjects participating in the clinical study, ten were excluded from the analysis based on unacceptable or missing spirometry data. Despite vigorous coaching, acceptable and/or repeatable determinations were not obtained. Data are reported only for subjects with acceptable baseline spirometry (n=633). The study participants were on average 49.2 (SD 13.0) years old, 169.6 cm (SD 94.3) in height, and had a BMI of 26.0 (SD 4.9) kg/m2. Older subjects were slightly shorter and older females had a higher BMI.

4.2 FinEsS II: the clinical study

Subjects were interviewed by one of the study nurses on the phone when making the appointment for the pulmonary function test measurement. The subjects were informed not to have the pulmonary function test measurements whilst recovering from any respiratory infection. During the clinical visit, all subjects were interviewed using a structured interview (see below), tested with flow-volume spirometry with bronchodilation testing, and subjects under 61 years of age were tested with a skin-prick test for common aeroallergens (Pallasaho, 2006; Pallasaho et al., 2006). Approximately one-third of the subjects were further randomly selected to take part in a second study visit the following day during which exhaled nitric oxide and histamine provocation testing was undertaken. The results from skin-prick, exhaled nitric oxide, and bronchial provocation testing are not reported here, and these methods are therefore not elaborated.

4.2.1 Structured interview

During the clinical visit, subjects were interviewed by a trained physician using a structured interview (Kotaniemi et al., 2005; Pallasaho, 2006). The FinEsS questionnaire is based on a questionnaire developed and validated in the Swedish Obstructive Lung

Disease in Northern Sweden (OLIN) studies (Lundbäck et al., 1991, 1993; Torén et al., 1993). It contains questions that originate from the British Medical Research Council (BMRC) (Medical Research Council's Committee on the Aetiology of Chronic Bronchitis, 1960), International Union Against Tuberculosis and Lung Disease (IUATLD) (Burney et al., 1989a, 1989b) and European Community Respiratory Health Survey (ECRHS) (European Community Respiratory Health Survey, 1996) questionnaires. The questionnaire contains 162 questions that deal with general health, respiratory signs and symptoms, diseases and medications, provoking factors, and risk factors for respiratory diseases. The structured interview questions are listed in Appendix 1 with translations to English.

Based on the questionnaire information, 18 men (6.9%) and 33 women (8.9%) had a previous asthma diagnosis, whereas only 5 men (1.9%) and 16 women (4.3%) had a previous COPD diagnosis. Although it is likely that some subjects with COPD might report themselves as having asthma, it is clear that COPD is underdiagnosed. One man and three women had previous diagnoses of both asthma and COPD. Chronic bronchitis was reported by significantly more subjects: 19 men (7.3%) and 20 women (5.4%). Forty-five men (17.2%) and 86 women (23.1%) reported regular or as-needed use of anti-asthmatic or reliever therapy, with many of them not recognizing a previous diagnosis of OAD. Inhaled corticosteroids were used irregularly by 2 men (0.8%) and 10 women (2.7%) and regularly by 8 men (3.1%) and 16 women (4.3%). A family history of OAD was reported by 43 men (16.5%) and 97 women (26.1%) (Chi-squared for gender difference, $p<0.01$).

4.2.2 Flow-volume spirometry

All subjects attempted to complete flow-volume spirometry, if no contraindications were present. *A priori*, recent respiratory or cardiac illnesses (<4 weeks), possible contagious lung infections (tuberculosis), recent abdominal surgery, and inability to cooperate in the testing were considered contraindications. Ten subjects were unable to complete satisfactory flow-volume spirometry. One subject had severe mental retardation, and the questionnaire was completed by her parent. One subject had a history of multiple strokes and another subject had a recent respiratory infection (despite advance guidance).

All subjects were advised to continue any regular medication. Only peroral antihistamine medication was to be discontinued for 3 days prior to the skin-prick testing, if possible, but short-acting β-sympatomimetics were to be withheld for 4 h and long-acting β2-sympatomimetics 12 h. Subjects were advised to refrain from smoking for at least 4 h, from coffee, tea, and heavy eating for 2 h, and from alcohol for at least 1.5 days prior to the study visit.

One flow-volume spirometer (VMax 20c, Sensor Medics, Yorba Linda, CA, USA) was used for all measurements. Spirometry was undertaken with the subject seated using nose clips and disposable bacterial filters. Two trained nurses performed all measurements. The calibration of the spirometer was checked with a 3-liter calibration

syringe (Sensor Medics®, Sensor Medics Corporation) once a day and whenever the spirometer software requested calibration. The subjects were first instructed on the measurement of slow vital capacity, which was repeated until three comparable measures were attained with a maximum of eight maneuvers. The three best values were selected. The subjects thereafter proceeded to forced expiratory maneuvers that were performed according to ATS 1994 standard. Up to three comparable maximum expiratory flow-volume maneuvers were recorded with a maximum of eight attempts. Inspiratory curves were registered in conjunction with the expiratory curves whenever feasible.

The beginning of the measurement was determined by back-extrapolation for timing of FET and timed volumes (FEV_t). The end of the FET measurement is defined in the spirometry software as the beginning of the end-expiratory plateau, which means that the measured FET systematically slightly underestimates the duration of the maneuver. The threshold of volume change detectable by the spirometer was under 25 ml/s. The FET reported by the spirometer software (Vision Software 05-2A; VMax System, Sensor Medics Corporation) was used.

Quality criteria for acceptable spirograms

The acceptability criteria for individual maneuvers were based on ATS 1994 standard. These stipulated that the extrapolated volume (EV) in each of the accepted spirograms be no greater than 150 ml or 5% of the respective FVC, whichever was greater. During the clinical study, it was further decided that data from subjects with two acceptable curves fulfilling the EV criterion and repeatability criteria (see below) could be used for some analyses, despite the third curves having excessive EV. The data from curves with excessive EV were not utilized in analyses.

Repeatability targets in the international standards have changed during the last years. In the ERS 1993 standard (Quanjer et al., 1993), the two largest FVC and FEV_1 were required to be within 100 ml or 5%, whichever was greater, and the two largest PEF to be within 10%. The ATS 1994 standard gave up measures relative to lung volume and set the limit for the two greatest FEV_1 and FVC at 200 ml (ATS, 1995). In the joint ATS/ERS standard in 2005, the repeatability limit was further reduced to 150 ml, with the exception of individuals with FVC<1.0 liter, when the limit was set at 100 ml.

During the design of the FinEsS studies, there was a general consensus to follow the same methodology and standards in the different Nordic centers to ensure comparability. In spirometry, the ATS 1994 standard was chosen. However, between the centers differences still occurred. In Helsinki, the repeatability targets were set based on the nationally accepted ERS 1993 standard, which was apparently chosen because the absolute repeatability targets were tighter and the inclusion of PEF was considered important. However, since the ERS standard included the use of a second criterion relative to the measured volume, the repeatability criterion was in fact slightly less stringent than the ATS criteria for subjects with high FEV_1 or FVC. Up to eight successive attempts

were made to achieve three comparable curves that would fulfill the acceptability and repeatability criteria.

Bronchodilation testing

All subjects also underwent bronchodilation testing unless specific predefined contraindications or other compelling reasons were present. Contraindications for bronchodilation testing included a history of significant cardiac arrhythmia and recent angina pectoris. One subject was excluded from bronchodilation testing due to cardiac symptoms following baseline spirometry and one subject on the grounds of history of arrhythmia. In addition, three subjects declined to take the bronchodilating medication.

The subjects were given 0.4 mg of salbutamol aerosol (Ventoline® Evohaler, GlaxoSmithKline, London, UK) in two separate doses through a spacer device (Volumatic®, GlaxoSmithKline, London, UK). Subjects then remained seated for 15 min, without smoking or consuming beverages other than water, after which a repeated spirometry was performed in an identical fashion to determine the bronchodilation response.

Evaluated spirometry variables and their selection

For all study subjects, the three best and comparable curves were selected for analysis both from the pre- and postbronchodilation spirometry. All completed MEFV maneuvers were saved in a computer file, but the data from the other curves were not used here. The best curve was defined as the one with the highest sum of FEV_1 and FVC of the accepted three curves. The second best curve was the one with the second highest sum of FEV_1 and FVC. For analysis, largest forced vital capacity (FVC), forced expiratory volume in six seconds (FEV_6), and forced expiratory volume in one second (FEV_1) were selected, and all other flow-values were selected from the best curve. FET corresponding to the best FVC and the best curve was selected. In assessment of intrasession repeatability (II), all three acceptable curves from prebronchodilation spirometry were collected. Subjects with excessive EV in one of the three selected curves were excluded from these analyses (II).

In the population, baseline spirometry was analyzed with the reference values from Viljanen and coworkers (1982). Baseline FVC, FEV_1, and FEV_1/FVC diminished with advancing age. Detailed spirometry statistics from the baseline spirometry are shown in Table 2.

Table 2. *Baseline spirometry statistics stratified by gender in the study population. Statistics presented as mean (SD). Predicted values from Viljanen et al., 1982.*

	Age group						
	20-29 years	30-39 years	40-49 years	50-59 years	60-69 years	70-79 years	20-79 years
Women	27	84	70	97	68	26	372
FVC (liters)	4.06 (0.57)	4.00 (0.48)	3.82 (0.57)	3.37 (0.49)	3.10 (0.49)	2.61 (0.48)	3.55 (0.66)
FVC% predicted	96.1 (9.3)	96.1 (10.5)	99.5 (11.4)	99.3 (12.7)	104.2 (13.5)	101.2 (17.9)	99.5 (12.6)
FEV1 (liters)	3.37 (0.44)	3.27 (0.37)	3.00 (0.47)	2.56 (0.46)	2.35 (0.37)	1.99 (0.37)	2.78 (0.59)
FEV1% predicted	92.6 (10.1)	93.1 (9.9)	94.9 (12.5)	92.8 (15.1)	98.9 (12.5)	96.7 (18.2)	94.6 (13.1)
FEV1/FVC (%)	83.4 (5.3)	81.8 (5.0)	78.4 (6.2)	75.6 (7.6)	76.3 (6.4)	76.4 (8.0)	78.3 (7.0)
FEV1/FVC% predicted	96.5 (6.0)	97.1 (6.0)	95.4 (7.4)	93.3 (9.4)	95.3 (7.9)	95.9 (10.0)	95.3 (8.0)
Men	14	68	62	60	42	15	261
FVC (liters)	5.49 (0.58)	5.67 (0.79)	5.26 (0.72)	4.87 (0.75)	4.37 (0.88)	4.05 (0.59)	5.08 (0.91)
FVC% predicted	97.7 (8.5)	98.0 (10.6)	97.0 (10.1)	98.5 (12.7)	99.7 (18.6)	100.0 (11.4)	98.3 (12.4)
FEV1 (liters)	4.35 (0.59)	4.46 (0.63)	4.13 (0.59)	3.67 (0.65)	3.11 (0.89)	3.08 (0.55)	3.90 (0.83)
FEV1% predicted	91.4 (11.8)	94.4 (10.8)	94.9 (11.0)	93.0 (15.2)	87.9 (23.8)	93.7 (15.0)	93.0 (15.0)
FEV1/FVC (%)	79.2 (7.8)	78.7 (5.4)	78.6 (5.3)	75.3 (7.3)	70.5 (11.7)	75.9 (4.8)	76.5 (7.8)
FEV1/FVC% predicted	93.7 (9.5)	96.5 (6.6)	97.9 (6.6)	94.2 (9.0)	87.5 (14.7)	93.3 (5.9)	94.5 (9.6)

4.3 Definitions

4.3.1 Smoking definitions

Smoking was defined in the questionnaire as smoking at least one cigarette per week or four cigarettes per month. An ever-smoker was anyone who had smoked regularly for at least one year. Current smokers included subjects that were smokers at the time of the study or had quit smoking within the last 12 months. Former smokers were required to have abstained from smoking for more than 12 months. Never-smokers were defined as those who had never regularly smoked for one year or more. Smoking pack-years were calculated for ever-smokers. For cigar smokers, a conversion factor of one cigar corresponding to 7 cigarettes was used as an approximation.

Of the study sample, 98 men (37.5%) and 194 women (52.2%) were lifetime never-smokers. Smoking was more common in men across the age groups, with the exception of 30- to 39-year-olds, in which group never-smokers made up 50% of both men and women. Mean smoking pack-years was also greater in men in all age groups.

Current environmental tobacco smoke (ETS) exposure in general was reported by 47 men (18.1%) and 64 women (17.3%). Previous ETS in the home was reported by 47.5% of men and 49.7% of women, whereas current ETS at home was reported by 6.9% and 9.5% of men and women, respectively. Previous and current ETS at home was more prevalent in women, particularly in older age groups. At work, 10.8% of men and 3.5% of women reported continuing ETS exposure. Exposure to occupational ETS was more prevalent in older age groups, clearly influenced by the strict antismoking legislation enacted in 1995 that prohibits smoking in offices and public places in Finland.

