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JANA KIVASTIK

TARTU UNIVERSITY
PRESS

Department of Physiology, University of Tartu, Tartu, Estonia

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Opponent: Professor Esko Länsimies, M.D., Ph.D. Department of Clinical Physiology and Nuclear Medicine, University of Kuopio, Finland

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CONTENTS

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original publications and on some unpublished data:

I J. Kivastik, P.-H. Kingisepp Lung function in Estonian children: effect of sitting height. *Clin Physiol* 1995; 15: 287–296.

II J. Kivastik, P.-H. Kingisepp Differences in lung function and chest dimensions in school-age girls and boys. *Clin Physiol* 1997; 17: 149–157.

III J. Kivastik, P.-H. Kingisepp Flow-volume loop parameters in healthy children and in children with respiratory symptoms. *Eesti Arst* 1999; 4: 291–294 (in Estonian).

IV J. Kivastik Review: Paediatric reference values for spirometry. *Clin Physiol* 1998; 18: 489–497.

ABBREVIATIONS

A	–	age,
ATS	–	American Thoracic Society,
BiacrD	–	biacromial diameter,
ERS	–	European Respiratory Society,
FEF_{25}, FEF_{50}, FEF_{75}	–	forced expiratory flows, when 25%, 50% and 75% of forced vital capacity has been exhaled,
FEF_{25-75} (or **MMEF**)	–	mean forced expiratory flow during the middle half of the forced vital capacity (or maximal mid-expiratory flow),
FEV_1	–	forced expiratory volume in one second,
FVC	–	forced vital capacity,
H	–	standing height,
PEF	–	peak expiratory flow,
R^2	–	coefficient of determination,
RSD	–	residual standard deviation,
SH	–	sitting height,
SR	–	standardised residual,
ThD	–	thoracic depth,
ThW	–	thoracic width,
TLC	–	total lung capacity,
VC	–	vital capacity.

1. INTRODUCTION

"When you can't breathe, nothing else matters"
(A trademark of the American Lung Association)

Asthma is a common disease in all parts of the world, and establishing the diagnosis is as important to clinical practitioners as it is to epidemiologists. Asthma has always been a clinical diagnosis based on a characteristic pattern of symptoms. The last decade, however, has seen increasing recognition of the importance of objective pulmonary function measurements in the clinical management of adult and paediatric asthma (Klein *et al.*, 1995; Taylor, 1997; National Asthma Education and Prevention Program, 1997). In practical terms, the diagnosis of asthma ought to rely on a careful history followed by spirometry in all cases.

Pulmonary function tests are useful for a number of reasons. They enable us to objectively follow the course of respiratory disease processes and to document the impact of both acute and long-term therapeutic interventions on those processes; to monitor the effects of environmental and occupational exposures and to assess the general condition of the child (Quanjer *et al.*, 1989; Castile, 1998).

The interpretation of results of lung function tests usually relies on comparison with reference or predicted values derived from a "normal" population. For physiologists, "normal" is the most representative of its class and reveals the smallest deviations from the average (Polgar, 1990). In normal children and adolescents the increase of height, as they grow older, is expected to go along with the corresponding development of pulmonary function. That is the reason why the age and height variables are considered good predictors of pulmonary function.

Several sets of reference values have been published over the last decades and "normality" for a given age and height varies considerably across these data. Furthermore, as for other anthropometric measures, such as height, birth cohort effects have been described — that is, mean values within each age group increased over time. Cohort effects should be considered a major argument for updating reference values on a regular basis; otherwise normal values gradually lose their sensitivity in the detection of abnormal conditions among younger cohorts.

2. REVIEW OF LITERATURE

2.1. History of lung function measurements

The need for fresh air was recognised in the second century by Galen who believed it reacted with the blood in the left heart and arteries to produce the "vital spirit". Harvey (1578–1657) demonstrated the circulation of the blood through the lung and Malpighi (1628–1694) showed the proximity of the capillaries to the smallest air spaces, which paved the way for a better understanding of lung function (Cotes, 1993).

The measurement of the air volume, which a human can inhale or exhale. was put on a quantitative basis two hundred years later in a report to the Royal Medical and Chirurgical Society. John Hutchinson, a London surgeon, had designed a spirometer for his research, and one of the outcome measurements he used was the "vital capacity" as "the greatest voluntary expiration following the deepest inspiration" (Hutchinson, 1846). In spirometer the movement of air to or from the lung causes changes in the position of a carefully balanced cylindrical bell, which leads to the recording of the volume changes on a volume-calibrated moving chart. Hutchinson studied more than two thousand men and showed that the vital capacity (VC) is related to the height, the VC in adults decreases with age and is reduced by excess weight and by lung disease. The first studies of VC in normal children were conducted by Emerson and Green in 1921, and by Stewart in 1922 (Dickman *et al.,* 1971).

It became apparent that vital capacity measurements did not fully evaluate ventilatory function. Early attempts to study dynamic aspects of ventilation failed mainly because the available tools were not sufficiently sensitive to follow instantaneous respiratory movements. A more accurate evaluation of the dynamic behaviour of the respiratory system became possible only after the description of the pneumotachograph (Fleisch, 1925). In 1933 Hermannsen was the first to record the subject's ability to hyperventilate maximally over a short time interval. After his description, which has remained a landmark in the development of clinical respiratory physiology, several investigators started to relate the sensation of dyspnoea to the maximum breathing capacity (Yernault, 1997).

French scientists tried to find a substitute for the maximum breathing capacity, which they disliked because of the following reasons: the directly measured maximal ventilation is tiring and cannot be repeated more than three to five times during the same session, it is difficult to measure correctly, and it needs a certain degree of training. The use of the proportion of the vital capacity which could be expired in one second ("*capacité pulmonaire utilisable ą l'effort*", the "pulmonary capacity usable on exercise") as a guide to airways obstruction was introduced by Tiffeneau in 1947. Despite the brilliant observations, the contri-

bution of French scientists remained ignored for a time by other countries. Only in 1957 the British Thoracic Society adopted recommendations concerning the terminology of the measurement of ventilatory capacity. The term "timed VC" was replaced by the expression "forced expiratory volume over a stated interval of time" and hence FEV_1 (Yernault, 1997).

In 1955 Fowler and colleagues, using pneumotachograms, provided evidence that the acceleration of the flow rate during the first several tenths of a second was so high that an accurate recording of this portion of the trace with a spirometer was considered uncertain. Therefore, they advocated measurement of the average flow over the middle of a rapid maximal expiration — this is how the maximal mid-expiratory flow (MMEF or FEF_{25-75}) was born (Yernault, 1997). The replotting of events during a forced expiration as flow against volume (Hyatt *et al.*, 1958), instead of volume against time, resulted in the flow-volume curve (Figure 1).

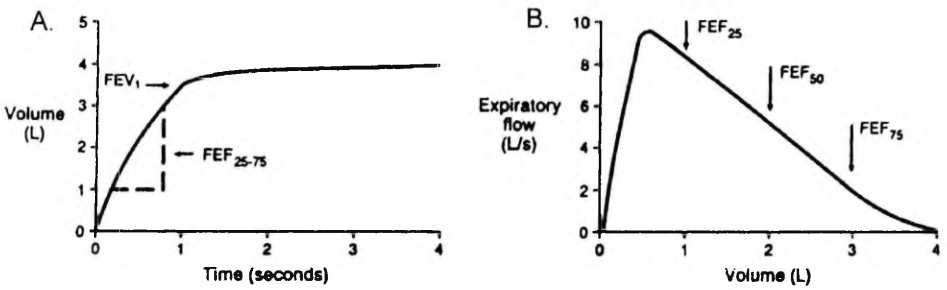


Figure 1. Two possibilities to record forced expiration. A. Volume recorded as a function of time, the spirogram. FEV_1, forced expiratory volume in 1 second. FEF_{25-75}, mean forced expiratory flow during the middle 50% of the forced vital capacity (FVC). B. Flow recorded as a function of volume, the flow-volume curve. FEF_{25}, FEF_{50}, FEF_{75}, forced expiratory flows when 25, 50 or 75% of FVC has been exhaled. (From Hyatt *et al., Interpretation of pulmonary function tests: a practical guide.* Philadelphia, Lippincott-Raven Publ. 1997).

The pulmonary function testing has witnessed many advances over the last three decades. The majority of these advances involve automatization of routine lung function measurements. The marketing of low-cost commercial spirometers and knowledge that spirometry is more sensitive than the clinical assessment of flow abnormalities has made the technology for these measurements widely available. The diffusing capacity test and body plethysmography have also become routine tests in lung function laboratories.

There are also many new techniques that are applicable primarily in the research setting. If the standard reporting procedures are firmly established, if large population studies are completed showing the range of normal and the

patterns of abnormality with disease — maybe then new methods like the use of the negative expiratory pressure technique to detect expiratory flow limitation, the forced oscillation technique to assess airway resistance, or the use of expired nitric oxide and carbon monoxide in the assessment of airway inflammation will be available for wider clinical application (Johnson *et al.*, 1999).

In Estonia, pulmonary function studies began in the years 1926–1932, when Alfred Fleish was a professor of physiology at the University of Tartu and used his pneumotachograph for research. Measurements of lung volumes and capacities by a water sealed spirograph in children resulted in presenting normal values (Vasar and Laidre, 1974; Silla and Teoste, 1989). No extensive studies registering the flow-volume loop in children have been carried out in Estonia.

2.2. Lung function from infancy through adulthood

2.2.1. Lung development and growth

At birth, the lung begins the function for which it was primarily designed during the prenatal development — gas exchange. The discontinuity provoked by the removal of lung water and its replacement by air and by the onset of respiration is, however, more a functional rather than a structural character. Lung development is indeed a continuous process that begins around the 26th day of gestation and lasts into postnatal life (Thurlbeck, 1982; Burri, 1997). In theory, normal lung growth starts when lung development is completed, but there is evidently no way to delineate this transition. Therefore, lung development blends imperceptibly into growth, and the latter blends into ageing (Burri, 1997).

The lung appears around the 26th day of gestation as a ventral diverticulum of the foregut. The epithelial tubule divides rapidly and the tubular tree preforms, through growth and branching, all the conductive airways down to their last generations by the 16th or 17th week of gestation. Thereafter, all airways from the bronchus to the terminal bronchiole increase linearly in diameter. This continues after birth — airways increase in diameter and length by two to three times between birth and adulthood (Jeffery, 1995).

True alveoli do not begin to develop until about 28th to 34th weeks of gestation and increase rapidly in number, size, and complexity (Farrell, 1982; Fisher *et al.*, 1990; Burri, 1997). The exponential growth of alveolar numbers has been generally accepted, although large variations between the estimated numbers at birth and at the end of maturation still exist. This is probably partly so because of large individual differences. The number at term varies: about one-third to one-half of the adult number (Jeffery and Hislop, 1995), or 15–20% of the adult number (Langston *et al.*, 1984). The earlier idea of reaching a plateau in the number of alveoli at approximately 8 years of age (Dunnill, 1962) was chal-

lenged in favour of the concept of a slow but continuously increasing number through adolescence (Emery and Wilcock, 1966). Some authors have stated later that alveolization might be completed within 12–24 months and would not last longer, except at a very reduced pace (Thurlbeck, 1982; Zeltner and Burri, 1987). From the practical point of view, these concepts put regenerative and corrective adaptations to an injury sustained at different ages into a different light. Further growth in lung volume occurs by an increase in alveolar diameter, resulting in the doubling of lung volume between the ages of 8 and 25. It is generally thought that the number of alveoli in an adult is 300 million (Dunnill, 1962; Farrell, 1982), but the final number may depend upon body length and may vary from 212 million to as high as 605 million (Angus and Thurlbeck, 1972).

Changes in the dimensions and numbers of the components of the respiratory tract are associated with concomitant changes in pulmonary function, especially in lung volumes. When the infant or young child is compared with the adult, however, certain parameters of pulmonary function remain unchanged if they are related to a standard reference, such as height or body surface area (Table 1).

Table 1. Comparison of lung function in the newborn and adult*

	Newborn	Adult
Body weight, kg	3	70
Body surface area, m^2	0.21	1.70
Lung surface area, m^2	2.8	64–75
Lung surface area, m^2/kg	≈1	≈1
Tidal volume, ml	20	490
Tidal volume, ml/kg	7	7
Alveolar ventilation, ml/min	400	4200
Alveolar ventilation, ml/m^2/min	2.3	2.3

* From Fisher *et al.* Pulmonary function from infancy through adolescence. In: Scarpelli EM. *Pulmonary physiology: fetus, newborn, child and adolescent.* 2nd ed. Philadelphia, Lea & Febiger, 1990; 421–445.

The description of lung function throughout life is not easy to complete. Because of difficulties in studying lung function in infants and young children (will be discussed in section 2.4.), it is possible that many patterns of physiologic development from the neonatal to school age will have to be established by forward or backward extrapolation of relatively few reliable data (Polgar and Weng, 1979). The recent development of measuring techniques for infants and small children and for older people will probably allow the completion of stud-

ies with the description of lung function changes from birth to senescence. So far several studies have focused on changes in pulmonary function from the preschool to the old ages, but the transitions between the early growth phase, maturation phase, young adult plateau, and the decline phase, have not been defined fully as yet (Polgar, 1990).

The data from subjects aged between 8 and 90 showed that FVC and FEV_1 increased up to the age of 20 in women and up to the age of 27 in men, and then started to decrease, two separate linear regression lines were derived for both genders (Knudson *et al.,* 1976). The other group described the development of spirometric variables by a number of linear models for several age intervals with intervening "breakpoints" (Figure 2). In their data FVC and FEV_1 of males increased slowly with age until the age of 12, and then increased rapidly until the age of 17 (FEV_1) or 18 (FVC), and continued to grow slowly until the onset of the decline at age 26. In females, the increased growth rate occurred earlier (age 10–16 years) and was less pronounced than in males. After that, FEV_1 continued to grow slowly until age 27 years, whereas FVC started to decline at age 17 years (Sherill *et al.,* 1992).

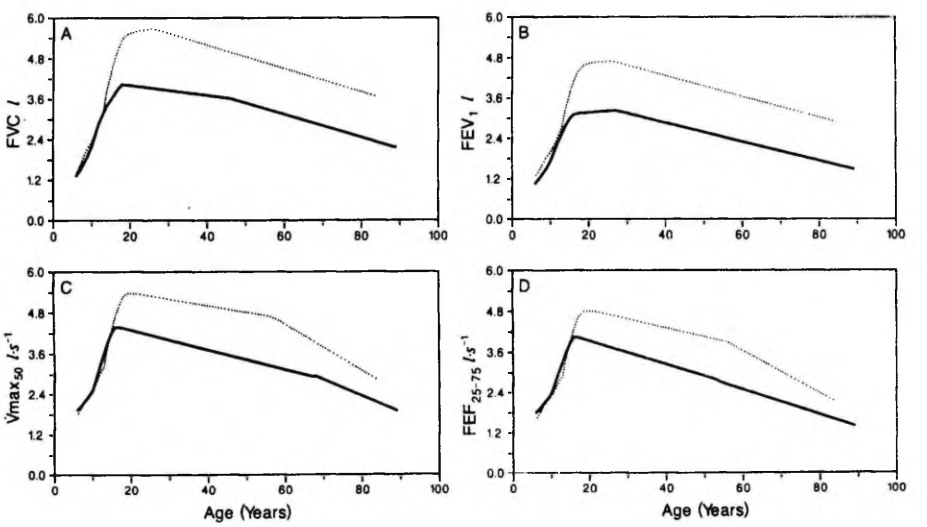


Figure 2. Predicted lung function curves for healthy subjects of an average height. Females are plotted using solid lines, males with dotted lines. Abbreviations as in Figure 1. $\dot{V}max_{50}$ is the same as FEF_{50} (From Sherrill *et al.* Continuous longitudinal regression equations for pulmonary function measures. *Eur Respir J* 1992; 5: 452–462).

One research team studied subjects aged 8–80 years and used piecewise polynomials with a single change point (20 years for males and 18 years for females) in the reference equations (Hankinson *et al.*, 1999). Others have found

that growth of the airways and increase of the size of the alveoli continues in females until the height ceases to increase with age, but continues at a slower pace in males till the mid 20s, attributed to the muscularity effect (Schrader *et al.*, 1988; Hibbert *et al.*, 1995).

The literature suggests that using only two equations, one for children and young adults and the other for older subjects, cannot adequately account for maturation as it interacts with growth and ignores an apparent period in the late teens, 20s, and early 30s in which pulmonary function appears relatively stable (Burrows *et al.*, 1983). This is in agreement with the paper by Kristufek *et al.* (1987) assuming that process of growth, maturation, and ageing are uninterrupted, and therefore they selected a single equation to cover the age range 6–81 years. In their data VC and FEV_1 increased up to 18 years in females and up to 21 years in males, after which they remained approximately constant up to 33 and 36 years respectively, then a physiological decline was observed.

2.2.2. Effects of gender and race

Gender differences in anatomic lung growth have been described well enough. The lungs of boys aged 6 weeks to 14 years were larger than those of girls of the same height. This was explained by more (but not larger) alveoli present in male lungs, and these differences were attributed to male sex hormones (Thurlbeck, 1982).

Several authors have reported increased flows and reduced resistance in the girls suggesting that the airway function is diminished in boys compared with girls during both infancy and childhood (Zapletal *et al.*, 1987; Rona and Chinn, 1993; Hibbert *et al.*, 1995; Merkus *et al.*, 1996; Stocks *et al.*, 1997; Becklake and Kauffmann, 1999). This can mainly be explained by differences in airway size, which implies that for the same lung volume, girls have larger airways than boys do. This may contribute to the higher prevalence of asthma and wheezing reported in boys compared with girls at all ages up to puberty (Weiss *et al.*, 1992; Gold *et al.*, 1994; Hibbert *et al.*, 1995).

To explain the marked variability of maximal expiratory flow rates between individuals with lungs of comparable volume, the term "dysanapsis" was proposed to describe what appeared to be this weak link between airway and lung size (Green *et al.*, 1974). This was attributed to disproportionate growth between the airways and the air spaces. A recent review of gender differences in lung function has stated that both in men and women, the growth of the lung parenchyma and its airways occurs independently, and that the configuration of the adult female lung is the result of proportional growth of its airways in relation to its parenchyma. However, the adult male lung is the result of dysanaptic growth — that is, growth of the airways has lagged behind in comparison with the lung parenchyma (Becklake and Kauffmann, 1999).

Men and women also differ as to the age when they reach the maximal values of lung function indices, as was described in section 2.2.1. Females appear to reach their maximal values earlier, at approximately age 16 to 18, whereas male lung volumes and flows usually continue to increase after the cessation of growth in height to age 25 or more. One possible reason is that muscle mass grows during the puberty, stimulated by androgens. Thus, muscle growth in males is much greater than in females, and it continues beyond puberty in males, reaching a maximum at around age 25, especially with training (Schrader *et al.,* 1988; Lebowitz and Sherrill, 1995; Merkus *et al.,* 1996).

Race has been consistently shown to be an important determinant of lung function. When compared with Caucasians, most other races usually show smaller lung volumes and lower forced expiratory flows (Neukirch *et al.,* 1988; Rahman *et al.*, 1990; Chinn and Rona, 1992; Jacobs *et al.,* 1992; Roizin *et al.,* 1993; Azizi and Henry, 1994; Connett *et al.,* 1994; Hankinson *et al.,* 1999). The reason for these differences is yet unclear. They may be related to the body proportions and in particular to a smaller ratio of sitting to standing height characteristic of the racial groups studied (Hsi *et al.*, 1983; Asher *et al.*, 1987; Connett *et al.*, 1994). Apart from discrepancies between races, also slight differences may exist between ethnic groups within the same race. There is abundant material of measurement on different groups of Caucasians living in various countries on various continents. However, as the confidence limits are too broad for any group, it is difficult to find any real differences between ethnic groups by comparing the measurements of different investigators. Ethnic differences in chest wall dimensions (Rahman *et al.*, 1990), environmental differences and socioeconomic factors, racial differences in lung growth and maturation, different heights and ages when pubertal changes start (Connett *et al.*, 1994), language and immigrant status (Polgar and Weng, 1979) — all these factors are also thought to be important in determining the lung function of ethnic groups.

2.2.3. Factors modifying lung development and growth

Lung development and growth may be influenced by several modulating factors, which can lead to an impaired lung function in one's later life. One concept that explains this association is "programming" — the permanent alterations of the structure and function of organs and tissues by factors during sensitive periods of rapid growth may change the function and development of specific diseases later in life. Factors implicated in "programming" of the respiratory system may be fetal nutrition, fetal exposure to maternal smoking during pregnancy, and exposure to environmental allergens or viral respiratory infections during infancy. Adverse influences during this period of growth may operate by diminishing airway or alveolar growth and hence the maximal lung and airway size attained, by increasing airway responsiveness to allergens, viruses and air

pollutants in later childhood or adult life, by impairing collagen and elastin development in the lung parenchyma with secondary effects on the airway function, or by some combination of all three. Finally, the age-related decline in respiratory function which commences in mid adult life may be more rapid or reach a critical threshold at an earlier age in those persons who did not achieve their maximal fetal and early childhood growth potential (Dezateux and Stocks, 1997).