Table 3. *Descriptive statistics of anthropometric and smoking history of the study sample stratified by gender and age groups. Data presented as mean (SD) unless otherwise indicated.*

	Age group						
	20-29 years	30-39 years	40-49 years	50-59 years	60-69 years	70-79 years	20-79 years
Women	27	84	70	97	68	26	372
height (m)	1.66 (0.07)	1.67 (0.05)	1.65 (0.06)	1.63 (0.06)	1.61 (0.05)	1.58 (0.05)	1.64 (0.06)
BMI (kg/m^2)	24.2 (5.4)	24.4 (5.4)	25.2 (5.2)	26.3 (5.2)	27.0 (4.3)	27.7 (5.7)	25.7 (5.2)
never-smokers n (%)	17 (63.0%)	42 (50.0%)	32 (45.7%)	42 (43.2%)	41 (60.3%)	20 (76.9%)	194 (52.2%)
former-smokers n (%)	4 (14.8%)	17 (20.2%)	17 (24.3%)	26 (26.8%)	18 (26.5%)	3 (11.5%)	85 (22.8%)
current smokers n (%)	6 (22.2%)	25 (29.8%)	21 (30.0%)	29 (29.9%)	9 (13.2%)	3 (11.5%)	93 (25.0%)
pack-years mean (s.d.)	1.4 (3.8)	4.3 (6.2)	6.4 (10.6)	10.8 (16.1)	9.2 (14.9)	8.3 (18.1)	7.4 (13.0)
under 10 pack-years n (%)	9 (33.3%)	26 (31.0%)	20 (28.6%)	20 (20.6%)	5 (7.4%)	1 (3.8%)	81 (21.8%)
10-29.9 pack-years n (%)	1 (3.7%)	16 (19.0%)	13 (18.6%)	23 (23.7%)	15 (22.1%)	1 (3.8%)	69 (18.5%)
30 pack-years or more n (%)	0 (0.0%)	0 (0.0%)	5 (7.1%)	12 (12.4%)	7 (10.3%)	4 (15.4%)	28 (7.5%)
Men	14	68	62	60	42	15	261
height (m)	1.78 (0.04)	1.81 (0.06)	1.79 (0.06)	1.77 (0.06)	1.74 (0.06)	1.74 (0.07)	1.78 (0.07)
BMI (kg/m^2)	24.6 (5.1)	26.6 (4.5)	26.0 (3.9)	27.1 (4.9)	26.5 (3.6)	26.9 (2.5)	26.5 (4.3)
never-smokers n (%)	6 (42.9%)	34 (50.0%)	22 (35.5%)	17 (28.3%)	13 (31.0%)	6 (40.0%)	98 (37.5%)
former-smokers n (%)	4 (28.6%)	11 (16.2%)	10 (16.1%)	20 (33.3%)	22 (52.4%)	7 (46.7%)	74 (28.4%)
current smokers n (%)	4 (28.6%)	23 (33.8%)	30 (48.4%)	23 (38.3%)	7 (16.7%)	2 (13.3%)	89 (34.1%)
pack-years mean (s.d.)	3.9 (5.4)	7.5 (10.5)	12.9 (17.3)	21.3 (22.9)	20.9 (23.5)	16.4 (27.4)	14.4 (19.6)
under 10 pack-years n (%)	6 (42.9%)	10 (14.7%)	14 (22.6%)	8 (13.3%)	9 (21.4%)	4 (26.7%)	51 (19.5%)
10-29.9 pack-years n (%)	2 (14.3%)	20 (29.4%)	17 (27.4%)	15 (25.0%)	4 (9.5%)	2 (13.3%)	60 (23.0%)
30 pack-years or more n (%)	0 (0.0%)	4 (5.9%)	9 (14.5%)	20 (33.3%)	16 (38.1%)	3 (20.0%)	52 (19.9%)

4.3.2 Definition of healthy and asymptomatic subjects

Based on the structured interview, previous medical conditions and prevailing symptoms were assessed to determine a subgroup of healthy asymptomatic adults. Based on the questionnaire, individuals were considered healthy and asymptomatic if they gave no positive answers to over 50 questions dealing with symptoms, diagnosed respiratory diseases, and use of pulmonary medications. Respiratory symptoms evaluated included wheezing, attacks of shortness of breath, sputum production, dyspnea, and dyspnea on exertion. Questions on respiratory symptoms used to identify study subjects who were not healthy and asymptomatic are listed in Table 4.

In addition to these questions, subjects reporting having a previous diagnosis of asthma, COPD, emphysema, chronic bronchitis, or any other major respiratory or medical condition were also excluded. The open question of “do you have any other pulmonary disease not listed here” was also evaluated on an individual basis. Uncomplicated hypertension and obesity as such were not considered significant if the subject did not report any of the aforementioned respiratory symptoms.

Table 4. *Questions on respiratory symptoms used to define healthy and asymptomatic subjects*

Healthy: subject excluded if meeting any one of these criteria (answer in parentheses)
Q16: Do you usually have phlegm when coughing or hawking, or do you have phlegm in your chest which is difficult to bring up most days in periods of (at least 3 months/year, during two successive years)?
Q19: Do you usually have wheezing, whistling, or a noisy sound in your chest when breathing? (yes)
Q21: Have you had wheezing or whistling in your chest at any time in the last 12 months? (yes) and Q22: Have you been at all breathless when the wheezing noise was present? (yes) and Q23: Have you had this wheezing or whistling when you did not have a cold? (yes)
Q33: Do you have to stop for breath when you walk at your own pace on level ground? (yes)
Q39: Have you had attacks of shortness of breath with wheezing or whistling in the last 12 months? (yes)
Q42: Has this happened in the last 12 months? (yes) (refers to Q41: have you ever been woken at night or early in the morning by an attack of shortness of breath with wheezing or whistling?)
Asymptomatic: subject excluded if meeting any one of these criteria (answer in parentheses)
Q08: Have you had long-standing cough during the last years? (yes)
Q10: Do you have this kind of cough most days a week in periods of more than two weeks? (yes)
Q12: Do you have this cough most days a week in periods of more than two weeks? (yes)
Q14: Do you usually bring up phlegm from your chest when coughing or hawking? (often)
Q15: Have you noticed phlegm in your chest which is difficult to bring up? (yes)
Q21: Have you had wheezing or whistling in your chest at any time in the last 12 months? (yes)
Q36: Have you had any attacks of shortness of breath or breathlessness in the last 12 months? (yes)
Q48-Q66 (except Q65): Factors that provoke wheezing or whistling, or attacks of shortness of breath, with or without cough: (3 or more “yes” answers) Factors including: furred animals, pollen, mold, smoke, dusty places, strong-smelling scents, car exhausts, air pollution, airway infections, medicines, food, psychological factors, cold air, physical exercise, occupational setting.

4.4 Statistical methods

Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS for Windows, version 15.01; SPSS, Chicago, IL, USA), with the exception of the 95% confidence intervals for the 95^{th} percentile values, which were calculated with Confidence Interval Analysis (CIA, version 2.1.2; Trevor Bryant, University of Southampton, Southampton, UK). Chi-square and Fisher's exact tests were used to analyze differences between groups. Normality of continuous variables was checked by the Kolmogorov-Smirnov test. Logarithmic transformation of variable was done, if necessary to achieve normality. Correlations were assessed with the Pearson correlation coefficient (r-value).

The variation of each variable in an individual (II) was assessed by its coefficient of variation (CoV) and the intraclass correlation coefficient (ICC). The CoV for each measurement was calculated by dividing the standard deviation of the three measurements with their mean. The ICC is an application of analysis of variance that produces measures of consistency or agreement of values within cases (Shrout & Fleiss, 1979; McGraw & Wong, 1996). The ICC for measurements with three repetitions (II) is calculated with the following formula:

$$ICC = (MS_B - MS_W)/(MS_B + 2*MS_W) \quad (1),$$

where MS_B is mean squares between groups and MS_W mean squares within a group. A one-way random effects model was used for the ICC. The agreement between changes in FVC and FEV_6 in response to bronchodilation (IV) was also assessed with ICC. The method described by Bland & Altman (1986) was used to demonstrate agreement between repeated measurements (II) (Chinn, 1991).

The effect of gender on bronchodilation (III) was assessed with an analysis of covariance (ANCOVA) model using height and baseline FEV_1/FVC ratio as covariates. Linear regression modeling was used to evaluate the role of different determinants in bronchodilation response in the population.

P-values of less than 0.05 were considered significant for all analyses other than correlations, for which a p-value of less than 0.01 was regarded as significant. Data are presented as mean (SD) unless otherwise indicated in the text.

5 Results

5.1 Forced expiratory time and its determinants

The average FET for the nonselected population sample was 10.7 (SD 4.3) s, and the histogram distribution is shown in Figure 7. The mean FET was 11.3 (4.4) s for men and 10.3 (4.3) s for women. The difference between men and women was not significant (p=0.265) when tested with ANCOVA using FEV_1/FVC ratio as a covariate. FET was over six seconds in 90.7% of men and 86.8% of women. In the population the upper 95th percentile of spirometric FET was 18.2 s.

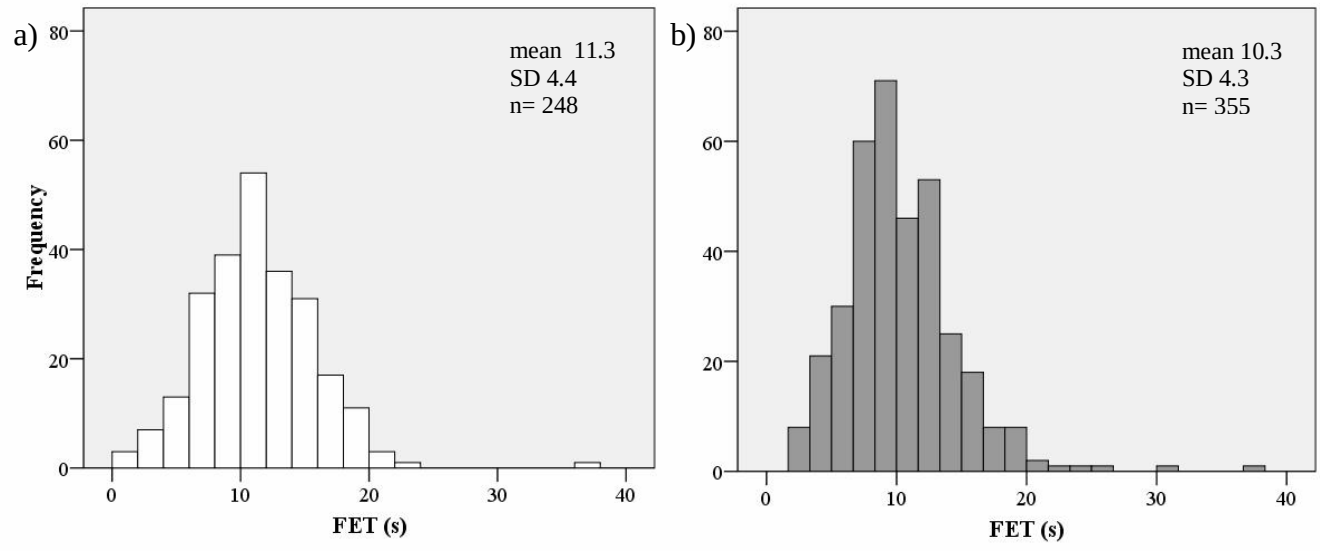

Figure 7 *Distribution of forced expiratory time (FET) in a) men and b) women in the general population*

Distribution of FET in relation to age and BMI is presented in Figure 8. FET increased with increasing age, with the greatest values in the age cohort of 50-59 years. BMI correlated also significantly with FET (r=0.243, p<0.01). Baseline FEV_1 and FVC had little effect on FET itself, but airflow limitation assessed by the FEV_1/FVC ratio showed a significant negative correlation with FET. The distribution of FET in relation to FEV_1, FVC, and the ratio of FEV_1/FVC are presented in Figure 9.

Previous smoking history in terms of pack-years smoked had a significant correlation with FET (r = 0.297, p<0.01) and FEV_1/FVC (r = -0.386, p<0.01). FET was slightly shorter and more evenly dispersed in healthy asymptomatic nonsmokers with a mean of 9.8 (SD 3.9) s. The mean value in healthy men was 10.1 (3.7) s and in women 9.7 (4.2) s. Also in healthy asymptomatic nonsmokers the FEV_1/FVC ratio was the most important determinant for FET (r= -0.491, p<0.01).

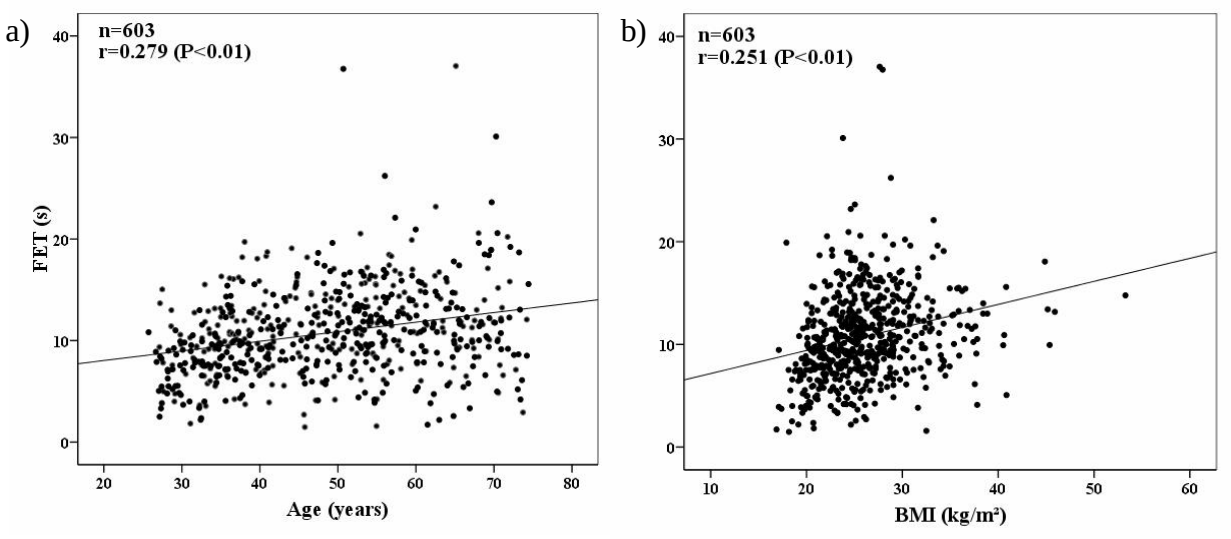

Figure 8 *Population distribution of forced expiratory time (FET) in relation to a) age and b) BMI (adapted from study I with permission)*