Conflicting data have been reported on the effect of *intrauterine growth retardation* on lung volumes in children. One study reported that FVC was decreased after adjustment for the gestational age, parental smoking, and social factors (Rona *et al.*, 1993), others found that lung volumes were normal, but expiratory flow values were reduced in children of low birthweight (Chan *et al.*, 1989; Nikolajev *et al.*, 1998). Small sample sizes and exclusion of preterm infants and those with perinatal problems have precluded a detailed examination of hypotheses regarding fetal nutrition. Individualised birth centiles and improved methods for the assessment of intrauterine growth retardation are required if the extent of the latter is to be recognised and its effects assessed (Dezateux and Stocks, 1997).

Reduced forced expiratory flows have been identified in school-age children in whom pneumonia, bronchitis, and other *lower respiratory tract illnesses* have been documented prospectively (Pistelli *et al.*, 1992; Weiss *et al.*, 1992; Borsboom *et al.*, 1993; Rona and Chinn, 1993; Mostgaard *et al.*, 1997; Droste *et al.*, 1999). However, these data do not resolve the question of whether reduced expiratory flow precedes or follows the initial episode of illness in one's early childhood. The follow-up studies of infants in whom lung function tests were performed before any illness developed showed that the initial lung function was lower in infants who later developed lower respiratory tract illnesses, suggesting that a pre-existing developmental condition of the lung may be involved in the pathogenesis of these illnesses (Martinez *et al.*, 1988; Tager *et al.*, 1993; Dezateux *et al.*, 1999).

Exposure to many environmental and social influences during fetal and early postnatal life continues throughout later childhood and adult life and the potentially adverse effects of earlier exposures may be difficult to distinguish from the later ones (Dezateux and Stocks, 1997). *Passive smoking* would be a typical example.

Fetal exposure to maternal smoking during pregnancy has been clearly demonstrated to be associated with increased health problems in infants and older children, including increased rates of wheeze-associated lower respiratory illness and pneumonia (ATS. Cigarette smoking and health, 1996; Morgan and Martinez, 1998). Maternal smoking seems to modify lung development so that the infant will have a diminished lower airway function and, as a result, has an increased risk of developing wheezing upon a viral infection of the bronchial

tree (Dezateux and Stocks, 1997). The impact of maternal smoking on wheezing illness may diminish later in childhood. It could be explained by the fact that the growth of the airways makes geometry of the small airways less relevant in producing symptoms after the pre-school years. In other words, children with early, transient wheezing grow out of their predisposition to wheeze unless they have developed true asthma (Martinez *et al.,* 1995).

One difficulty in determining the timing of the impact of maternal smoking on the infant lung function has been that most measurements have been conducted in early infancy after a relevant period of postnatal, passive exposure to maternal smoking. This has made it difficult to know if the impact of maternal smoking was truly an *in utero* one or was it due to postnatal exposure. Several studies suggest that the negative impact is substantially prenatal in its timing (Martinez *et al.,* 1995; Morgan and Martinez, 1998; Gilliland *et al.*, 2000). A study of 108 preterm infants prior to discharging them from hospital (no postnatal exposure to tobacco smoke), provided confirmatory evidence that these *in utero* effects on lung function are evident prior to the middle of the third trimester; indeed, prior to any significant effect of smoking on the overall well-being as assessed by birthweight (Hoo *et al.*, 1998). Another research team carried out lung function tests within 72 hours of delivery and found that maternal smoking was associated with a significant reduction in birthweight and length, also with a reduction in static compliance in boys and conductance in girls, but no reduction in lung volume was observed when related to weight (Milner *et al.,* 1999). Adverse effects of antenatal maternal smoking represent a good reason to develop intervention strategies to prevent the acquisition of the smoking habit in adolescents and to aid pregnant women in effective smoking cessation as soon as possible in pregnancy (ATS. Cigarette smoking and health, 1996).

Postnatal exposure of children to smoke also seems to have some effect, as smoking by household members is associated with some increase in respiratory symptoms and decrease in forced expiratory flows (Burchfiel *et al.,* 1986; Rona and Chinn, 1993; Haby *et al.,* 1994; Cuijpers *et al.,* 1995; Cunningham *et al.,* 1996; Cook *et al.,* 1998; Burr *et al.,* 1999). Amongst older children, there may be found already some *active smoking*, which is associated with evidence of mild obstruction and slowed growth of lung function in non-asthmatic adolescents (Gold *et al.,* 1996; Burr *et al.,* 1999). Furthermore, the main effects of cigarette smoking on lung function will show in adulthood — current smokers have a lower FEV_1, a shortening of the plateau phase of the FEV_1 level that generally occurs between 20 and 30 years of age, and an accelerated decline in FEV_1 after that when compared to those who formerly or never smoked (Ulrik, 1999). All these associations show a dose-response relationship. A faster-than-expected annual fall in FEV_1 is the most useful finding in identifying smokers who are likely to develop severe pulmonary impairment (ATS. Cigarette smoking and health, 1996).

Studies of the *effects of training* on lung volumes have been performed since the early 1960s. Swimming has been studied most extensively and appears to be the only sport associated with a marked increase in lung volumes and maximal expiratory flows (Gaultier and Crapo, 1997). However, it is unclear whether the superior lung function found in swimmers is due to genetic influences or the result of training. Some research groups have found that the swimmers had the highest lung volumes already before the training had begun, on the other hand, the number of years of swimming and/or the earlier age at which training begins seems to have a significant bearing on the subsequent lung function (Doherty and Dimitriou, 1997). No study has measured alveolar distensibility in child swimmers, but normal distensibility was reported in young adult swimmers, suggesting that their large lungs could be achieved by an increase in alveolar number, rather than by enlarged alveoli (Armour *et al.*, 1993).

Diet is a relatively new area of interest in the field of pulmonary function. A possible reason seems to be that the most common fatal diseases of the respiratory system — lung cancer and chronic obstructive pulmonary disease — are so clearly related to tobacco smoking that other factors have caught little attention (Sridhar, 1995). Interest in vitamin C arose out of a belief that accelerated decline in pulmonary function in smokers might be due to deficiencies of proteolytic enzymes, this raised the possibility that antioxidant vitamins might be protective factors in the respiratory system (Britton *et al.*, 1995; Grievink *et al.*, 1998). Several studies have shown that frequent fresh fruit consumption is associated with higher lung function in both children (Cook *et al.*, 1997) and adults (Strachan *et al.*, 1991; Carey *et al.*, 1998; Grievink *et al.*, 1998; Tabak *et al.*, 1999; Butland *et al.*, 2000). There is also some evidence that the response of the airways to histamine correlates with the intake of sodium (Burney *et al.*, 1986) and that the dietary intake of magnesium has been shown to have an independent, beneficial influence on lung function and wheezing (Britton *et al.*, 1994).

2.3. Anthropometric parameters and lung function

The development of lung volumes and flows in children is highly correlated with an increase in *standing height*, probably the most widely used anthropometric index in paediatrics. Therefore, most of the published reference values of lung function are based on standing height.

During puberty (see the next section) and different races reveal different body proportions (ratio of sitting height to standing height). The use of *sitting height* (SH) as the indicator of trunk size in the prediction equations for lung parameters would be more exact because trunk development might be more closely

associated to lung development (Hsi *et al.*,1983; Schrader *et al.*, 1984; DeGroodt *et al.*, 1986; Asher *et al.*, 1987; Connett *et al.*, 1994).

In mammals, a proportional relationship has been established between body mass, lung volumes, and ventilatory function (Fisher *et al.*, 1990). On this basis *body mass* seems to be a plausible independent variable in the prediction equation, but this is fraught with hidden dangers. Abnormal situations like sickness or unhealthy eating habits can easily disturb the relation between body mass and lung function (DeGroodt *et al.*, 1986).

Body mass is the sum of its constituents, which include body muscle and fat. The muscle component can influence the maximal respiratory pressures and, hence, all indices of which inspiratory capacity forms a part, and peak expiratory flow. The fat component can influence the total lung capacity (TLC) and its subdivisions, the work of breathing and, in some circumstances, the airway calibre (Cotes, 1993). In cross-sectional studies an atypical body mass can reflect an excess or diminution in either fat or muscle, or both. The effects of these variables on lung function have opposite signs, hence they tend to cancel out each other. Therefore, the overall contribution of body mass to cross-sectional descriptions of ventilatory capacity is relatively small. Weight may also be abnormal for given heights in those with diseases for whom the reference equations are primarily developed (Lebowitz and Sherrill, 1995).

The effects of obesity on pulmonary function have been extensively investigated in adults, as body mass usually increases from youth to the middle age and then diminishes, some of the age-related decline in lung function could be due to the associated changes in body mass (Cotes, 1993; Quanjer *et al.*, 1993; Chinn *et al.*, 1996). Men tend to deposit fat centrally, whilst in women the deposition is often peripheral, the effect of weight gain on lung function has therefore been shown to be greater in men (Chen *et al.*, 1993). Fewer studies have addressed the problem of obesity in children. In children with 147–300% ideal body weight, reductions in diffusing capacity, ventilatory muscle endurance, expiratory reserve volume, FEV_1 and FEF_{25-75} have been found (Inselman *et al.*, 1993). Children showed similar sex differences of fat distribution patterns as adults — there was a positive correlation between lung function and body mass index in normal boys and girls, and in overweight girls, but a negative correlation in overweight boys (Fung *et al.*, 1990).

Standing height may be unobtainable in some patients referred for pulmonary function testing, owing to inability to stand or difficulties in measuring because of thoracic cage deformity. The most conventional method in these cases is the measurement of *arm span* and the subsequent estimation of height using a fixed arm span to height ratio or specific regression equations with arm span (Hibbert *et al.*, 1988; Parker *et al.*, 1996; Aggarwal *et al.*, 1999).