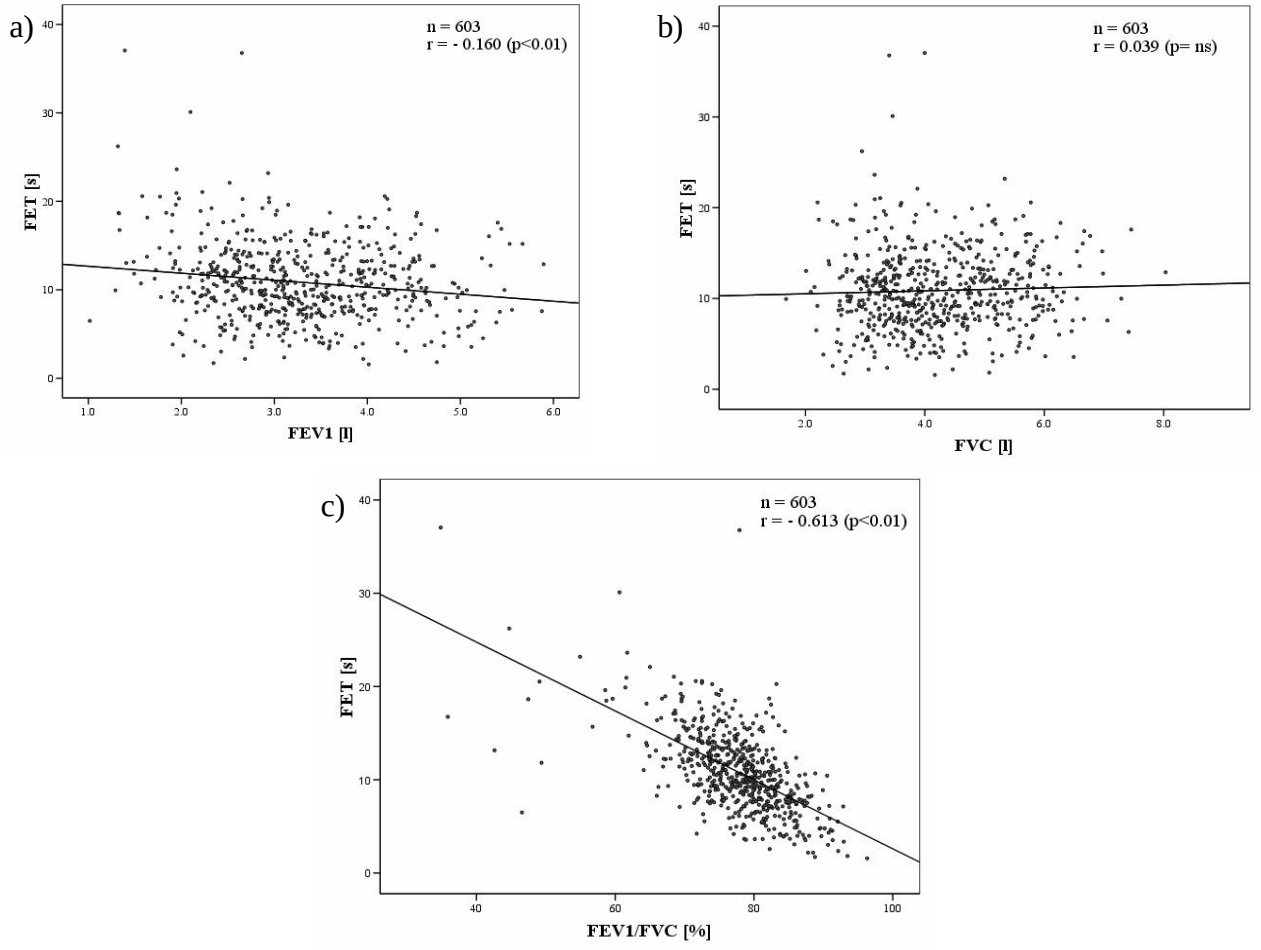

Figure 9 *Distribution of forced expiratory time (FET) in the general population in relation to a) baseline forced expiratory volume in one second (FEV_1), b) baseline forced vital capacity (FVC), and c) the ratio of FEV_1/FVC at the baseline (adapted from study I with permission)*

5.2 Intrasession repeatability of spirometry

The intrasession repeatability was analyzed from the three acceptable prebronchodilation spirometry maneuvers for the population sample. The stricter quality criteria reduced the sample to 603 subjects, 248 men and 355 women. Repeatability was assessed in terms of the difference between the two largest FEV_1, PEF, FEV_6, and FVC values. FET values corresponding to the two best curves were selected, with the best curve defined as the greatest sum of FEV_1 and FVC. In addition, the coefficients of variation (CoV) and intraclass correlation coefficients (ICCs) were calculated.

In terms of absolute and relative difference, FEV_1, FEV_6, and FVC were equally repeatable with mean differences around 45 ml and 1.3%. The difference of FET was on average -0.0 s or -2.0%, with the best curves having slightly shorter FET compared to next best curves resulting in negative average changes.

The mean CoV was 1.4% for FVC, FEV_6, and FEV_1, but for FET it was 11.3%. The ICC for FET was 0.873, and for FVC, FEV_6, and FEV_1 0.996. The upper 95th percentile of difference between the FET corresponding to the best and second-best curves was 2.7 s and 23.7% of the best-curve FET. Figure 10 presents a modified Bland-Altman plot showing the difference between the values of two best curves FET is plotted against the average of these two values.

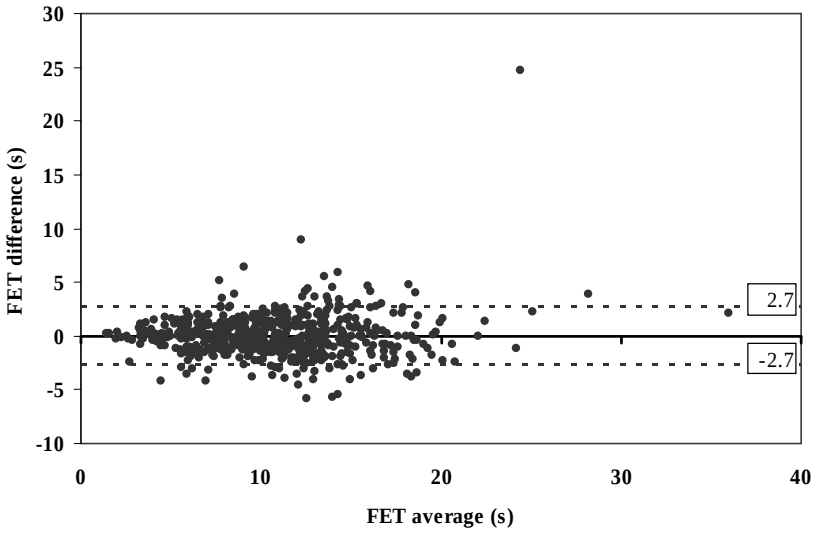

Figure 10 *A modified Bland-Altman plot of the intrasession repeatability of forced expiratory time (FET)(Reprinted from study II with permission)*

Repeatability of FET measured in terms of CoV did not differ significantly between men and women. Of the subjects, 11.6% had best-curve FET of < 6 s. The distribution of the CoV as a function of age and baseline lung function measures of FEV_1, FVC, and FEV_1/FVC is shown in Figure 11. The CoV of FET was slightly larger for older participants ($r=0.109$, $p<0.01$). Other anthropometric or spirometric variables including FET itself had little effect. The exclusion of outliers had no significant effect.

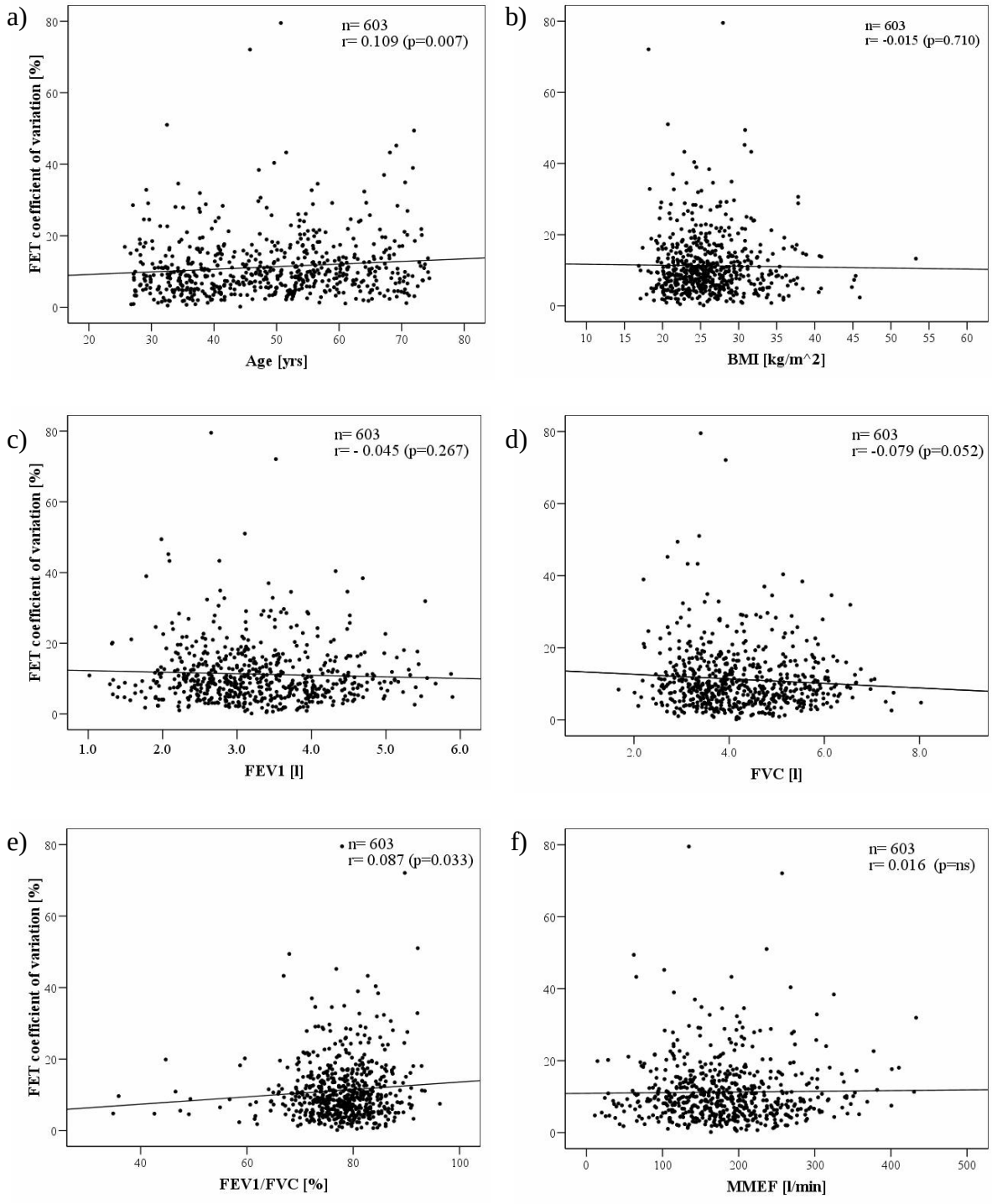

Figure 11 *Distribution of intrasession coefficient of variation (CoV) of forced expiratory time (FET) in relation to a) age, b) body mass index (BMI), c) forced expiratory volume in one second (FEV_1), d) forced vital capacity (FVC), e) FEV_1/FVC, and f) maximum mid-expiratory flow (MMEF)*

Variability of FEV_6 in terms of CoV was slightly more pronounced in older individuals (r=0.261, p<0.01) and in those with low baseline FEV_1 (r= -0.252, p<0.01) or FVC (r= -0.237, p<0.01). Subjects with airflow limitation, measured in terms of reduced FEV_1/FVC ratio, had slightly smaller variability of FET (CoV 10.6% vs. 11.4%, ICC 0.897 vs. 0.840), but slightly higher variability of both FEV_6 (1.5% vs. 1.3%) and FVC (1.7% vs. 1.3%). The intrasession repeatability of FEV_6 was slightly but not significantly better than that of FVC for individuals with airflow limitation. The difference between the largest FEV_6 and FVC increased almost linearly with FET over 6 s.

5.3 Bronchodilation response

Of the original population sample (n=633), five subjects did not participate in the bronchodilation testing, reducing the study sample to 628 subjects (368 women, 260 men).

5.3.1 FEV_1 response to bronchodilation

Population sample

The absolute and relative changes of FEV_1 after inhaled salbutamol with respect to baseline spirometry are shown in Figure 12. Both absolute and relative change of FEV_1 showed normal or near-normal distribution within the population. FEV_1 increased on average 77.2 (SD 109.7) ml or 2.5% (3.9%) of baseline FEV_1. A gender difference was found, with an average change in FEV_1 for men of +107.4 (130.6) ml or 3.0% (4.3%), and for women +55.9 (86.1) ml or 2.2% (3.7%), but the gender difference was not significant when tested with analysis of covariance using height and baseline FEV_1/FVC ratio as covariates. In 2.7% of both genders, FEV_1 decreased more than 100 ml, and in 19.6% the decrease was below 100 ml. PEF increased on average 1.8% (7.0%).

Baseline FEV_1/FVC ratio was the strongest factor influencing change in FEV_1 in the population sample. The relationships between change in FEV_1 and baseline FEV_1, and the ratio of FEV_1/FVC are demonstrated graphically in Figure 13. No significant gender difference was present in either absolute FEV_1 response (p= 0.642) or relative change (p=0.918) when adjusted for height and baseline FEV_1/FVC ratio. Absolute change in FEV_1 slightly, but significantly, increased with increasing baseline FVC (p<0.01), but relative change did not. The 95^{th} percentile of change in FEV_1 was 260 ml (95% CI 247-311) and 8.5% (7.7-10.7) in the whole population.

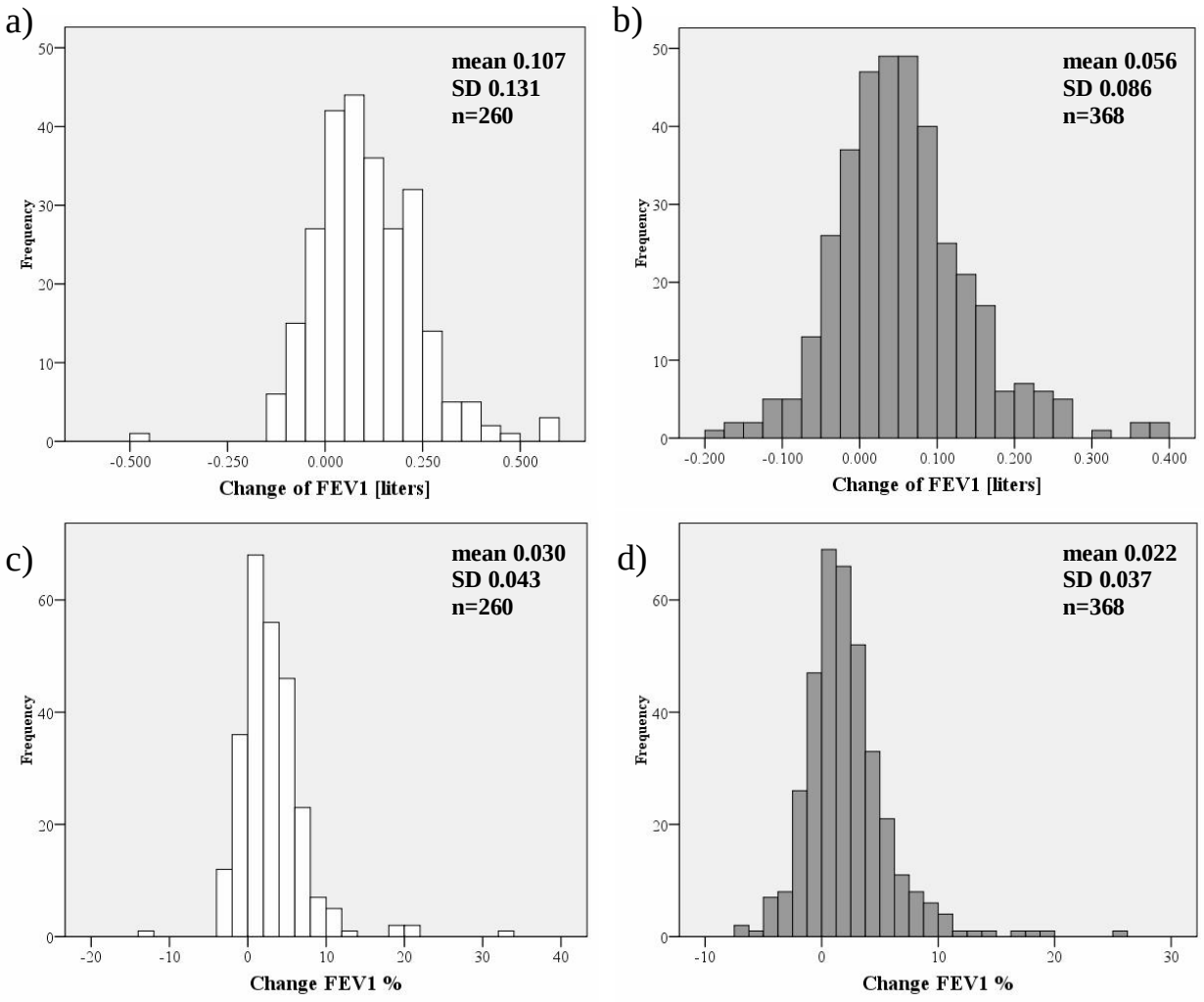

Figure 12 *Histogram distribution of absolute change of FEV_1 in the bronchodilation test in a) men and b) women, and the change relative to baseline in FEV1 in c) men and d) women..*

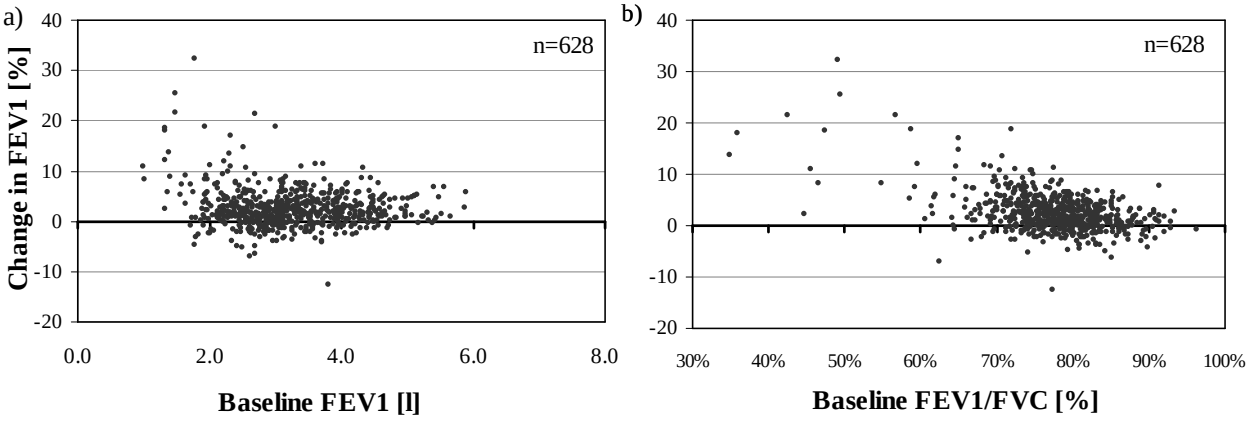

Figure 13 *Change of FEV_1 in relation to a) baseline FEV_1 and b) baseline FEV_1/FVC-ratio in the population (adapted from III with permission)*

The combined effects of different anthropometric and spirometric determinants on the change in FEV_1 were assessed with a linear regression model. Age, gender, and baseline FVC were significant for absolute change, with age, gender, and baseline airflow limitation were significant in the relative change model. However, the effect of anthropometric variables, such as age and height, was too weak to have any clinical significance, which can be verified from Figure 14.

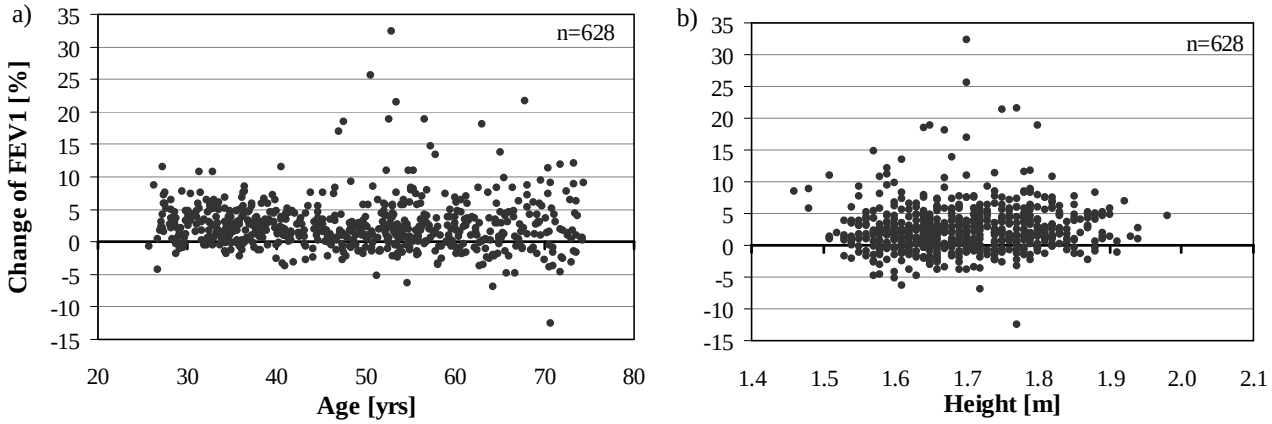

Figure 14 *Change of FEV_1 in relation to a) age, and b) height in the population sample*

Healthy asymptomatic nonsmokers

Among healthy asymptomatic nonsmokers (n=219), the mean absolute change of FEV_1 was +62.0 (89.7) ml or +1.8% (2.6%); among men +97.6 (107.3) ml or 2.3% (2.6%) and among women +43.1 (72.4) ml or 1.5% (2.6%). Greater than 100 ml reductions in FEV_1 after bronchodilation were seen in 2.6% and 2.1% of healthy asymptomatic nonsmoking men and women, respectively. Both absolute and relative change in FEV_1 showed normal or near-normal distribution. Overall, the 95th percentile of change in FEV_1 was 240 ml (95% CI 224-254) and 5.9% (5.6-7.7).

Height, baseline FVC, and age had the strongest independent effects on the absolute change of FEV_1, and FEV_1/FVC-ratio and age on the relative change of FEV_1 in healthy asymptomatic nonsmokers. The effect of gender on the height and baseline FEV_1/FVC ratio-adjusted absolute (p=0.380) or relative FEV_1 response (p=0.618) was not significant.

5.3.2 FEV_6, FVC, and FET responses to bronchodilation

The absolute and relative changes of FVC and FET are shown in Figure 15. In the bronchodilation test, 23.1% of men and 33.2% of women had greater than 2.5% reduction in FVC. The mean change in FVC was -42.8 (122.4) ml or -1.0% (3.3%). The upper 95th percentile for change in FVC was 137.0 ml and 4.0%. The mean change in FET was -0.2 (2.7) s or 0.4% (23.9%), with a 95th percentile of 3.4 s or 44.0%.

Table 5. *Change of FEV_6, FVC, and FET during bronchodilation test in the general population stratified by gender*

	Men (n=260)			Women (n=368)			
	mean (SD)	95% CI	95th percentile	mean (SD)	95% CI	95th percentile	Gender difference (p-value)
change of FEV1 [ml]	107.4 (130.6)	91.4 - 123.3	335.3	55.9 (86.2)	47.1 - 64.8	214.5	<0.001
change of FEV1 % from baseline	3.0 (4.3)	2.5 - 3.5	8.6	2.2 (3.7)	1.8 - 2.6	8.4	0.009
change of FEV6 [ml]	-2.1 (137.7)	-18.9 - 14.8	195.8	-21.4 (93.5)	-31.0 - -11.8	144.9	0.036
change of FEV6 % from baseline	0.1 (3.5)	-0.3 - 0.6	4.8	-0.5 (3.1)	-0.8 - -0.2	5.1	0.023
change of FVC [ml]	-35.6 (147.6)	-53.6 - -17.6	170.2	-48.1 (100.9)	-58.4 - -37.8	132.2	n.s.
change of FVC % from baseline	-0.6 (3.4)	-1.0 - -0.2	3.6	-1.2 (3.2)	-1.6 - -0.9	4.4	0.016
change of FET [s]	-0.1 (2.6)	-0.5 - 0.2	3.2	-0.3 (2.7)	-0.5 - 0.0	3.7	n.s.
change of FET % baseline	-0.6 (21.2)	-3.2 - 2.0	34.7	1.2 (25.6)	-1.4 - 3.8	48.6	n.s.

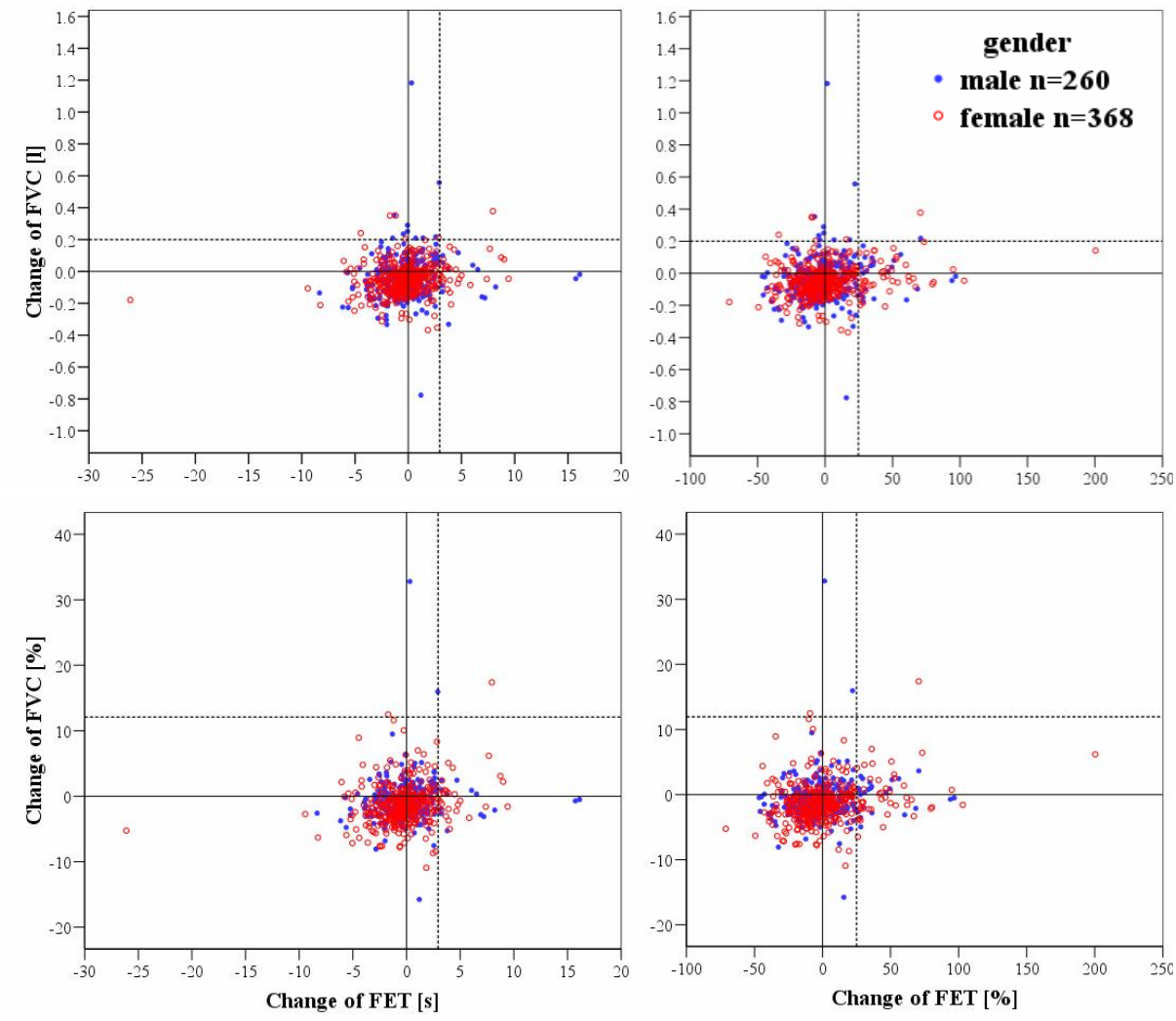

Figure 15 *Concurrent relative and absolute changes in FVC and FET in the bronchodilation test with 0.4 mg salbutamol in the general population. The dotted lines represent 12% and 200 ml from baseline changes for FVC and 3.0 s or 24% from baseline changes for FET*

FEV_6 also on average decreases, but the reduction is less marked than in FVC, with a mean of -13.4 (114.2) ml or -0.2% (3.3%) and a 95th percentile of 169.0 ml and 5.0% from baseline. The concurrent changes in FEV_6, FVC, and FET in the bronchodilation test are outlined in Table 6. The concurrent change in FEV_6 and FVC are demonstrated in Figure 16. FEV_6 decreased significantly more in women both in absolute and in relative measures, whereas the gender difference was only significant in relative change in FVC. Age, height, weight, or BMI did not correlate significantly with changes in FVC, FEV_6, or FET during the bronchodilation test.