2.4. Problems in paediatric lung function testing

Lack of cooperation and coordination limits the application of routine procedures, such as peak flow measurement and spirometry in children below 5–6 years of age. However, a wide variety of methods has now been developed for use both in ventilated and spontaneously breathing infants. Equipment for assessing respiratory function in small children has to be specially modified to minimise dead space and resistance, to meet safety requirements, and to achieve satisfactory sensitivity and frequency response in the presence of rapid respiratory rates and relatively low signal / noise ratios. Application of these techniques requires further evaluation and standardisation, and nevertheless, the assessment of lung function in infants and young children will probably remain far more time-consuming than in adults (ATS / ERS statement. Respiratory mechanics in infants, 1993)

While considerable attention has been paid to the designing reliable pulmonary function tests in infants, children aged 3 to 5 years remain without reliable and reproducible objective measures of their pulmonary function (Kanengiser and Dozor, 1994; Castile, 1998). The children of that age can rarely generate spirometry test results that meet ATS and ERS acceptability standards set for adults, mainly because of the total time of forced exhalation being shorter than one second in smaller children. Producing FEV_1 remains an age-dependent function that may improve with training. Using $FEV_{0.5}$ or $FEV_{0.75}$ instead suggested by some researchers (Quanjer *et al.,* 1989; Cotes, 1993; Koillinen *et al.,* 1998) have not gained wide acceptance. Impedance measurements by the impulse oscillation technique and respiratory resistance measurements by the interrupter technique, both performed during normal tidal breathing and requiring only passive cooperation from the child, have been recommended for use in children 3 to 6 years old (Bisgaard and Klug, 1995).

Performing spirometry with small children needs a skilled technician who can explain and demonstrate the test and answer the questions, as this can significantly improve initial performance (Castile, 1998). Especially younger children are likely to need training in pre-test sessions in the performance of lung function tests, and doing so while the child is well can provide valuable cooperation and information later when he or she is ill (Mueller and Eigen, 1994; Studnicka *et al.,* 1998). It is often recommended to ask the child to "try to blow out the candles on a birthday cake and continue blowing until the technician tells you to stop" as a better explanation of forced exhalation (Castile, 1998). Some authors have reported that directly visualised flow-volume curves were helpful, but others have found them distracting to young children. Sometimes burning candles or changing lights on the screen have been recommended (Kanengiser and Dozor, 1994).

During recent years the potential effects of puberty on lung growth have been studied. The finding that no single linear or power curvilinear relationship

describes correctly the relationship between forced ventilatory manoeuvres and height throughout childhood was first noted by Dickman *et al.* (1971). Sudden changes both in standing height and lung function take place during the adolescent growth spurt, but the lung growth appears to lag behind the increase in standing height (DeGroodt *et al.*, 1986; Jaeger-Denavit and Alphonse, 1990; Wang *et al.*, 1993; Borsboom *et al.*, 1993 and 1996; Lebowitz and Sherrill, 1995). It is possible that the use of sitting height in predicting lung function in adolescents would be more appropriate than using standing height, because adolescent spurts in lung and trunk growth could be closer in time (Schrader *et al.*, 1984; DeGroodt *et al.*, 1986).

There appears also to be an element of "maturation" during adolescence, which is not totally explained by growth, and it is reflected in the high positive age effects for male subjects between the ages of 12 to 13 years through age 18 or 19. Similar high age effects are seen in girls starting at age 11 or 12 and ending at 15 to 16 years of age (Burrows *et al.*, 1983).

It is more likely that the true growth pattern before and after puberty is more accurately represented by multiple equations and discontinuous regression lines, but then care should be taken to avoid abrupt changes in the predicted values from one line to the other (Quanjer *et al.*, 1989). For example, correction factors for pubertal stages can be used (Rosenthal *et al.*, 1993).

2.5. Reference values for children

In a book published in 1971 Polgar and Promadhat attempted for the first time to present all the available information on pulmonary function testing in children. The anatomic and functional growth of the respiratory system was mentioned as the fundamental reason for the necessity to present data on growing children with a dynamic approach, as opposed to much simpler ways for adults. The collection of these data resulted in calculated "summary curves" for each variable, which could be used as average prediction standards (Polgar and Promadhat, 1971).

More recently, about 50 publications from 1950 to 1986 were compiled in one report (Quanjer *et al.*, 1989) and several numbers of papers offering reference values have published after that. Regardless of the efforts in the standardisation of pulmonary function testing in the last decade, there are still large discrepancies between different predictions, either for adults or for children. Factors contributing to these differences include sample selection, population demographics, inclusion of current or past smokers, inadequately documented potential for occupational exposure and variation in equipment, techniques, and computational methods (Glindmeyer *et al.*, 1995).

To define a "normal" population from which reference standards can be derived, it is useful to adopt the recommendations on defining a "healthy" child (Taussig *et al.*, 1980):

1) no present acute and no past or present chronic disease of the respiratory system,

2) no major respiratory disease such as congenital anomalies, destructive type of pneumonia, or thoracic surgery in the past medical history,

3) no systemic disease which directly or indirectly is known to influence the respiratory system and general state of health,

4) no more than incidental smoking experience,

5) no history of an upper respiratory tract infection during the previous three weeks.

Most authors of reference equations have used these or similar inclusion criteria for their reference population, some have fixed also the conditions of the surrounding environment (Kristufek *et al.*, 1987). One research group included all children, and suggested that, when the subjects had not had any major thoracic, neurological and systemic diseases, then further selection on the basis of reported respiratory symptoms seems to have only minor effects on lung volumes, but flows can be more affected (Pistelli *et al.*, 1992). Therefore, the minimal number, severity and nature of trivial respiratory disease episodes that would still allow an individual to be counted in reference population studies for a "normal" pattern of development have to be determined (Polgar, 1990).

There is no agreement what is the best model to represent the relationship between a lung function index and an independent variable. Apart from the power function and the exponential function, linear relationships can still be used in situations, where the age range was small or where the population had been artificially divided into narrow age ranges (Quanjer *et al.*, 1989).

Mostly, the age 18 is used as the cut-off between paediatric and adult predictive equations. One reason is that most reference equations for children are based on subjects with a maximal age of 16 to 18 years. The age range of 18–20 years tends to be studied quite seldom, they are excluded from studies both on adolescents and adults. Recommendations on reference values for ventilatory indices assume that there is no change in ventilatory function between the ages 18 to 25 years in cross-sectional studies, so that an age of 25 years can be used in the regression equations (Quanjer *et al.*, 1993). More studies are needed for this age group because young adults between 18 and 25 years of age could be a heterogeneous group in terms of pulmonary function growth. That is, some are still growing (have not reached the adult level), some are in the plateau phase and some have already begun to decline (Wang *et al.*, 1993).

There is a fundamental difference of philosophy over the application of reference equations — the European ideal is for a set of standardised equations, which would be applicable in all laboratories (Quanjer *et al.*, 1993), while the North American view is that each laboratory should choose equations from the literature which best suit to that laboratory (ATS. Lung function testing, 1991).

Reference values should be chosen from a study based on the same techniques that will be used and a healthy population similar to the population being tested in that particular laboratory. This requires examining the population characteristics, such as age range as well as gender and race composition. After a reference standard is chosen, a small number of healthy children should be tested, and the results should be compared with the chosen values from the literature (Quanjer *et al.*, 1989; Pattishall, 1990; Stocks and Quanjer, 1995). Unfortunately, it has been shown that reference values were often chosen because they were available in the pulmonary function test equipment software, rather than because they had been analysed and found to be the best for the local population (Ghio *et al.*, 1990; Pattishall, 1990).

3. AIMS OF THE PRESENT STUDY

The main objective of this cross-sectional study was to describe the relationships between anthropometric parameters and lung function in children throughout the school-age and to find out how the respiratory diseases and symptoms may change these relationships. Accordingly, the present study had the following specific aims:

1. To find out whether the differences in the performance of the lungs of boys and girls of the same height may be explained by differences in sitting height and thoracic size.

2. To investigate if an impaired lung function could be demonstrated in symptomatic schoolchildren, even in the absence of asthma diagnosis.

3. To compare lung function test results from healthy non-smoking schoolchildren with different reference values from the literature.

4. To develop reference equations for dynamic spirometry for Estonian children and adolescents.

4. MATERIALS AND METHODS

4.1. Study area and subjects

Estonia is a country near the Baltic Sea, with an area of 45,226 km^2, and the overall population in 1992 was about 1.53 million. The ethnic composition in 1992 was as follows: Estonians approximately 60%, Russians 30%, and others 10%. There were 137,133 students in 553 Estonian-language primary or secondary schools in the academic year 1992/93 (Ministry of Education).

The cross-sectional study was carried out at eight different schools in Estonia from September 1992 through to April 1995. The schools were chosen from the two biggest towns in Estonia (Tallinn with a population of 471,600 and Tartu — 113,400 inhabitants according to "Estonia. A Reference Book, 1993") and from one county in Northern Estonia (Loo and Saku Secondary Schools in Harju county) and one in Southern Estonia (Antsla Secondary School in Võru county).

In each selected school, random sampling of classes was used and all children who were at school on the day of examination were offered to participate. 1,469 children received questionnaires for their parents.

The study was approved by the Ethics Committee of the University of Tartu.

4.2. Questionnaires

Each child received a questionnaire concerning respiratory symptoms and diseases, a medical history, and drug intake. The questionnaire was completed at home with the aid of the child's parents. Table 2 lists the questions used in the present analysis.

Table 2. Questions on asthma or respiratory symptoms in the questionnaire (translated from Estonian)

Quest. No.	
Q1	Has a doctor ever diagnosed your child as having asthma?
Q2	Has your child had frequent cough (more than three months per year)?
Q3	Has your child had shortness of breath?
Q4	Has your child had wheezing or whistling in the chest?
Q5	Is your child currently receiving any treatment?

Smoking habits were asked directly from the child. The child was considered as a smoker, if he or she smoked more than one cigarette per week. The school-doctor's reports were also used to find specific diagnoses. The decimal age (accuracy to 0.1 years) was calculated from the actual date and date of birth.

4.3. Anthropometric measurements

Standing height and body weight were measured in all subjects without wearing shoes. *Standing height* was measured, as the child stood erect, with heels close together and the arms hanging naturally at the sides. The external auditory meatus and the lower border of the orbit were in a plane parallel with the floor.

Sitting height was measured while the child was in an upright sitting position, from the vertex of the head to the base of the seat. Both heights were measured using the metal anthropometer and read to the nearest millimetre.

Weight in light indoor clothing was measured using beam platform scales and recorded to the nearest 0.5 kg.

Thoracic dimensions were measured with a large metal sliding calliper with the subject standing, at the end of normal expiration. Thoracic width (ThW, transverse chest diameter) and depth (ThD, antero-posterior chest diameter) were measured at the level of the fourth rib, biacromial diameter (BiacrD) between acromions (the lateral ends of scapulas).

4.4. Lung function tests

The spiroanalyser Pneumoscreen II (Erich JAEGER GmbH, Hoechberg, Germany) was used to register the static and dynamic lung parameters. The measurement of flow was carried out by a pneumotachographical, open system, the volume was determined by electronical, digital integration. The analyser was calibrated with 1 litre syringe each time the unit was switched on.

During the test, three to four children were watching the performance of their classmate in order to reduce the need for instructions before the start of the test. The child was sitting during the test, a noseclip was used. After exhaling as deeply as possible each child was asked to breathe in to total lung capacity, subsequently blow out as hard and fast as possible to residual volume, and then similarly to breathe in back to TLC. The maximum envelope of at least three similar flow-volume loops was analysed. In this study, the following volumes and flows (corrected to body temperature and pressure, saturated with water vapour conditions) were examined:

* forced vital capacity — FVC,
* forced expiratory volume in one second — FEV_1,
* peak expiratory flow — PEF,
* forced expiratory flows when 25, 50 and 75% of FVC had been exhaled — FEF_{25}, FEF_{50} and FEF_{75},
* mean forced expiratory flow during the middle 50% of the FVC — FEF_{25-75}.

4.5. Statistical analysis

Descriptive data were treated by univariate analysis. When dividing material into the age groups, children in the age range from 5.0 to 5.9 years were included in age group 5 and so on. When dividing into height groups, the material was subdivided into 5-cm intervals (Table 3).

Table 3. Height groups

Group	Height interval in cm	Group	Height interval in cm	Group	Height interval in cm	Group	Height interval in cm
1	<120	5	135–139.9	9	155–159.9	13	175–179.9
2	120–124.9	6	140–144.9	10	160–164.9	14	180–184.9
3	125–129.9	7	145–149.9	11	165–169.9	15	185–189.9
4	130–134.9	8	150–154.9	12	170–174.9	16	>189.9

Inter-group differences for boys and girls were assessed for statistical significance using an unpaired Student's t-test. The chi-square test was used for testing differences in the prevalence of respiratory symptoms between boys and girls. The Pearson correlation and partial correlation analyses were used to assess relationships between lung function and anthropometric variables.

Stepwise multiple regression analysis was performed with lung function parameters as dependent variables and age, anthropometric parameters, respiratory symptoms, and illnesses as independent variables. Independent variables were included in the model if they were significant at $p<0.05$.

When comparing our data with reference values from the literature, standardised residuals (SR) were calculated for the children from each reference equation as follows:

$$SR = \frac{\text{observed value} - \text{predicted value}}{RSD}$$

where RSD is the residual standard deviation from the literature. As the equations with the weakest relation of standardised residuals to age were preferred, this relationship was tested for each equation in regression models with SR as the dependent and age as the independent variable.

Statistical significance was set at 0.05 level. The analyses were made using Statistica for Windows 5.0 (Statsoft Inc., USA) statistical software.

5. RESULTS

5.1. Main characteristics of the subjects

From 1,469 children who were offered to participate five children did not agree to make the tests and nine brought incompletely answered questionnaires. Finally, the data of 1,455 children aged 5–18 years were obtained and analysed. Geographical distribution of children studied is given in Table 4.

Table 4. Distribution of children

Region	Number of boys	Number of girls	Total
Northern Estonia			
Tallinn (2 schools)	144	226	370
Loo	40	47	87
Saku	104	80	184
Southern Estonia			
Tartu (3 schools)	335	311	646
Antsla	60	108	168
Total	683	772	1,455

The 1,455 study subjects were separated by gender, the number of children in age groups is given in Figures 3 and 4. The range of standing height was 109 to 185 cm in girls and 106 to195 cm in boys, and of weight 18 to 90 kg and 15 to 96 kg, respectively. Comparison of basic somatic characteristics with recent anthropometric tables (Grünberg *et al.*, 1998) showed that most of the children studied were within the normal growth curves for height and weight for Estonian children, except 12 boys above the 97th pecentile and 6 boys below the 3rd percentile for height, 9 boys above the 97th percentile and 9 boys below the 3rd percentile for weight, 14 girls above the 97th percentile and 14 girls below the 3rd percentile for height, 5 girls above the 97th percentile and 17 girls below the 3rd percentile for weight.

Figure 3. Distribution of boys (n=683) by age. Each column represents two age groups.

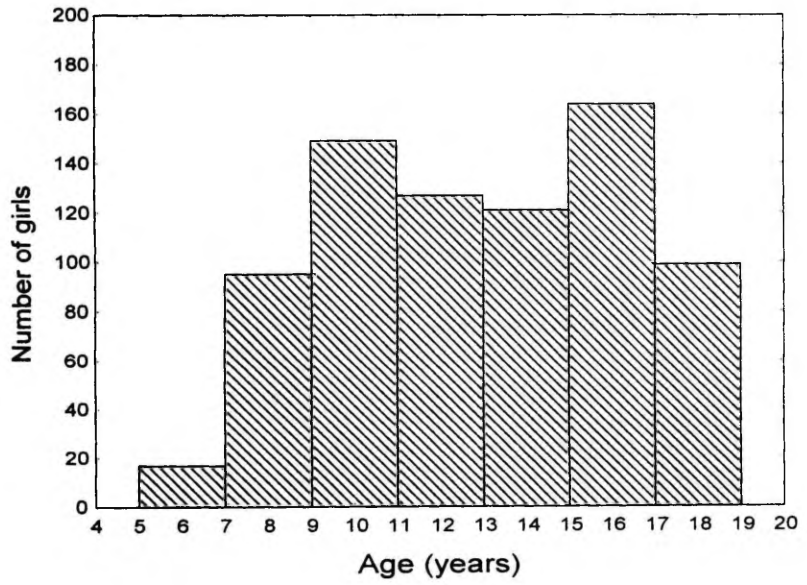


Figure 4. Distribution of girls (n=772) by age. Each column represents two age groups.

5.2. Gender differences in lung function and effects of pubertal growth spurt (I, II)

A nonlinear increase in spirometric indices with increasing height as well as age was found (Figures 5 and 6). Plots of lung function variables according to stature or age showed a heteroscedastic distribution, i.e. the scatter increased at increased height or age. Data of FEV_1 were available for 578 boys and 569 girls because the duration of forced expiration in some children, especially the younger ones, was less than one second.

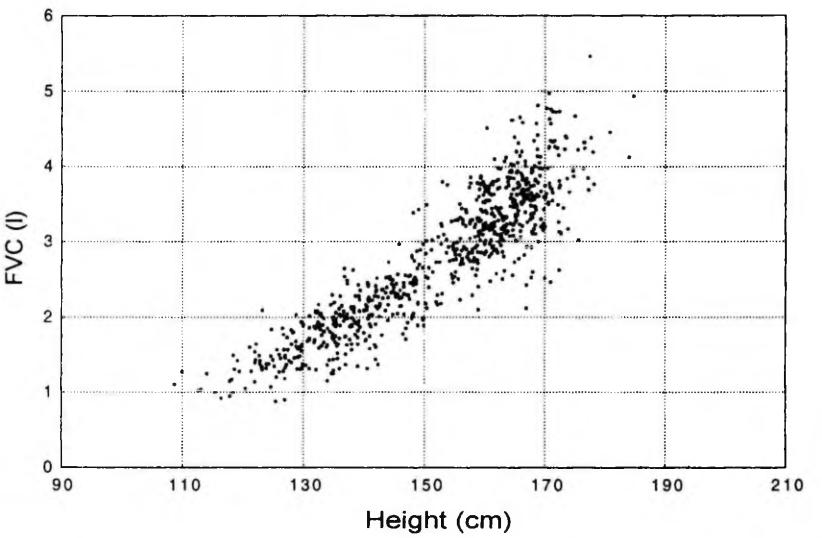


Figure 5. Forced vital capacity as a function of standing height in girls (n=772).

When plotting the mean values of standing height as a function of age, the growth spurt in standing height, an important indicator of the onset of puberty, was from 11 to 13 years in girls and from 13 to 15 years in boys (I). Most lung function parameters underwent also the biggest changes in these age periods, growth spurts were more pronounced in boys (Figure 7). Until the age of 11 years, boys had higher values for FVC and PEF, the differences for FEV_1, FEF_{50} and FEF_{75} were not significant. As the growth spurt began earlier in girls, at the ages of 12 and 13 years their flow values were higher than in boys of the same age. Teenage girls never had higher values of FVC and FEV_1. After the age of 14 years, FVC, FEV_1 and PEF were much higher in boys, while differences in values of FEF_{50} and FEF_{75} were not found.

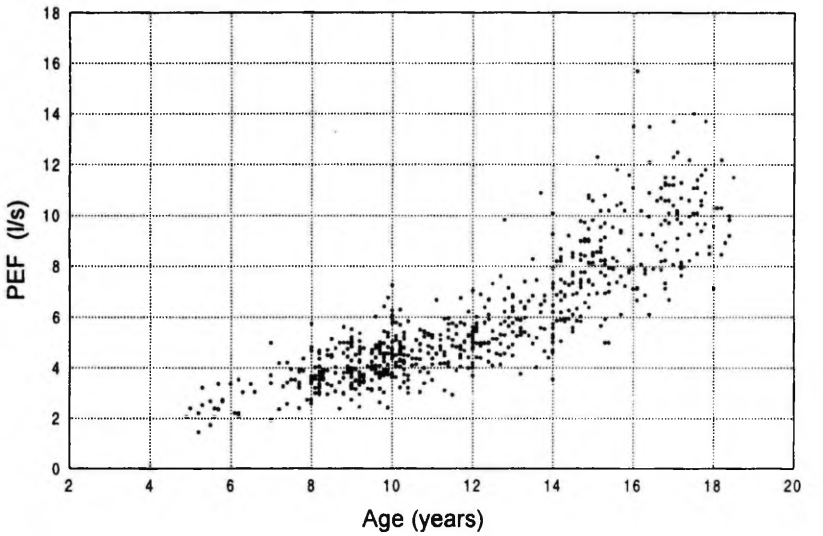


Figure 6. Peak expiratory flow as a function of age in boys (n=683).