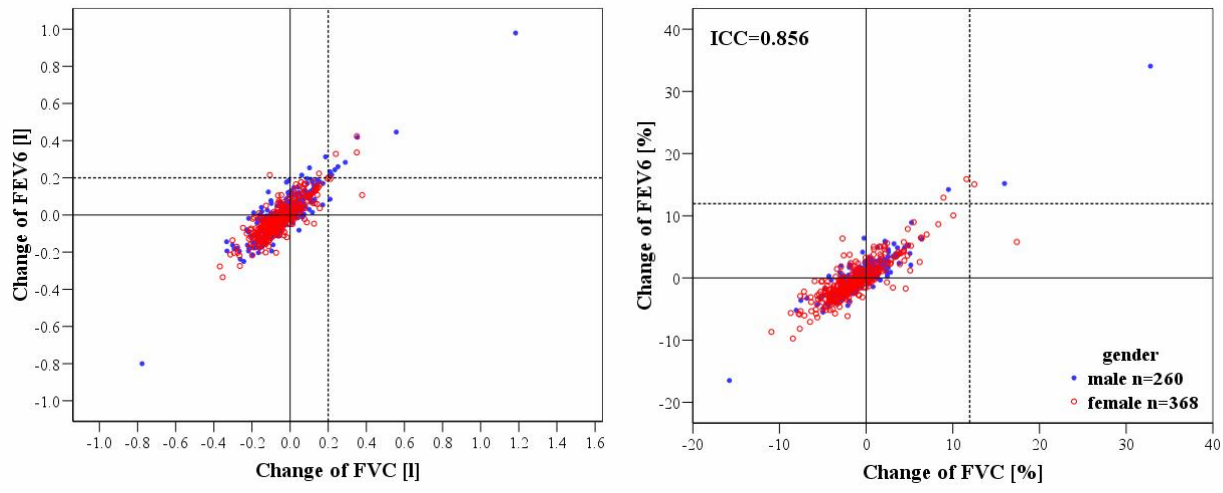

Figure 16 *Concurrent change in FVC and FEV_6 in the bronchodilation test in the general population. The dotted lines represent +12% from baseline and +200 ml limits*

Four subjects (0.6% of population) had a change in FVC from baseline of 12% or greater and at least 200 ml. Using the same threshold value, six subjects had a significant change of FEV_6. One individual had a significant increase in FVC, but an insignificant increase in FEV_6, and for her this increase in postbronchodilation FVC was caused by an increase of FET of 8 s and 71% relative to baseline FET. This subject can easily be noted from Figure 16. On the other hand, two subjects had a significant increase with FEV6 but not with FVC, and both of them had a shorter FET in postbronchodilation spirometry.

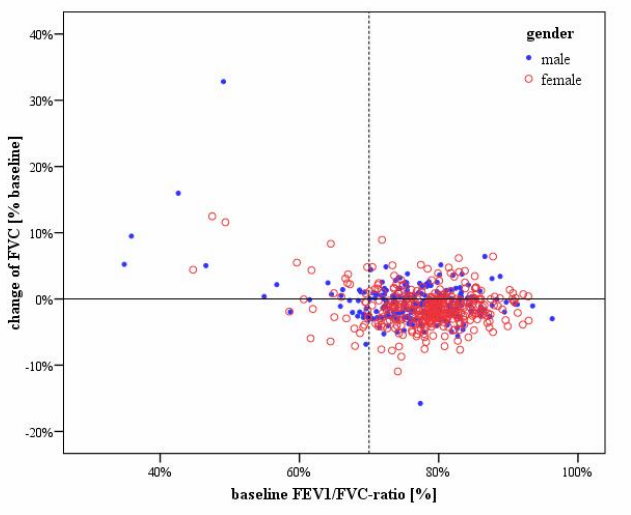

Figure 17 *Change in FVC in relation to baseline FEV_1/FVC ratio in the general population. The dotted line shows $FEV_1/FVC=70\%$ limit defined by the GOLD criteria*

The relationship of change in FVC to postbronchodilation spirometry variables, reflecting obstruction and its grade, is displayed in Figure 17. Volume bronchodilation became increasingly common as the ratio of FEV_1/FVC decreased. The average change in FVC was positive for subjects with baseline FEV_1/FVC ratio <LLN.

6 Discussion

6.1 Methodology

This study is a part of a larger FinEsS study on respiratory epidemiology. The study methodology reflects the international cooperation and its challenges. The original intention was that a uniform methodology be followed in the different centers to enable international comparisons. For flow-volume spirometry, the ATS 1994 Update of the Spirometry Standard was chosen. However, national differences still prevailed; for example, in Helsinki, the spirometry repeatability criteria were based on ERS 1993 criteria, possibly because they were considered to be more stringent. In bronchodilation testing, the dose of salbutamol differed between the centers, with Swedish centers using 800 µg of salbutamol. Also posture varied, with spirometry conducted seated in Finland, but standing in Sweden. This made it impossible to compare spirometry data between centers. It would have been much easier had the ATS 1994 criteria been uniformly followed, although some of these considerations, such as posture, were not unambiguously stated in the standard.

Much discussion has been held on the methodology of FET measurements and patient instruction. The spirometry procedures followed regular specialist pulmonary function testing practices. In Helsinki, all measurements were undertaken by two trained and experienced technicians. Patients were vigorously coached to achieve a plateau and to fulfill end-of-test criteria. There was no set time limit after which patients would have been less vigorously coached, but in reality the nurses likely tended to stop encouraging patients at individually common practice levels. The nurses did not know in advance that expiratory times would be evaluated, but they conducted the spirometry sessions following regular practices. The findings therefore reflect the situation encountered in normal pulmonary function testing and are not a result of specially designed FET measurements. Our intention was not to evaluate FET as a diagnostic variable per se, but we considered it a potentially relevant quality measurement early on in the analysis.

FET values were taken as measured by the computer software. In reality, the expiratory time is usually longer since the computer software and sensor do not include the end-expiratory plateau in the reported value.

This is a population study and the subjects represent a random population sample. Subjects were instructed to continue their regular medication, with the exception of oral antihistamines, which were discontinued for three to five days before the skin Prick-testing. Short-acting β-agonists were asked to be avoided 4 h and long-acting β-agonists for 12 h previous to testings, but failure to do so did not result in exclusion of the patient from the study. Since patients with asthma continued their regular therapeutic medication, the subjects with previously diagnosed asthma had very few positive responses in bronchodilation testing. This should be taken into consideration in evaluating the results. However, temporary discontinuation of anti-asthmatic medication was not deemed

possible since corticosteroids should be discontinued for at least one month; discontinuation of asthma medication would likely result in more symptomatic subjects. Population studies should reflect actual situations in the population. Subjects with irreversible airflow obstruction (reduced FEV_1/FVC) could, however, show reversibility following a trial of corticosteroids, and this cannot be reflected in a single cross-sectional study.

6.2 Main results

6.2.1 Forced expiratory time in flow-volume spirometry

The earliest studies on FET have assessed the usability of auscultated FET as a simple diagnostic test for detection of chronic obstruction (Rosenblatt & Stein, 1962; Lal et al., 1964; Macdonald et al., 1975; Kern & Patel, 1991; Holleman et al., 1993). Auscultated FET was found to be a clinically potentially relevant measure for the bedside diagnosis of airflow obstruction when pulmonary function measurements were not readily available, but it was surpassed by the ready availability of peak flow meters (PEF) and the rapid development of spirometers that became available for more accurate diagnosis in primary care (Holleman et al., 1993). Spirometric FET has been studied surprisingly little. Spirometry standards have previously taken FET into consideration only in evaluation of sufficiently long exhalations during forced expiratory maneuvers and set a limit of 6 s for minimum duration of the exhalation (Quanjer et al., 1993; ATS, 1995).

FET has been a measure of increasing interest as the joint ATS/ERS Task Force on Interpretation of Spirometry stipulated that when only FVC increases significantly (>12% and >200 ml) during bronchodilation testing it must be verified that this is not caused by longer exhalations in postbronchodilator spirometry (Pellegrino et al., 2005).

In previous studies, FET has been shown to be prolonged in conditions causing airflow limitation and obstruction (Kern & Patel, 1991, 1994; Vandevoorde et al., 2005). The diagnostic utility with either auscultated or spirometric FET is very poor.

We have shown that FET is on average 10.7 s in standard flow-volume spirometry (I), a value that is slightly larger than in previous reports on normal controls, being at approximately the same level as in obstructed subjects (Hankinson et al., 1977; Vandevoorde et al., 2005). Airflow limitation measured by reduced FEV_1/FVC ratio was the strongest determinant for FET, and differences in FET are inherently affected by the prevalence of airflow limitation and age distribution in the subjects under investigation. This is the first report on an unselected general adult population in an epidemiological study. The lower values reported based on register data from tertiary care pulmonary function laboratories might reflect a greater incidence of restrictive diseases in patient samples than in our population sample.

We have demonstrated that besides a reduced FEV_1/FVC ratio, age has a positive correlation with FET. Also the difference between FVC and FEV6 increases with age. FEV_1/FVC is known to diminish during normal aging. The significance of reduced FEV_1/FVC in asymptomatic older adults is controversial. Mannino and coworkers (2003, 2006) have shown that reduced FEV_1/FVC<70% while FEV_1/FVC is still above the lower limits of normal reference values is associated with greater morbidity and mortality. In a separate report, FEV_1 in itself was found to be a predictor of greater mortality of all causes (Knuiman et al., 1999; Schünemann et al., 2000). In the older age cohorts, history of childhood infections, accumulated smoking pack-years, and prevalence of disease are also greater confounding variables.

In this study, FET was shown to be less repeatable than the main parameters from flow-volume spirometry. This is in line with previous literature. Cochrane et al. (1977) and recently Tsai et al. (2006) have reported coefficients of variation for FET around 11-14%, which are larger than for any other flow-volume spirometry variable. This is the first population study on FET and the first study to report changes in FET during bronchodilation testing. A prolongation of FET of 3 s is suggested to be considered excessive based on the intrasession repeatability (I).

In bronchodilation testing (IV), FET was shown to seldom increase — only one subject had an increase of FET of over 3 s. Since FET varies more than other spirometry variables, it should be measured from the same curve as the FVC during bronchodilation testing.

6.2.2 FEV_1 response to bronchodilation in the general population

In bronchodilation testing, FEV_1 increased in the population 2.5% from baseline – 3.0% in men and 2.2% in women. This is in line with earlier Nordic studies (Johannessen et al, 2005, 2006; Lehmann et al., 2006, 2007) and population studies elsewhere (Dales et al., 1988). Airflow limitation (reduced FEV_1/FVC) in baseline spirometry was found to be the strongest determinant of change in FEV_1. Greater lung volumes, namely FVC and FEV_1 levels, were also associated with slightly larger changes in FEV_1. Men had somewhat larger responses than women, but the difference was partially caused by a greater prevalence of airflow limitation and greater height and FVC in men. When these confounding variables were controlled, the gender difference was not statistically significant. Older subjects had slightly lower changes in FEV_1, which have been attributed to fatigue during testing, possible differences in β-receptor levels on bronchial smooth muscle, and smaller FVC, FEV_1, and particularly FEV_1/FVC. The age-related reduction in change in FEV_1 can also be slightly affected by the smaller prevalence of asthma in older age cohorts.

Despite the multitude of studies on bronchodilation and methodology, there is a surprising scarcity of unselected population materials in this field. We show that negative changes in bronchodilation testing are common, a phenomenon often discarded as outliers or poor quality. In this study (III), we have demonstrated that FEV_1 bronchodilation is

significant at a lower level than previously thought, around 9% from baseline. The current standard sets the limit at 12% of baseline and 200 ml. There were, however, a number of potential confounders in this study. Subjects continued their regular medication, which means that asthmatics usually received adequate treatment, and hence, reversible airflow limitation was seen less often. In addition, spirometry maneuvers affect the results. During spirometry, inspiratory spirometry was regularly measured in all individuals. Women and older subjects possibly had less bronchodilation responses since they potentially could have more fatigue during testing.

Bronchodilation response was shown to be slightly dependent on age, gender, and baseline airflow limitation (III).

6.2.3 FEV_6 and FVC response to bronchodilation in the general population

Determination of FVC bronchodilation response with flow volume spirometry is challenging. Changes in FVC only indirectly reflect changes in lung compartments, e.g. RV. The FVC maneuver can be physically demanding for subjects with airflow limitation. Previous studies have reported contradictory results in the necessity of body pletysmography in detecting volume responders. FVC is known to be dependent on expiratory time (Glindmeyer et al., 1987) especially in subjects with airflow limitation, which was also verified in our studies (I, II, IV). Moreover, we have shown that the difference between FVC and FEV_6 increases as FET increases and also during aging (I, II).

The “new” requirement in the ATS/ERS 2005 standard of consideration of FET when only FVC increases in bronchodilation testing follows reports on severely obstructed subjects and patients with emphysema (Cerveri et al., 2000; Newton et al., 2000; O’Donnell et al., 2001). Bronchodilation response tends to initially be in terms of flow (measured with FEV_1) when airflow limitation is mild, but with worsening severity of obstruction the bronchodilation response is more often detected in terms of volume (measured with FVC) (Cerveri et al., 2000; Newton et al., 2000; O’Donnell et al., 2001; Schermer et al., 2007; Tashkin et al., 2008).

In Study II, we observed that FEV_6 is as repeatable as FVC in the population and in subjects with $FEV_1/FVC<LLN$, in fact showing slightly better reproducibility for FEV_6 than for FVC. This is most likely due to prolonged FET in obstructed subjects and greater variation in FET. In Study IV, FEV_6 was shown to differentiate positive responders even more reliably than FVC since it recognized the one case where the increase in FVC was due to longer FET in postbronchodilation spirometry. This increase in FVC due to longer exhalation in postbronchodilation spirometry could be recognized only with the consideration of change in FET or FEV_6. “Isolated volume bronchodilation” is rare in the population; in our sample, true FVC bronchodilation in the absence of FEV_1 bronchodilation and without increases in FET was not found. One subject had an increase in FVC due to prolongated FET. The limit for significant change in FEV_6 in bronchodilation test is suggested to be around 6%, which is below the documented

repeatability of FEV_6. The use of FEV_6 would eliminate the need for controlling exhalation times and would identify volume responders without prolonged FET. Change in FEV6 also identified those two subjects whose change in FVC fell below significant levels due to shorter postbronchodilator FET (IV).

Decreases in both FVC and FEV_6 during the bronchodilation test were surprisingly common. The trend towards negative changes in FVC has been reported earlier (Johanessen et al., 2006), but is largely unrecognized. In some studies, negative changes in bronchodilation testing have been considered the result of technical flaws (Goedhart et al., 2004). Since neither the expiratory time, extrapolated volume, or peak expiratory flow changed, it indicates that the expirations had equally forceful beginnings and continued efforts, i.e. the maneuvers do not seem to be prematurely terminated. Negative changes might be caused by increased collapsibility as a result of reduced airway smooth muscle tone with β2-agonists or by increased physiological airway collapsibility in healthy adults. On the contrary, those subjects with clearly reduced FEV_1/FVC-ratio indicating bronchial obstruction showed increased FVC after bronchodilation (IV).