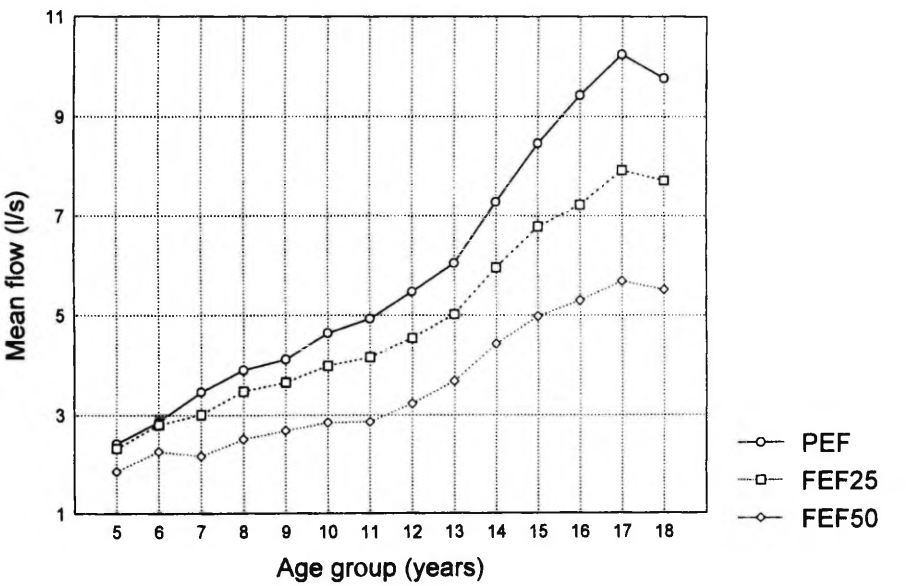


Figure 7. Mean values of flows by age groups in boys (n= 683).

As from the age of 14 years the boys were significantly taller than girls, the height should also be considered when comparing two sexes. Paper II presents mean values of different lung function variables as the function of height. There

was a sudden discontinuity in most values in girls between 150.0 and 159.9 cm and in boys between 160.0 and 169.9 cm. Among children less than 150.0 cm in height, boys had higher values for FVC, FEV_1, and PEF. The differences in FEF_{25}, FEF_{50}, and FEF_{75} were not significant. Between heights of 150.0 cm and 164.9 cm, when girls typically undergo pubertal growth spurt, most of the female spirometric variables were higher than the male ones (except for FVC, FEV_1, and PEF, where the differences were non-significant). After 165.0 cm, when boys typically are in their pubertal growth spurt, male FVC, FEV_1, and PEF results were significantly higher than the female values, the differences increasing with height. The differences in FEF_{25}, FEF_{50}, and FEF_{75} were again not significant.

To examine the effects of gender on the dimensions of expiratory flow relative to lung volume, we divided PEF, FEF_{50}, and FEF_{75} for each subject by his or her FVC (paper II). All volume-adjusted flows were greater in females than males, however, in PEF/FVC the difference was significant only in the height range 145.0–164.9 cm. FEF_{50}/FVC and FEF_{75}/FVC continued to be higher in girls until the late adolescence.

5.3. Relationship between the growth of anthropometric and lung function parameters (I, II)

The relationships between anthropometric parameters and lung function were analysed by using data from 1,187 children who had complete anthropometric measurements.

The mean data of sitting height and thoracic parameters by height groups showed quite similar patterns as in lung function variables. In children less than 150.0 cm males had mostly higher values for sitting height and all three thoracic size indices. Between heights of 150.0 and 164.9 cm SH and biacromial diameter were significantly greater in girls, the differences in chest width and depth were not significant. For individuals taller than 165.0 cm sitting height was yet greater in girls, but all thoracic dimensions were significantly higher in boys.

The correlation matrices shown in Table 5 indicate positive correlation of all anthropometric variables with lung function parameters in both sexes. In general, correlation coefficients were mostly higher for boys than for girls, higher for FVC and PEF than for flows from the later part of expiration, and higher for standing and sitting height than for thoracic dimensions.

It was possible to see if the observed close correlation between thoracic measures and lung function variables remain when adjusted for age and standing height by calculating the partial correlation coefficients separately for boys and for girls (Table 6). The partial correlation coefficients in girls were

often not different from zero, in boys partial correlation coefficients were systematically higher than in girls, and all, except those for FEF_{75}, were significant. A stronger association between sitting height and lung function parameters in boys was found also using stepwise regression analysis (paper I), where in boys sitting height was always selected as an independent variable into the regression model, and in girls standing height was selected instead.

Table 5. Correlation coefficients* between lung function and anthropometric parameters

	Boys (n=552)				Girls (n=635)			
	FVC	PEF	FEF_{50}	FEF_{75}	FVC	PEF	FEF_{50}	FEF_{75}
Age	0.89	0.85	0.78	0.67	0.85	0.80	0.71	0.60
Weight	0.92	0.85	0.80	0.68	0.87	0.77	0.71	0.58
Height	0.93	0.86	0.82	0.71	0.90	0.81	0.75	0.66
SH	0.94	0.87	0.82	0.72	0.88	0.80	0.75	0.66
BiacrD	0.91	0.84	0.78	0.67	0.86	0.77	0.71	0.59
ThW	0.90	0.82	0.75	0.63	0.84	0.72	0.65	0.50
ThD	0.79	0.70	0.69	0.58	0.69	0.59	0.56	0.46

* all significant at $p<0.05$

Table 6. Partial correlation coefficients (after controlling for age and standing height) between respiratory indices and anthropometric parameters

	Boys (n=552)				Girls (n=635)			
	FVC	PEF	FEF_{50}	FEF_{75}	FVC	PEF	FEF_{50}	FEF_{75}
SH	0.32*	0.25*	0.16*	0.16*	0.10*	0.02	0.09*	0.09*
BiacrD	0.30*	0.19*	0.09*	0.02	0.20*	0.08	0.07	-0.03
ThW	0.46*	0.20*	0.09*	-0.01	0.37*	0.11*	0.06	-0.09*
Th D	0.30*	0.09*	0.13*	0.06	0.31*	0.12*	0.14*	0.06

* $p<0.05$

5.4. Effects of respiratory symptoms and diseases (III)

A questionnaire included questions about physician-diagnosed asthma and respiratory symptoms. The effects of reported symptoms or illnesses on lung volumes and flows were assessed, by defining a dummy variable "respiratory problems" as positive when any of the symptoms or diseases had been reported. The study group included 110 boys (16.1%) and 120 girls (15.5%) with reported

respiratory symptoms or illnesses. Only 12 boys (1.76%) and eight girls (1.04%) reported a doctor-diagnosed asthma. These percentages did not differ between two genders (p=0.75 and p=0.24 respectively, χ^2-test).

Stepwise regression analyses of FVC, PEF, FEF_{25}, FEF_{50}, and FEF_{75} on age, standing height, and dummy variable "respiratory problems" were made separately for boys and girls. The selected independent variables and coefficients of determination are presented in Table 7. The reduced values were found in peak expiratory flow, FEF_{25} and FEF_{50} in symptomatic girls (Figure 8).

Table 7. Results of the stepwise regression analysis

Lung Parameter	Boys (n=683)		Girls (n=772)	
	Variables selected*	R^2	Variables selected	R^2
FVC	A, H	0.88	A, H	0.84
PEF	A, H	0.77	A, H, RP	0.72
FEF_{25}	A, H	0.73	A, H, RP	0.67
FEF_{50}	A, H	0.66	A, H, RP	0.62
FEF_{75}	H	0.48	A, H	0.46

* $p<0.05$

R^2, coefficient of determination; A, age (years); H, standing height (cm); RP, dummy variable "respiratory problems" (positive — 1, negative — 0).

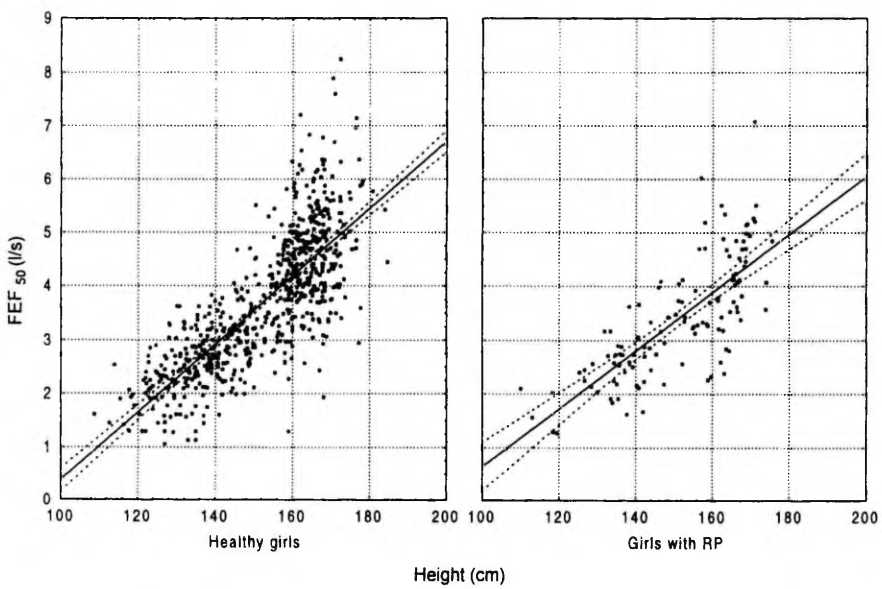


Figure 8. Measured values of FEF_{50} and linear regression lines in healthy girls (n=652) and in girls with respiratory problems (n=120). Dotted lines are 95% confidence limits for the regression line.

5.5. Comparison with reference values from the literature

Although in boys the differences between lung function in healthy children and children with respiratory problems were not significant, we decided to exclude all subjects who reported respiratory symptoms or illnesses from the comparison of healthy children's data with reference values from the literature.

Fifty-two boys and 14 girls reported smoking more than one cigarette per week (Table 8). The youngest boy who smoked was 12.5 years old and the girl — 15.5 years old. When comparing lung function in boys who were smokers and who were not, we often found mean values in height-groups to be bigger in smokers. The smokers were also older than non-smokers of the same height-group in most groups.

Table 8. Frequency table of smoking and respiratory problems

	Girls		Boys	
	Without respiratory problems	With respiratory problems	Without respiratory problems	With respiratory problems
Non-smokers	643	115	527	104
Smokers*	9	5	46	6
Total	652	120	573	110

* smokers were those who smoked more than one cigarette per week.

So, we included data from 1,170 healthy non-smoking children (643 girls and 527 boys) in the comparison with seven sets of reference equations from the literature (first authors: Haby, Koillinen, Kristufek, Nysom, Pistelli, Quanjer, and Schrader). All reference values were derived for subjects of Caucasian origin and were published in 1987–1998. Table 9 provides a brief description of the studied reference populations. Paper IV summarises the methods and regression models used by authors.

Koillinen, Kristufek, and Quanjer with colleagues considered the whole age range of children studied by us; two sets were for ages 7–11 years and two for ages 12–18 years. Two groups reported reference values only for forced vital capacity and forced expiratory volume in one sec, others included also predictions for forced expiratory flows. Three sets of equations included standing height as the only independent variable, others also considered age and/or weight in the predictions.

Table 9. Demographic characteristics of the reference populations of seven sets of equations from the literature

First author, a year of publication	Country of the study	Number of participants	Age (years)
Haby 1994	Australia	1,278	8–11
Koillinen 1998	Finland	199	5–17
Kristufek 1987	Czechoslovakia	1,024**	6–81
Nysom 1997	Denmark	176	13–18
Pistelli 1992	Italy	2,176	7–11
Quanjer 1995	The Netherlands, Austria, UK, Spain, Italy	5,861	6–21
Schrader 1989*	The Netherlands	142	12–18

* from Quanjer 1989
** 218 of them were 6–18 years.

Table 10 gives the pulmonary function test results of the participants, expressed as standardised residuals and regression coefficients of SR on age based on different sets of reference values. For 43 of the 60 equations used in this study, the mean SR differed significantly from zero, and in 40 equations SR was significantly related to age.

Table 10. Pulmonary function of Estonian schoolchildren. Mean standardised residuals and regression coefficients of standardised residuals on age (age coefficient)

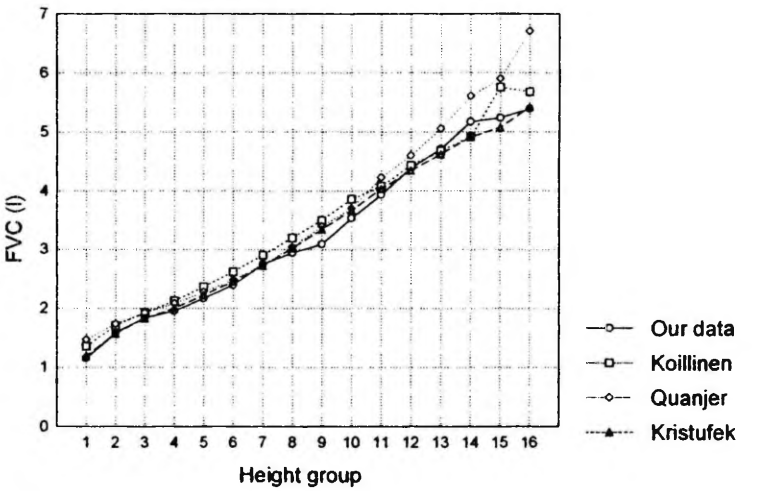
Index	First author	Boys		Girls	
		Mean (SD)	Age coeff. (SE)	Mean (SD)	Age coeff. (SE)
FVC	Haby	0.76 (1.56)*	0.50 (0.09)*	0.22 (1.51)*	0.47 (0.09)*
FVC	Koillinen	−0.70 (1.10)*	0.05 (0.02)*	−1.07 (1.21)*	0.10 (0.01)*
FVC	Kristufek	−0.20 (1.34)*	0.03 (0.02)	−0.45 (1.36)*	0.07 (0.02)*
FVC	Nysom	−0.16 (0.96)*	−0.05 (0.05)	−0.39 (1.12)*	−0.01 (0.05)
FVC	Pistelli	−0.39 (1.26)*	0.24 (0.07)*	−0.95 (1.33)*	0.36 (0.07)*
FVC	Quanjer	−0.64 (1.30)*	−0.02 (0.02)	−0.87 (1.26)*	0.06 (0.02)*
FVC	Schrader	0.11 (1.26)	0.03 (0.05)	0.05 (1.11)	0.17 (0.03)*
FEV_1	Haby	0.55 (1.22)*	0.24 (0.08)*	0.17 (1.21)	0.24 (0.09)*
FEV_1	Koillinen	−0.69 (0.91)*	0.03 (0.01)	−0.90 (1.08)*	0.10 (0.02)*
FEV_1	Kristufek	0 (1.02)*	0.08 (0.02)*	0.10 (1.06)*	0.09 (0.02)*
FEV_1	Nysom	−0.16 (0.89)*	0.01 (0.04)	−0.26 (1.03)*	−0.02 (0.04)
FEV_1	Pistelli	−0.69 (0.97)*	0.05 (0.06)	−0.98 (1.04)*	0.22 (0.06)*
FEV_1	Quanjer	−0.42 (1.06)*	−0.05 (0.02)*	−0.68 (1.08)*	0.02 (0.02)

Index	First author	Boys		Girls	
		Mean (SD)	Age coeff. (SE)	Mean (SD)	Age coeff. (SE)
FEV_1	Schrader	0.10 (1.13)	0.09 (0.04)*	0.13 (1.07)*	0.21 (0.03)*
PEF	Haby	0.33 (1.18)*	0.09 (0.07)	−0.02 (1.29)	0.30 (0.08)*
PEF	Koillinen	0.04 (0.85)	0 (0.01)	−0.03 (0.98)	0.03 (0.01)*
PEF	Kristufek	0.42 (1.19)*	0.11 (0.02)*	0.82 (1.30)*	0.13 (0.02)*
PEF	Pistelli	−0.38 (0.88)*	0.01 (0.05)	−0.49 (1.06)*	0.21 (0.06)*
PEF	Schrader	−0.46 (1.35)*	0.24 (0.05)*	−0.61 (1.46)*	0.29 (0.04)*
FEF_{25}	Schrader	−0.41 (1.15)	0.15 (0.04)*	−0.44 (1.06)*	0.17 (0.03)*
FEF_{50}	Koillinen	−0.25 (0.89)*	−0.03 (0.01)*	−0.03 (0.79)	0.01 (0.01)
FEF_{50}	Kristufek	−0.27 (1.42)*	0.08 (0.02)*	0.29 (1.33)*	0.13 (0.02)*
FEF_{50}	Pistelli	−0.88 (0.90)*	−0.09 (0.05)	−0.91 (0.90)*	0.04 (0.05)
FEF_{50}	Schrader	−0.11 (1.17)	0.09 (0.04)*	0.06 (0.97)	0.14 (0.03)*
FEF_{75}	Kristufek	−0.12 (1.53)	0.08 (0.02)*	0.30 (1.50)*	0.14 (0.02)*
FEF_{75}	Pistelli	−0.51 (0.96)*	−0.13 (0.05)*	−0.42 (0.98)*	0.04 (0.05)
FEF_{75}	Schrader	0.12 (1.19)	0.12 (0.04)*	0.33 (1.19)*	0.19 (0.03)*
FEF_{25-75}	Haby	0.15 (1.27)	−0.15 (0.09)	0.10 (1.18)	0.16 (0.08)
FEF_{25-75}	Pistelli	−1.17 (1.01)*	−0.12 (0.06)*	−1.12 (0.90)*	0.06 (0.05)
FEF_{25-75}	Schrader	−0.11 (1.16)	0.14 (0.04)*	0.09 (0.96)	0.16 (0.03)*

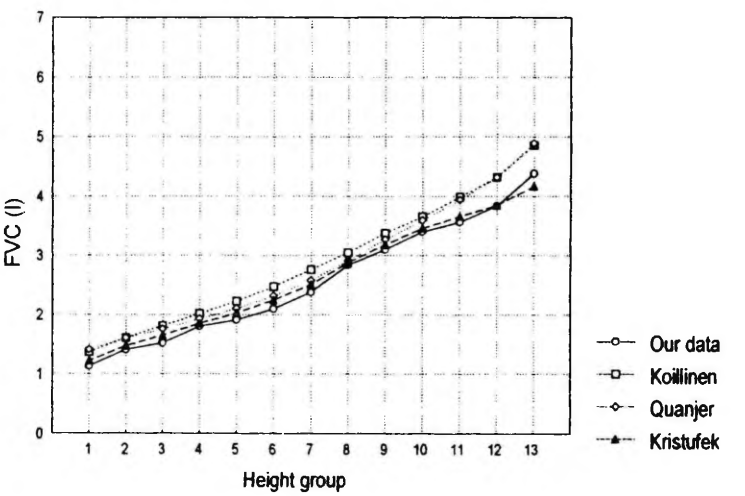
* mean value or regression coefficient significantly different from zero ($p<0.05$). SD, standard deviation; SE, standard error of regression coefficient.

Figure 9 (A–F) shows the mean values of our data by height groups compared with calculated normal values using three equations from the literature, which dealt with the whole age range. Reference values were quite close in smaller children, but in taller children curves started to diverge and in the last height group the differences between the calculated reference values were over 1 litre for FEV_1 and 2 l/s for PEF. Our results were usually lower than those reported by Koillinen and Quanjer and higher than those reported by Kristufek. Therefore, it was difficult to decide which of them would be the most suitable one to use in Estonia.

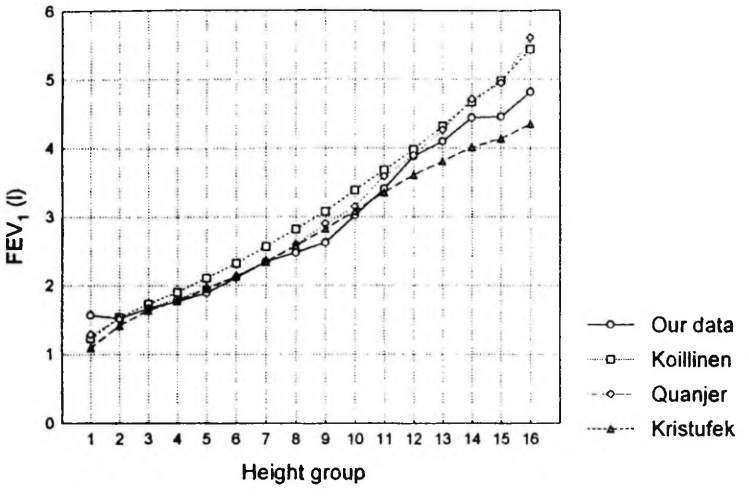
Figure 9 (A–F). Our mean data in comparison with three sets of reference values (from Kristufek *et al.*, 1987; Quanjer *et al.*, 1995; Koillinen *et al.*, 1998). Height groups as in Table 3.