Prolongation of expiratory maneuvers during bronchodilation testing has been proposed to reflect a form of bronchodilation itself (de la Hoz, 2002; Newton et al., 2002; Tsai et al., 2006). The possibility of prolonged FET representing a form of bronchodilation warrants further consideration, but this cannot be analyzed from our data. The so-called “volume bronchodilation” is controversial in flow-volume spirometry, with many authors feeling a need to use pletysmography to identify volume response. Smith and coworkers (1992) found that FEF25-75% were higher at baseline spirometry in subjects who required pletysmography to identify bronchodilation response. Light and coworkers, by contrast, observed pletysmography to yield no benefit in the assessment of volume response. The significant limit of bronchodilation responses and the repeatability of pletysmography are less well documented. Furthermore, pletysmography is not widely available, whereas flow-volume spirometry is a fundamental diagnostic procedure.

In our population sample, FEV_6 performed even better than FVC in the bronchodilation test. Possibly, FEV_6 could also identify reversibility caused by early small airways obstruction. The use of flow values reflecting small airways dysfunction, namely MEF50 and MMEF, has been hindered by great intrasession and short-term variability and dependence of instantaneous flow values on the lung volume at which they are measured. This is particularly problematic during bronchodilation testing, when FVC can both increase and decrease significantly. FEV_6 is the cumulative volume of air expelled during the first 6 s of a forced expiratory maneuver starting from a back-extrapolated time zero. In early airflow limitation in small airways in the early stages of COPD, the FET is not yet markedly prolonged and changes in small airways are most likely also reflected in changes in FEV_6. In moderate to severe COPD, airflow limitation is more prominent in large airways, but in this subgroup volume and expiratory time changes are more likely.

7 Conclusions

1. FET was around 10 s in the general population and in healthy nonsmokers, but longer in subjects with airflow limitation and in the elderly (I).
2. FEV_1, FEV_6, and FVC are equally repeatable within a session, but FET varies considerably more. Anthropometric and spirometric variables, including FET, had little effect on repeatability. A change of 3 s in FET was considered significant (II). FEV_6 was equally repeatable also in subjects with airflow limitation.
3. FEV_1 response to bronchodilation was significant around 9% from baseline in the population sample and around 6% from baseline in healthy nonsmokers. Age, gender, and baseline FVC were the most significant determinants (III).
4. FVC, FEV_6, and FET in general decreased in the bronchodilation test. A significant increase of FEV_6 to bronchodilation was around 6% from the baseline. The most significant determinant for FEV_6 response was baseline FEV_1/FVC. FVC response caused by longer exhalation was detected with flow-volume spirometry using FEV_6, which proved to be also a suitable surrogate measure of FVC reversibility. The use of FEV6 in lieu of FVC removes the need to control expiratory time. Therefore it might be useful especially in the primary care (IV).

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Appendix 1

FinEsS tutkimus *The FinEsS Study*

Hengityssairauksien haastattelu *Respiratory questionnaire*

Helsinki

1. Syntymäaika *Date of birth*

2. FinEsS numero *FinEsS number*

3. Rotu *Ethnic origin*: valkoinen rotu *Caucasian*; musta rotu *Negroid*; keltainen rotu *Oriental*; muu *Other*

4. Sukupuoli *Gender*: mies *male*; nainen *female*

5. Otos *Sample*

6. Koodit *Coding: country; center; area; nationality [not used in Helsinki]*

7. Väestötiheyden luokitus (ei käytössä Helsingissä) *Population density category (not used in Helsinki)*

Yskä ja limannousu *Cough and phlegm*

8. Onko Sinulla ollut viime vuosina pitkäaikaista yskää? *Have you had long-standing cough during the last years?* ei *no*; kyllä *yes*

9. Yskitkö tai köhitkö yleensä aamuisin? *Do you usually cough in the morning?* ei *no*; kyllä *yes*

vastaa kysymykseen 10 vain jos vastasit **kyllä** kysymykseen 9. *If you answered **YES** to question 9, please answer question 10:*

10. Onko Sinulla tällaista yskää tai köhää aamuisin useimpina viikon päivinä yli kahden viikon jaksoissa? *Do you have this cough most days a week in periods of more than two weeks?* ei *no*; kyllä *yes*

11. Yskitkö tai köhitkö muuhun aikaan päivästä tai öisin? *Do you usually cough during other times of the day, or at night?* ei *no*; kyllä *yes*

vastaa kysymykseen 12 vain jos vastasit **kyllä** kysymykseen 11. *If you answered YES to question 11, please answer question 12:*

12. Onko sinulla tällaista yskää tai köhää useimpina viikon päivinä yli kahden viikon jaksoissa? *Do you have this cough most days a week over periods of more than two weeks?* ei *no*; kyllä *yes*

vastaa kysymykseen 13 vain jos vastasit **kyllä** kysymykseen 10 tai 12: *If you answered YES to question 10 or 12, please answer question 13:*

13. Onko Sinulla tällaista yskää… *Do you have this cough…* harvakseen silloin tällöin? *sparsely now and then?*; yleensä/tavallisesti talvella? *generally/commonly in winter?*;

pitkin vuotta jaksoittain tai kaikkina päivinä? *intermittently or continuously throughout the year?*

14. Nouseeko yskiessä tai köhiessä keuhkoistasi yleensä limaa? *Do you usually bring up phlegm from your chest when coughing or hawking?* ei *no*; silloin tällöin *now and then;* usein *often*

15. Onko Sinulla keuhkoissa limaa, jota on vaikea saada irtoamaan? *Do you have phlegm on your chest that is difficult to bring up?* ei *no;* kyllä *yes*

16. Esiintyykö Sinulla yskäjaksoja, jolloin useimpina päivinä yskiessä tai köhiessä keuhkoistasi yleensä nousee limaa tai onko keuhkoissa limaa, jota on vaikea saada irtoamaan? *Do you usually have phlegm when coughing or hawking, or do you have phlegm on your chest that is difficult to bring up most days in periods of ?* ei, tai <3kk/vuosi *no, or <3 months;* vähintäin 3kk/vuosi *at least 3 months/year;* kahtena peräkkäisenä vuonna vähintäin 3kk/vuosi *at least 3 months/year, over 2 successive years*

vastaa kysymykseen 17 vain jos rastitit kysymyksen 16 viimeisen vaihtoehdon: *If you answered **YES** to alternative three of question 16, please answer question 17:*

17. Kuinka monen vuoden ajan? *For how many years?* ___ vuotta *years*

vastaa kysymykseen 18 vain jos rastitit kysymyksen 16 ensimmäisen vaihtoehdon: *If you answered NO to alternative three of question 16, please answer question 18:*

18. Onko Sinulla koskaan ollut pitkäaikaista yskää tai limannousua keuhkoista pitkäkestoisina jaksoina? *Have you ever had long-standing cough or long-standing periods with phlegm in your chest?* ei *no;* kyllä *yes*

Hengityksen vinkunat *Wheezing and whistling*

19. Esiintyykö Sinulla ajoittain vinkuvaa tai muutoin poikkeavan äänekästä hengitystä? *Do you sometimes have wheezing, whistling, or otherwise unusually noisy breathing?* ei *no;* kyllä *yes*

20. Oletko koskaan havainnut hengityksesi vinkuvan (keuhkoissa)? *Have you ever noted wheezing or whistling in your chest?* ei *no;* kyllä *yes*

21. Onko Sinulla ollut hengityksen vinkunaa kertaakaan viimeisten 12 kuukauden aikana? *Have you had wheezing or whistling in your chest at any time in the last 12 months?* ei *no;* kyllä *yes*

vastaa kysymyksiin 22-24 (25) vain jos vastasit **kyllä** kysymykseen 21 *If you answered YES to question 21, please answer questions 22-24 (25):*

22. Onko Sinulla ollut vähäisintäkään hengenahdistusta vinkunan yhteydessä? *Have you been at all breathless when the wheezing noise was present?* ei *no;* kyllä *yes*

23. Onko Sinulla ollut hengityksen vinkunaa silloinkin kun et ole ollut flunssainen? *Have you had this wheezing or whistling when you did not have a cold?* ei *no;* kyllä *yes*

24. Onko hengityksesi vinkuvaa tai poikkeavan äänekästä viikon useimpina päivinä? *Do you have wheezing, whistling, or a unusually noisy breathing most days of the week?* ei *no;* vain jaksoittain *yes, but only periodically*; kyllä, pitkin vuotta *yes, throughout the year*

mikäli vastasit: JAKSOITTAIN kysymykseen 24, merkitse minkä kuukausien aikana *If you answered PERIODICALLY to question 24, please list the months:*

25. Kuukaudet jolloin hengityksen vinkunoita esiintyy *The months in which wheezing or whistling was present:*

Hengenahdistus yleensä *Breathlessness in general*

26. Onko Sinulla liikuntavaikeuksia muusta syystä kuin keuhko- tai sydänsairauden vuoksi? *Are you disabled for any reason other than heart or lung trouble?* ei *no/not applicable;* kyllä *yes*

vastaa kysymykseen 27 vain jos vastasit **kyllä** kysymykseen 26 *If you answered YES to question 26, please answer question 27:*

27. Mistä syystä? *For what reason?* aivoverenkiertosairaus *cerebrovascular disease*; lihassairaus *myopathy*; raajojen liikkuvuus rajoittunut *limited movement of the extremities*; muut syyt *other*

28. Oletko pyörätuolin käyttäjä? *Do you use a wheelchair?* ei *no;* kyllä *yes*

29. Esiintyykö Sinulla koskaan hengenahdistusta tai hengitysvaikeutta? *Do you ever have trouble breathing?* ei, *no*; kyllä *yes*

vastaa kysymykseen 30 vain jos vastasit **kyllä** kysymykseen 29 *If you answered YES to question 29, please answer question 30:*

30. Esiintyykö Sinulla tällaista hengenahdistusta tai hengitysvaikeutta? *Do you have this trouble:* jatkuvasti, hengitys ei koskaan ole täysin kunnossa *continuously, your breathing is never completely normal*; toistuvasti, mutta hengitys palautuu aina tavalliseksi *repeatedly, but your breathing always gets returns to normal*; vain harvoin *only rarely*

31. Esiintyykö Sinulla hengenahdistusta tai hengitysvaikeutta kiirehtiessäsi tasamaalla tai kun kävelet ylös loivaa mäkeä tai noustessasi rappuja yhden kerrosvälin omalla vauhdillasi? *Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill or one flight of stairs at your normal pace?* ei *no*; kyllä *yes*

vastaa kysymyksiin 32-34 vain jos vastasit **kyllä** kysymykseen 31 *If you answered YES to question 31, please answer questions 32-34:*

32. Hengästytkö, kun kävelet tasamaalla ikäistesi henkilöiden kanssa? *Do you get short of breath when you walk with other people of your own age on level ground?* ei *no*; kyllä *yes*

33. Joudutko pysähtymään hengähtääksesi välillä kun kävelet omalla vauhdillasi tasamaalla? *Do you have to stop for breath when you walk at your own pace on level ground?* ei *no;* kyllä *yes*

34. Hengästytkö pukeutuessasi tai riisuutuessasi? *Do you get short of breath when dressing or undressing?* ei *no;* kyllä *yes*

Kohtauksittainen hengenahdistus ja ahtauden tuntu hengityksessä *Attacks of shortness of breath or chest tightness*

35. Onko Sinulla koskaan ollut hengenahdistuskohtauksia tai ajoittain esiintyvää poikkeavan tuntuista hengästymistä? *Have you ever had attacks of shortness of breath or periodically occurring breathlessness?* ei *no;* kyllä *yes*

36. Onko Sinulla ollut yhtään hengenahdistuskohtausta tai hengästymiskohtausta viimeisten 12 kuukauden aikana? *Have you had any attacks of shortness of breath or breathlessness in the last 12 months?* ei no; kyllä *yes*

vastaa kysymykseen 37 vain jos vastasit **kyllä** kysymykseen 35 tai 36 *If you answered YES to question 35 or 36, please answer question 37:*

37. Onko hengityksesi normaalia hengenahdistuskohtausten välillä tai ennen kohtausten alkua? *Is your breathing "normal" before attacks start or between attacks of breathlessness?* ei *no;* kyllä *yes*

38. Onko Sinulla ollut koskaan hengenahdistuskohtausta ja samanaikaisesti hengityksen vinkunaa? *Have you ever had any attacks of shortness of breath with wheezing or whistling?* ei *no;* kyllä *yes*

vastaa kysymykseen 39 ja 40 vain jos vastasit **kyllä** kysymykseen 38 *If you answered YES to question 38, please answer questions 39 and 40:*

39. Onko Sinulla ollut hengenahdistuskohtausta ja samalla hengityksen vinkunaa viimeisten 12 kuukauden aikana? *Have you had attacks of shortness of breath with wheezing or whistling in the last 12 months?* ei *no;* kyllä *yes*

40. Minkä ikäisenä Sinulla oli ensimmäinen hengenahdistuskohtaus samalla esiintyneen hengityksen vinkunan kanssa? *How old were you when you had the first attack of shortness of breath with wheezing or whistling?*ikä *age* ___ v *years*

41. Oletko koskaan herännyt yöllä tai varhain aamulla hengenahdistuskohtauksen ja samanaikaisen hengityksen vinkunan vuoksi? *Have you ever been woken at night or early in the morning by an attack of shortness of breath with wheezing or whistling?* ei *no*; kyllä *yes*

vastaa kysymykseen 42 vain jos vastasit **kyllä** kysymykseen 41 *If you answered YES to question 41, please answer question 42:*

42. Onko näin käynyt viimeisten 12 kuukauden aikana? *Has this happened in the last 12 months?*: ei *no;* kyllä *yes*

vastaa kysymykseen 43 vain jos vastasit **kyllä** kysymyksiin 36, 39 tai 42 *If you answered YES to question 36, 39, or 42, please answer question 43:*

43. Kuinka monta hengenahdistuskohtausta, vinkunan kanssa tai ilman, Sinulla on ollut viimeisten 12 kuukauden aikana? *How many attacks of shortness of breath, with or without wheezing, have you had in the last 12 months?* a) ei yhtään *none*; b) ehkä kerran *maybe one*; c) kahdesta viiteen kertaan *two to five times*; d) yli viisi kertaa, mutta ei useimpina kuukausina *more then five times but not most months*; e) useimpina kuukausina mutta ei useimpina viikkoina *most months, but not most weeks*; f) useimpina viikkoina mutta ei useimpina päivinä *most weeks, but not most days*; g) useimpina päivinä *most days*; h) jaksoittain useimpina viikkoina *periodically, most weeks*; i) jaksoittain useimpina päivinä *periodically, most days*

44. Onko Sinulla koskaan ollut ahtauden tunnetta rinnassa? *Have you ever had a feeling of tightness in your chest?* ei *no;* kyllä *yes*

vastaa kysymykseen 45 vain jos vastasit **kyllä** kysymykseen 44 *If you answered YES to question 44, please answer question 45:*

45. Onko tällaista tuntemusta ollut viimeisten 12kk aikana? *Has this happened in the last 12 months?* ei *no;* kyllä *yes*

46. Oletko koskaan herätessäsi kokenut ahtauden tunnetta rinnassa? *Have you ever woken with a feeling of tightness in your chest?* ei *no;* kyllä *yes*

vastaa kysymykseen 47 vai jos vastasit **kyllä** kysymykseen 46 *If you answered YES to question 46, please answer question 47:*

47. Onko näin käynyt viimeisten 12kk aikana? *Has this happened in the last 12 months?* ei *no;* kyllä *yes*

Tekijöitä, jotka aiheuttavat Sinulle hengityksen vinkunaa tai hengenahdistus-kohtauksia, yskän kera tai ilman yskää *Factors provoking wheezing or whistling, or attacks of shortness of breath, with or without cough*

48. Karvaiset eläimet *Furred animals*, esim.: koira, kissa, lehmä, hevonen, kani jne *examples: dog, cat, cow, horse, rabbit, etc*.: ei *no;* kyllä *yes*

49. Siitepölyaltistus *Pollen exposure*, esim.: lehdet, ruoho, ulkokukat *examples: leaves, grass, outdoor flowers*: ei *no;* kyllä *yes*

50. Homeen haju tai homealtistus *Smell of mold or mold exposure:* ei *no;* kyllä *yes*

51. Tupakan savu tai haju *Smoke or smell of tobacco*: ei *no;* kyllä *yes*

52. Pölyisissä olosuhteissa yleensä *Dusty places in general*: ei *no;* kyllä *yes*

53. Voimakkaat tuoksut tai hajut *Strong smelling scents* (deodorantit, mausteet, painomuste, savukaasut, puhdistusaineet, kukkien tuoksut jne *deodorants, spices, printing ink, fumes, cleaners, flowers, etc*.): ei *no;* kyllä *yes*

54. Autojen pakokaasut *Car exhaust*: ei *no;* kyllä *yes*

55. Muut ilmansaasteet *Air pollution, other than car exhaust*: ei *no;* kyllä *yes*

56. Hengitystieinfektiot, nuhakuumeet *Airway infections, colds*: ei *no;* kyllä *yes*

57. Lääkkeet *Medicines*: ei *no;* kyllä *yes*

jos kyllä, mitkä lääkkeet? *if YES, which medicines?*_____

58. Ruoka *Food*, esim.: kala, äyriäiset, pähkinät, siemenhedelmät *Examples: fish, shellfish, nuts, seeded fruits*: ei *no;* kyllä *yes*

Jos **kyllä,** mikä ruoka? *If YES, which foods?* _____

59. Psyykkiset tekijät tai stressi *Psychological factors or stress*? ei *no;* kyllä *yes*

60. Kylmä ilma *Cold air*? ei *no;* kyllä *yes*

61. Muu säätila kuten kostea ilma, tuulinen, sumuinen tai lämmin ilma *Other weather conditions such as damp, windy, foggy, or warm weather*? ei *no;* kyllä *yes*

62. Tuleeko Sinulle fyysisen rasituksen jälkeen välittömästi tai muutaman minuutin kuluttua hengenahdistusta ja hengityksen vinkunaa? *Do you get shortness of breath **with** wheezing immediately or some minutes **after** physical effort?* ei *no;* kyllä *yes*

63. Tuleeko Sinulle fyysisen rasituksen aikana hengenahditusta ja hengityksen vinkunaa? *Do you get shortness of breath **with** wheezing **during** physical effort?* ei *no;* kyllä *yes*

64. Onko Sinulla ollut koskaan hengenahdistuskohtauksia ja hengityksen vinkunoita tai astman oireita työpaikallasi? *Have you ever had attacks of shortness of breath with wheezing or whistling or symptoms of asthma at your workplace?* ei *no;* kyllä *yes*

vastaa kysymykseen 65 vain jos vastasit **kyllä** kysymykseen 64 *If you answered YES to question 64, please answer question 65:*

65. Onko näin käynyt viimeisten 12kk aikana? *Has this happened in the last 12 months?* ei *no;*kyllä *yes*

66. Saatko hengenahdistusta ja hengityksen vinkunaa muista syistä kuin yllä mainittu? *Do you get shortness of breath with wheezing due to causes other than those specified above?* ei *no;* kyllä *yes*

jos **kyllä;** täsmennä: *If YES:specify:* _____

Astma ja krooninen keuhkoputken tulehdus (krooninen bronkiitti) *Asthma and chronic bronchitis*

67. Onko Sinulla koskaan ollut astmaa? *Have you ever had asthma?* ei *no;* kyllä *yes*; en tiedä *don't know*

68. Onko lääkäri todennut Sinulla olevan astmaa? *Have you been diagnosed as having asthma by a doctor?* ei *no;* kyllä *yes;* en tiedä *don't know*

69. Onko Sinulla esiintynyt astmaa lapsuuden aikana tai hengityksen vinkunoita varhaisessa lapsuudessa? *Have you had wheezing or whistling in your chest in early childhood or asthma during childhood?* ei *no;* kyllä *yes;* en tiedä *don't know*

70. Käytätkö tai oletko aiemmin käyttänyt astmalääkkeitä säännöllisesti tai tarvittaessa? *Do you currently use or have you earlier used asthma medicine regularly or as needed?* ei *no;* kyllä *yes*

71. Onko lääkäri määrännyt Sinulle mitään astmalääkettä? *Have you been prescribed any asthma medicines by a doctor?* ei *no;* kyllä *yes*

vastaa kysymyksiin 72-76 vain jos vastasit **kyllä** johonkin kysymyksistä 67-71 *If you answered YES to any of questions 67-71, please answer questions 72-76:*

72. Minkä ikäinen olit kun lääkäri kertoi Sinulla olevan astmaa tai määräsi sinulle astmalääkettä? *How old were you when a doctor told you that you had asthma or prescribed asthma medicine for you?* Ikä *Age* ___ v *years*

73. Minkä ikäinen olit kun Sinulla oli ensimmäinen astmakohtaus tai astmaan liittyvä tapahtuma tai oireinen astmajakso? *How old were you when you had your first attack of asthma or episode or period with asthma or symptoms of asthma?* Ikä *Age* ___ v *years*

74. Minkä ikäinen olit kun Sinulla oli viimeisin astmakohtaus? *How old were you when you had your most recent attack of asthma or symptoms of asthma?* Ikä *Age* ___ v *years*

75. Onko Sinulla ollut ylipäänsä mitään astmaoireita viimeisten 12 kuukauden aikana? *Have you had any symptoms of asthma during the last 12 months?* ei *no;* kyllä *yes*

76. Oletko käyttänyt mitään astmalääkkeitä viimeisten 12 kuukauden aikana? *Have you used any asthma medicines in the last 12 months?* ei *no;* kyllä *yes*

77. Onko lääkäri todennut Sinulla olevan kroonista keuhkoputken tulehdusta tai keuhkon laajentumaa? *Have you been diagnosed as having chronic bronchitis or emphysema by a doctor?*: ei *no;* kyllä *yes;* en tiedä *don't know*

78. Mikä on oma käsityksesi, onko Sinulla kroonista keuhkoputken tulehdusta? *In your opinion, do you have chronic bronchitis?* ei *no;* kyllä *yes;* en tiedä *don't know*

79. Mikä on oma käsityksesi, onko Sinulla keuhkon laajentumatautia? *In your opinion, do you have emphysema?* ei *no;* kyllä *yes;* en tiedä *don't know*

jos **kyllä vastauksia** kysymyksissä 76-79, täsmennä kysymykset 80-93, **mikäli** olet käyttänyt jotain kyseessä olevaa **lääkettä hengityssairauden vuoksi viimeisten 12kk aikana** *If you answered **YES** to questions 76-79, please answer questions 80-93 **if** you have used any of the **medicines in question for respiratory disease during the last 12 months:***

80. Hengitettävää, avaavaa (lyhytvaikutteista β2-agonistit) lääkettä? *Inhaled short-acting β2-agonists?* ei *no;*silloin tällöin *now and then;* useampina päivinä viikossa *most days a week*

vastaa myös kysymykseen 81, jos edellisessä muu kuin **ei** vaihtoehto *If you answered now and then or most days a week, please answer question 81:*

81. Milloin aloitit hengitettävän lyhytvaikutteisen avaavan (β2-agonistit) lääkkeen käytön? *When did you start using inhaled short-acting β2-agonists?*alle 1v sitten *less than 1 year ago;* 1-5 vuotta sitten *1-5 years ago;* yli 5 vuotta sitten *more than 5 years ago*

82. Hengitettävää kortisonivalmistetta? *Inhaled corticosteroids?* ei *no;* silloin tällöin *now and then;* useimpina päivinä viikossa *most days a week*

vastaa kysymyksiin 83 ja 84, jos edellä kysymyksessä 82 vastasit: silloin tällöin tai useimpina päivinä viikossa *If you answered now and then or most days a week, please answer questions 83 and 84:*

83. Milloin aloitit hengitettävän kortisonivalmisteen käytön? *When did you start using inhaled corticosteroids?* alle 1 vuosi sitten *less than 1 year ago;*1-5 vuotta sitten *1-5 years ago;* yli 5 vuotta sitten *more than 5 years ago*

84. Mikä on nykyinen annos? *What is your current dose?* <200µg/vrk, 200-800µg/vrk, >800µg/vrk [vrk=*day*]

85. Antikolinergistä lääkettä? *Anticholinergics?* ei *no;* silloin tällöin *now and then;* useimpina päivinä viikossa *most days a week*

86. Kromoglikaatteja tai nedokromiilia? *Chromoglycates or nedochromile?* ei *no;* silloin tällöin *now and then;* useimpina päivinä viikossa *most days per week*

87. Hengitettävää pitkävaikutteista avaavaa (β2-agonistit) lääkettä? *Inhaled long-acting β2-agonists?* ei *no;*silloin tällöin *now and then;* useimpina päivinä viikossa *most days a week*

88. Avaavaa lääkettä (β2-agonistit) tablettimuodossa? *Peroral β2-agonists?* ei *no;* silloin tällöin *now and then;* useimpina päivinä viikossa *most days a week*

89. Teofylliinivalmistetta? *Methylxanthines?*ei *no;* silloin tällöin *now and then;* useimpina päivinä viikossa *most days a week*

90. Avaavaa lääkettä sumuttimella (spiralla tms.)? *Bronchodilating liquids via nebulizer?* ei *no;* silloin tällöin *now and then;* useimpina päivinä viikossa *most days a week*

91. Kortisonivalmistetta tablettimuodossa? *Peroral corticosteroids?* ei *no;* silloin tällöin *now and then;* useimpina päivinä viikossa *most days a week;* vain keuhkosairauden pahenemisvaiheiden yhteydessä *only during exacerbations of respiratory disease*

jos **ei** kysymykseen 91, vastaa myös kysymykseen 92 *If you answered NO to question 91, please answer question 92:*

92.Oletko aiemmin käyttänyt kortisonivalmistetta tablettimuodossa? *Have you previously used oral corticosteroids?* ei *no;* kyllä *yes*

vastaa kysymykseen 93 vain jos vastasit **kyllä** kysymykseen 92 *If you answered YES to question 92, please answer question 93:*

93. Miksi lopetit kortisonitablettien käytön? *Why did you stop?* aloitin hengitettävän kortisonin *started with inhaled steroids;* sairaus lievittyi *improved;* muu syy *other*

reasons; käytin vain keuhkosairauden pahenemisvaiheen yhteydessä *used only during exacerbations of the respiratory disease*

Yskänlääkkeet ja limaairroittavat lääkkeet ***Antitussive or expectorative medicine***

94. Käytätkö tai oletko aiemmin käyttänyt limaa irroittavaa tai yskänlääkettä enemmän kuin vain tilapäisesti flunssien aikana? *Do you currently use or have you earlier used expectorative or antitussive medicines more often than rarely during common colds?* ei *no;* kyllä *yes*

vastaa kysymykseen 95 ja 96 vain jos vastasit **kyllä** kysymykseen 94 *If you answered YES to question 94, please answer questions 95 and 96:*

95. N-asetyylikysteiini valmistetta? *N-Acetylcysteine?* ei *no;* kyllä *yes*

96. Muuta limaairroittavaa tai yskänlääkettä? *Other expectorative or antitussive medicines?* ei *no;* kyllä *yes*

Lääkkeet nuhaoireisiin, nenäntukkoisuuteen ja silmäoireisiin ***Medicines for rhinitis or conjunctivitis***

97. Käytätkö tai oletko aiemmin käyttänyt pitkäaikaisesti tai toistuvasti lääkettä nuhaan tai silmätulehdukseen? *Do you currently use or have you earlier used medicines for rhinitis or conjunctivitis?*ei *no;* kyllä *yes*

vastaa kysymyksiin 98-100 vain jos vastasit **kyllä** kysymykseen 97 *If you answered YES to question 97, please answer questions 98-100:*

98. Antihistamiini tablettimuodossa? *Peroral antihistamines?* ei *no;* kyllä *yes*

99. Kortisoninenäsuihketta? ei, kyllä *(Nasal corticosteroids? no; yes)*

100. Muuta nenä- ja silmäoireiden lääkehoitoa (esim. kromoglykaatti) *Other medications for the nose or the eyes (e.g. chromoglycate)?* ei *no;* kyllä *yes*

Terveyspalveluiden tarve ***Need for health care services***

101. Onko Sinulla ylipäänsä mitään hengitysongelmia tai yskävaivoja tai limannousuongelmia? *Have you at all had any breathing problems or problems with cough or phlegm?* ei *no;* kyllä *yes*

102. Oletko koskaan joutunut hakeutumaan lääkärille tai muuhun hoitoon hengenahdistuksen tai hengityksen vinkunan vuoksi? *Have you ever consulted a physician or other medical care because of breathlessness, shortness of breath, or wheezing in your chest?* ei *no;* kyllä *yes*

103. Oletko koskaan joutunut hakeutumaan lääkärille tai muuhun hoitoon pitkäaikaisen yskän tai limannousun vuoksi? *Have you ever consulted a physician or other medical care because of long-standing cough or phlegm in your chest?* ei *no;* kyllä *yes*

vastaa kysymyksiin 104-115 jos vastasit **kyllä** yhteenkin kysymykseen 101-103 *If you answered YES to question 101, 102, or 103, please answer questions 104-115:*

104. Oletko joutunut hakeutumaan lääkärille hengitysoireiden, yskän tai limannousun vuoksi viimeisten 12kk aikana? *Have you consulted a physician because of breathing problems or cough or phlegm during the last 12 months?* ei *no;* kyllä *yes*

vastaa kysymykseen 105 jos vastasit **kyllä** kysymykseen 104 *If you answered YES to question 104, please answer question 105:*

105. Kuinka monta kertaa olet joutunut hakeutumaan lääkärille hengitys-, yskä tai limannousuongelmien vuoksi viimeisten 12kk aikana? *How many times have you consulted a physician for breathing problems or cough or phlegm during the last 12 months?____*

106. Käytkö säännöllisesti lääkärillä hengitysongelmien vuoksi? *Do you regularly see a physician because of your breathing problems?* ei *no;* kyllä *yes*

107. Oletko hengitysvaivojen tai yskä- ja limannousuongelmien vuoksi käynyt keuhkolääkärillä tai allergologian erikoislääkärillä? *Have you consulted a specialist in lung medicine or allergology because of your breathing problems or cough or phlegm?* ei *no;* kyllä *yes*

vastaa kysymykseen 108 vain jos vastasit **kyllä** kysymykseen 107 *If you answered YES to question 107, please answer question 108:*

108. Onko allergian selvittämiseksi tehty ihopistokoe? (= ns. PRICK-testi) *Was a skin test performed (= so-called skin-prick test)?* ei *no;* kyllä *yes*

vastaa kysymykseen 109 vain jos vastasit **kyllä** kysymykseen 108 *If you answered YES to question 108, please answer question 109:*

109. Löytyikö PRICK-testissä allergisuutta? *Was the skin-prick test positive?* ei *no;* kyllä *yes*

110. Oletko koskaan joutunut päivystysluonteisesti hoitoon hengitysvaivojen vuoksi? *Have you ever been to an emergency ward because of breathing troubles?* ei *no;* kyllä *yes*

111. Oletko ollut sairaalahoidossa hengitysongelmien vuoksi? *Have you been treated as an inpatient in a hospital because of breathing problems?* ei *no;* kyllä *yes*

112. Oletko tyytyväinen lääkäripalvelujen saatavuuteen kun olet tarvinnut apua hengitysvaivoihisi? *Were you satisfied with the availability of medical care when needed for your breathing problems?* ei *no;* kyllä *yes;* en ole tarvinnut *not applicable*

113. Koetko, että hengenahdistus tai hengästyneisyys tai hengityksen vinkuna häiritsee päivittäistä elämääsi? *In your experience, does breathlessness or shortness of breath or wheezing affect your daily life?* ei *no;* silloin tällöin *now and then;* usein *often*

114. Koetko että yskä tai limannousu häiritsevät päivittäistä elämääsi? *In your experience, does cough or phlegm affect your daily life?* ei *no;* silloin tällöin *now and then;* usein *often*

115. Kuinka paljon mielestäsi hengitysoireesi haittaavat jokapäiväistä elämääsi? *In your opinion, how much do your respiratory symptoms affect your daily life?* ei lainkaan

not at all; vähäisesti *slightly;* ajoittain kohtalaisen runsaasti *sometimes moderately;* kohtalaisen runsaasti *moderately;* runsaasti *severely*

Muut kuin ahtauttavat keuhkosairaudet *Lung diseases other than obstructive lung diseases*

116. Onko Sinulla muuta keuhko- tai hengityselinsairautta kuin astma, krooninen bronkiitti tai emfyseema? *Do you have or have you had any other lung or airway disease other than asthma, chronic bronchitis, or emphysema?* ei *no;* kyllä *yes*

vastaa kysymykseen 117 vain jos vastasit **kyllä** kysymykseen 116 *If you answered YES to question 116, please answer question 117:*

117. Mitä muuta sairautta? *Specify:*___

118. Onko Sinulla ollut tuberkuloosi (TBC)? *Have you had tuberculosis (TB)?* ei *no;* kyllä keuhkotbc *yes, lung tuberculosis*; kyllä, muu tbc *yes, other tuberculosis*

119. Onko Sinulla tai onko Sinulla ollut heinänuhaa tai allergista nuhaa tai silmätulehdusta? *Do you have or have you had hay fever or allergic rhinitis or conjunctivitis?* ei *no;*kyllä *yes*

120. Vaivaako Sinua usein tukkoinen tai vuotava nenä? *Are you often bothered by a stuffy or runny nose?* ei *no;* kyllä *yes*

121. Onko Sinulla tai onko ollut nenäpolyyppeja? *Do you have or have you had nose polyps?* ei *no;* kyllä *yes*

122. Onko Sinulla tai onko ollut (edes lapsuudessa) pitkäaikaista ihottumaa? *Do you have or have you had (even as a child) eczema?* ei *no;* kyllä *yes*

123. Onko Sinulla tai onko ollut mitään tässä mainittua sydänvikaa tai sydänsairautta? *Do you have or have you had heart disease or heart problems?* ei mitään *no;* angina pectoris *yes, angina;* sydäninfarkti *yes, heart attack;* sydämen vajaatoiminta *yes, heart insufficiency;* rytmihäiriöitä *yes, heart dysrhythmia*; muu sydänvika *yes, other cardiopathy*

124. Käytätkö nykyisin sydänlääkitystä? *Do you currently use cardiac medication?* ei *no;* yksi lääke *yes, one drug;* kaksi lääkettä *yes, two drugs;* kolme lääkettä *yes, three drugs*; neljä lääkettä tai enemmän *yes, four drugs or more*

125. Onko Sinulla tai onko ollut verenpainetautia? *Do you have or have you had hypertension?*ei no; kyllä *yes*

126 Onko Sinulla nykyään käytössä verenpainelääkitystä? *Do you currently use any medication for hypertension?* ei *no;* kyllä *yes*

126a. Käytätkö β-salpaajalääkettä? *Do you currently use β-blocker medication?* ei *no;* kyllä *yes*

127. Onko Sinulla jotain muuta kroonista sairautta, jota ei ole edellä mainittu? *Do you have any other disease not already mentioned?*ei *no;* kyllä *yes*

127a. Käytätkö sen vuoksi lääkitystä? *Do you use regular medication for this condition?* ei *no;* kyllä *yes* (vastaa tähän jos vastasit **kyllä** kysymykseen 127 *answer this question only if you answered YES to question 127*)

Lapsuusaika *Childhood*

128. Tupakoiko jompikumpi vanhemmistasi tai joku samassa taloudessa asuvista kotonasi lapsuutesi aikana? *Did either of your parents or someone in your home or close environment smoke while you were growing up?* ei *no;* äiti *mother;* isä *father;* muu *other person*

129. Oliko teillä kotona tai lähiympäristössä karvaisia lemmikkieläimiä kun olit alle viiden vuoden ikäinen? *Did you have furred animals in your home or close environment before you were five years old?* ei *no;* kyllä *yes*

130. Onko Sinulla ollut jokin vakava hengitystieinfektio kun olit alle viiden vuoden ikäinen, esim. hinkuyskä tai keuhkokuume tai kurkunpääntulehdus? *Have you had any severe respiratory infection before the age of five years, e.g. whooping cough, pneumonia, or croup?* ei *no*; kyllä *yes*; en tiedä *don't know*

131. Nukuitko yleensä samassa makuuhuoneessa muiden lasten kanssa alle viiden vuoden ikäisenä? *Did you regularly share your bedroom with any other children before the age of five years?* ei *no;* kyllä *yes;* en tiedä *don't know*

132. Kuinka monta sisarusta Sinulla on/oli? *How many sisters or brothers do you have or did you have?*____

133. Kuinka monta vanhempaa sisarusta Sinulla on/oli? *How many older sisters or brothers do you have or did you have?*___

134. Olitko päivähoidossa leikkikoulussa tai lastentarhassa muiden lasten kanssa kun olit alle viiden vuoden ikäinen? *Did you go to a playschool or nursery with older children before the age of five years?* ei *no;* kyllä *yes;* en tiedä *don't know*

135. Asuitko viiden ensimmäisen ikävuotesi aikana? *During your first five years of life, where did you live?* kerrostalohuoneistossa *apartment*; omakoti-, rivi tai paritalossa *house*

136. Missä asuit viiden ensimmäisen elinvuotesi aikana? *During your first five years of life, did you live in the ?* maaseudulla *countryside;* taajamassa *suburb;* kaupungissa *town/city*

Ammatti/työ *Occupation/work*

137. Mikä on nykyinen työtilanteesi? *What is your current working status?* a) opiskelijana *studying;* b) työssä *working;* c) työnhakijana *job-seeker;* d) varhaiseläkkeellä *early retirement pension;* e) sairauseläkkeellä *disability pension;* f) vanhuuseläkkeellä *retirement pension/old age pension;* g) määräaikaiseläkkeellä/sairauspäivärahalla (>6kk) *temporary sick leave (>6 months);* h) kotityössä *housewife/-husband;* i) muu *other;* j) asepalveluksessa *military service;* k) ei tietoa *no information*; l)

työttömyyseläkkeellä *unemployment pension;* m) osa-aikaeläkkeellä *part-time pension*

138. Mikä on nykyinen tai viimeisin työsi? *Which is your current or last profession?*___ NYK, SEI

139. Onko Sinulla ollut muuta työtä, joka on kestänyt yli viisi vuotta? *Have you had any other profession lasting more than five years?* ei *no;* kyllä *yes*

vastaa kysymykseen 140 vain jos vastasit **kyllä** kysymykseen 139 *If you answered YES to question 139, please answer question 140:*

140. Mikä työ/Mitä töitä? *What profession(s)?*___ NYK SEI

141. Kuinka monta vuotta olet asunut nykyisessä asuinkunnassasi? *How many years have you been living in your current municipality?* ___ vuotta *years*

142. Kuinka monta vuotta olet asunut nykyisessä asunnossasi? *How many years have you been living in your current place of residence?*___ vuotta *years*

Tupakan käyttö *Smoking and nicotine use*

143. Oletko *Are you a* … ei-koskaan polttanut *never-smoker;* ei-tupakoitsija *nonsmoker;* entinen tupakoitsija *ex-smoker;* nykyinen tupakoitsija *current smoker*

144. Oletko koskaan tupakoinut yhtä vuotta? *Have you ever smoked for one year?* ei *no;* kyllä *yes*

(keskimäärin vähintään yksi savuke päivässä tai ainakin yksi sikari viikossa tai vähintään 30 grammaa piipputupakkaa kuukaudessa – yhteensä yhden vuoden ajan *on average, one or more cigarettes a day or one or more cigars a week or 30 gr or more of tobacco a month for one year)*

145. Kuinka vanha olit kun aloit tupakoida? *How old were you when you started to smoke?* ___ vuotias *years*

146. Altistutko tai oletko altistunut tupakansavulle kotiympäristössäsi? *Are you or have you been exposed to tobacco smoke in your home environment?* ei *no;* kyllä, aiemmin, ei enää *yes, earlier, not now;* kyllä, vieläkin *yes, even now*

147. Altistutko tai oletko altistunut tupakansavulle työympäristössäsi? *Are you or have you been exposed to tobacco smoke in your working environment?* ei *no;* kyllä, aiemmin, ei enää *yes, earlier, not now;* kyllä, vieläkin *yes, even now*

148. Altistutko yleensä toisten ihmisten tupakoinnille? *Are you often exposed to tobacco smoking of other people?* ei *no;* kyllä *yes*

149. Oliko äitisi tupakoitsija raskausaikana kun hän odotti Sinua? *Was your mother a smoker when she was pregnant with you?* ei *no;* kyllä *yes;* en tiedä *don't know*

150. Polttiko äitisi säännöllisesti Sinun varhaisen lapsuutesi aikana? *Did your mother smoke regularly during your early childhood?* ei *no;* kyllä *yes;* en tiedä *don't know*

151. Polttiko isäsi säännöllisesti Sinun varhaisen lapsuutesi aikana? *Did your father smoke regularly during your early childhood?* ei *no;* kyllä *yes;* en tiedä *don't know*

Entiset tupakoitsijat *Previous smokers*

152. Kuinka vanha olit kun lopetit tupakoinnin? *How old were you when you stopped smoking?* ___ vuotias *years*

153. Kuinka monta tupakkaa poltit keskimäärin päivässä ennen kuin lopetit? *How many cigarettes per day did you smoke on average before you stopped smoking?* en yhtään *none*; 1-4; 5-14; 15-24; ≥25

154. Kuinka paljon piipputupakkaa poltit keskimäärin viikossa ennen kuin lopetit? *How much pipe tobacco per week did you smoke on average before you stopped smoking?* en yhtään *none*; <50 g; 50-100 g; >100 g

Nykyiset tupakoitsijat *Current smokers*

155. Kuinka monta savuketta poltat keskimäärin päivässä? *How many cigarettes do you smoke on average per day?* en polta *don't smoke;* 0-4; 5-14; 15-24; ≥25

156. Kuinka monta savuketta olet polttanut keskimäärin päivässä siitä alkaen kun aloitit tupakoinnin? *How many cigarettes per day have you smoked on average since you started smoking?*en polta *don't smoke*; 0-4; 5-14; 15-24; ≥25

157. Jos poltat sikareja, kuinka monta poltat nykyisin keskimäärin päivässä? *If you are a cigar-smoker, how many do you smoke on average per day?* en polta *don't smoke*; 0-1; 2-4; ≥5

158. Kuinka monta sikaria olet polttanut keskimäärin päivässä siitä lähtien kun aloitit? *How many cigars per day have you smoked on average since you started smoking?* en polta *don't smoke*; 0-1; 2-4; ≥5

159. Kuinka paljon piipputupakkaa olet käyttänyt keskimäärin viikossa siitä alkaen kun aloitit? *If you use pipe tobacco, how much do you use on average per week?* en käytä *don't use*; <50 g; 50-100 g; >100 g

160. Kuinka paljon piipputupakkaa olet käyttänyt keskimäärin viikossa siitä alkaen kun aloitit? *How much pipe tobacco per week have you used on average since you started smoking?* en käytä *don't use*; <50 g; 50-100 g; >100 g

161. Oletko yrittänyt lopettaa tupakointia? *Have you tried to quit smoking?* ei *no;* kyllä *yes*

162. Oletko ollut välillä polttamatta? *Have you had any smoke-free periods?* ei, tai yhteensä alle 1 vuoden ajan *no, or altogether for less than 1 year*; kyllä *yes,* yhteensä *altogether for* ____ vuotta *years*