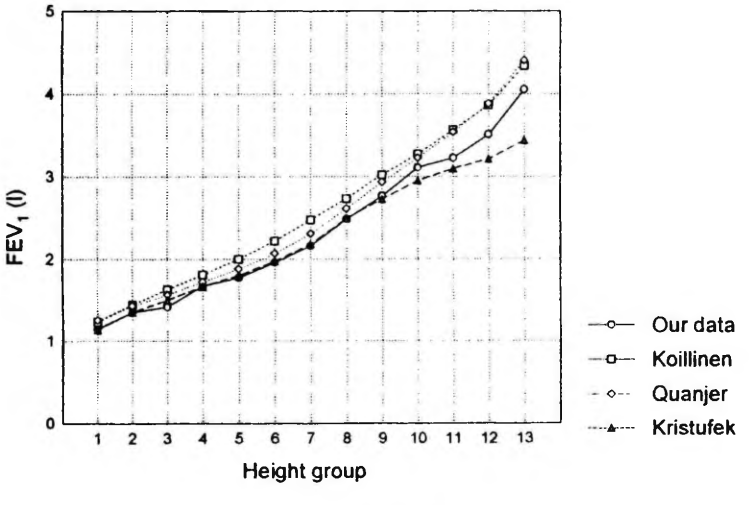
A – FVC in boys



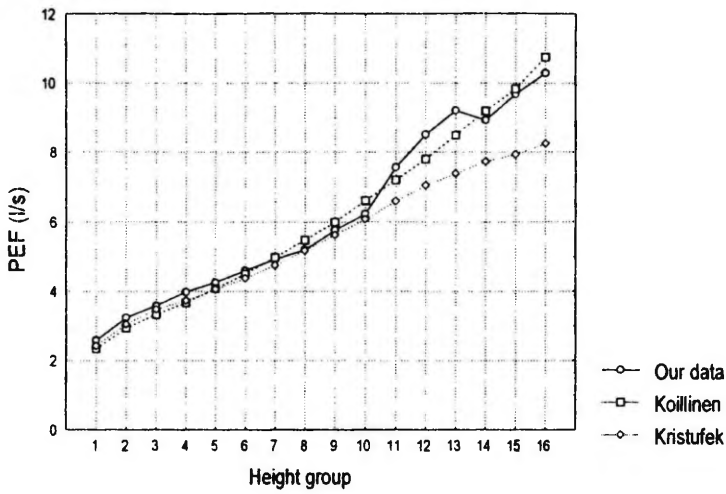
B – FVC in girls



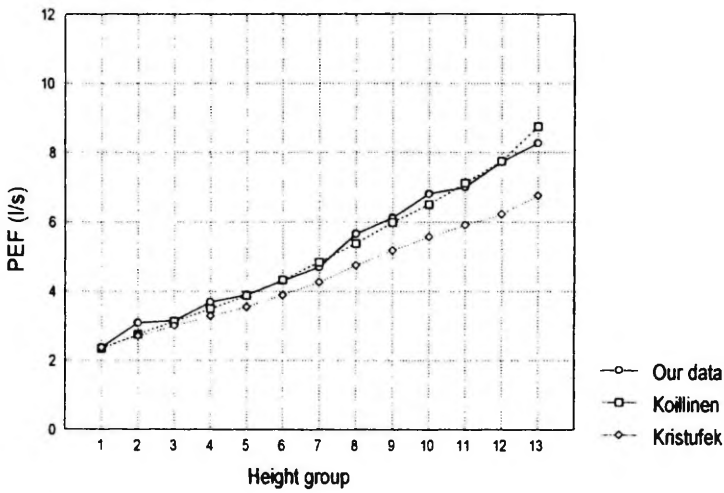
C – FEV_1 in boys



D – FEV_1 in girls



E – PEF in boys



F – PEF in girls

5.6. Specific reference values for Estonian schoolchildren

The graphic analysis of lung function values plotted against height showed that the relationship between functional data and height was non-linear, the variability of spirometric measures increasing with height and age. A logarithmic transformation was then used to linearise this relationship and to stabilise the variance. As an example, Figure 10 shows the data of transformed FVC in girls.

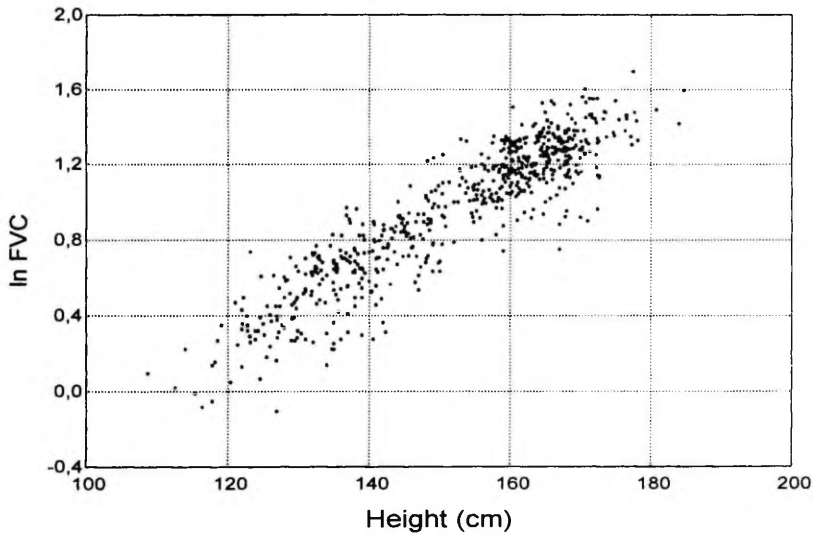


Figure 10. Data of ln FVC as a function of height in healthy non-smoking girls (n=643).

Stepwise regression analysis was made separately for two sexes using the following equation:

$$\ln y = a + b \cdot \ln H + c \cdot \ln A,$$

where y is the spirometric variable, a, b, and c are regression coefficients, H is the standing height in cm and A is the age in years.

Table 11 presents regression equations for natural logarithms of the spirometric variables. As in boys sitting height was a better predictor of lung function, we derived regression equations also by means of sitting height instead of standing height (Table 12).

Table 11. Results of regression analysis using standing height and age as independent variables

Function	Regression coefficients			RSD	R^2
	Intercept (SE)	ln Height (SE)	ln Age (SE)		
			Boys		
ln FVC	−10.583 (0.516)	2.106 (0.129)	0.435 (0.059)	0.135	0.893
ln FEV1	−11.554 (0.504)	2.371 (0.127)	0.234 (0.061)	0.121	0.884
ln PEF	−8.122 (0.701)	1.712 (0.176)	0.499 (0.080)	0.183	0.791
ln FEF_{50}	−10.687 (0.405)	2.367 (0.081)	NS	0.238	0.623
ln FEF_{75}	−10.673 (0.572)	2.241 (0.114)	NS	0.336	0.426
ln FEF_{25-75}	−10.842 (0.433)	2.376 (0.086)	NS	0.248	0.621
			Girls		
ln FVC	−10.136 (0.502)	1.969 (0.120)	0.484 (0.044)	0.133	0.864
ln FEV_1	−10.134 (0.531)	1.964 (0.126)	0.456 (0.046)	0.118	0.858
ln PEF	−7.344 (0.719)	1.482 (0.172)	0.619 (0.064)	0.191	0.742
ln FEF_{50}	−7.932 (0.805)	1.590 (0.192)	0.475 (0.071)	0.213	0.655
ln FEF_{75}	−8.684 (1.248)	1.609 (0.298)	0.506 (0.111)	0.331	0.459
ln FEF_{25-75}	−7.511 (0.848)	1.465 (0.202)	0.518 (0.074)	0.209	0.673

SE, standard error of regression coefficient, NS, regression coefficient non-significant ($p>0.05$).

Table 12. Results of regression analysis using sitting height and age as independent variables

Function	Regression coefficients			RSD	R^2
	Intercept (SE)	ln SH (SE)	ln Age (SE)		
			Boys		
ln FVC	−10.038 (0.466)	2.235 (0.133)	0.542 (0.052)	0.126	0.909
ln FEV_1	−10.769 (0.468)	2.455 (0.135)	0.392 (0.057)	0.119	0.892
ln PEF	−8.053 (0.629)	1.918 (0.179)	0.559 (0.070)	0.170	0.824
ln FEF_{50}	−8.994 (0.828)	2.180 (0.236)	0.270 (0.092)	0.224	0.667
ln FEF_{75}	−11.469 (0.582)	2.757 (0.133)	NS	0.318	0.486
ln FEF_{25-75}	−9.571 (0.926)	2.312 (0.264)	0.224 (0.103)	0.237	0.662
			Girls		
ln FVC	−9.100 (0.501)	2.019 (0.140)	0.488 (0.049)	0.131	0.863
ln FEV_1	−9.322 (0.520)	2.066 (0.144)	0.456 (0.051)	0.114	0.866
ln PEF	−6.468 (0.664)	1.511 (0.184)	0.604 (0.065)	0.173	0.765
ln FEF_{50}	−7.953 (0.776)	1.868 (0.216)	0.404 (0.076)	0.203	0.674
ln FEF_{75}	−10.044 (1.145)	2.264 (0.319)	0.319 (0.113)	0.300	0.513
ln FEF_{25-75}	−8.083 (0.835)	1.867 (0.234)	0.416 (0.082)	0.202	0.691

SE, standard error of regression coefficient, NS, regression coefficient non-significant ($p>0.05$).

Residual analyses were made for each parameter to determine whether variances changed with age. Residual plots were considered for all functions, where residuals were defined as (actual value — predicted value). For example, Figure 11 presents such a plot of residuals versus age in girls. Examination of the residuals for each model did not reveal any violations of the assumption of normality.

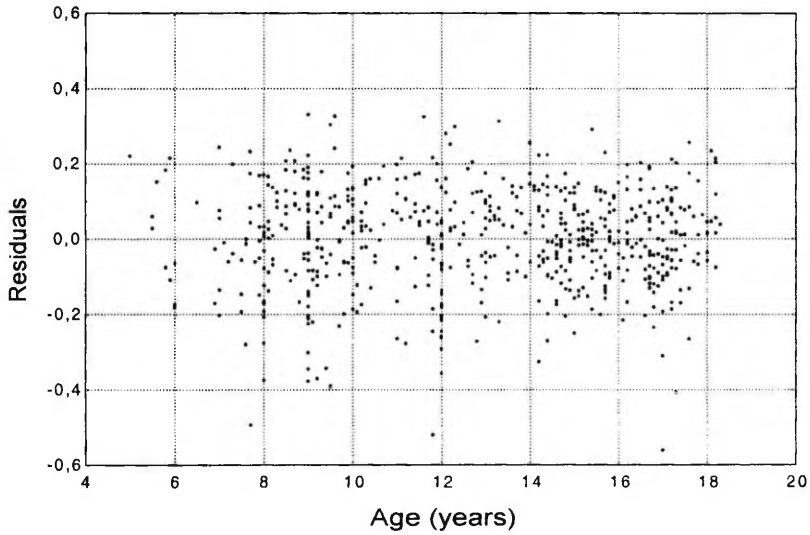
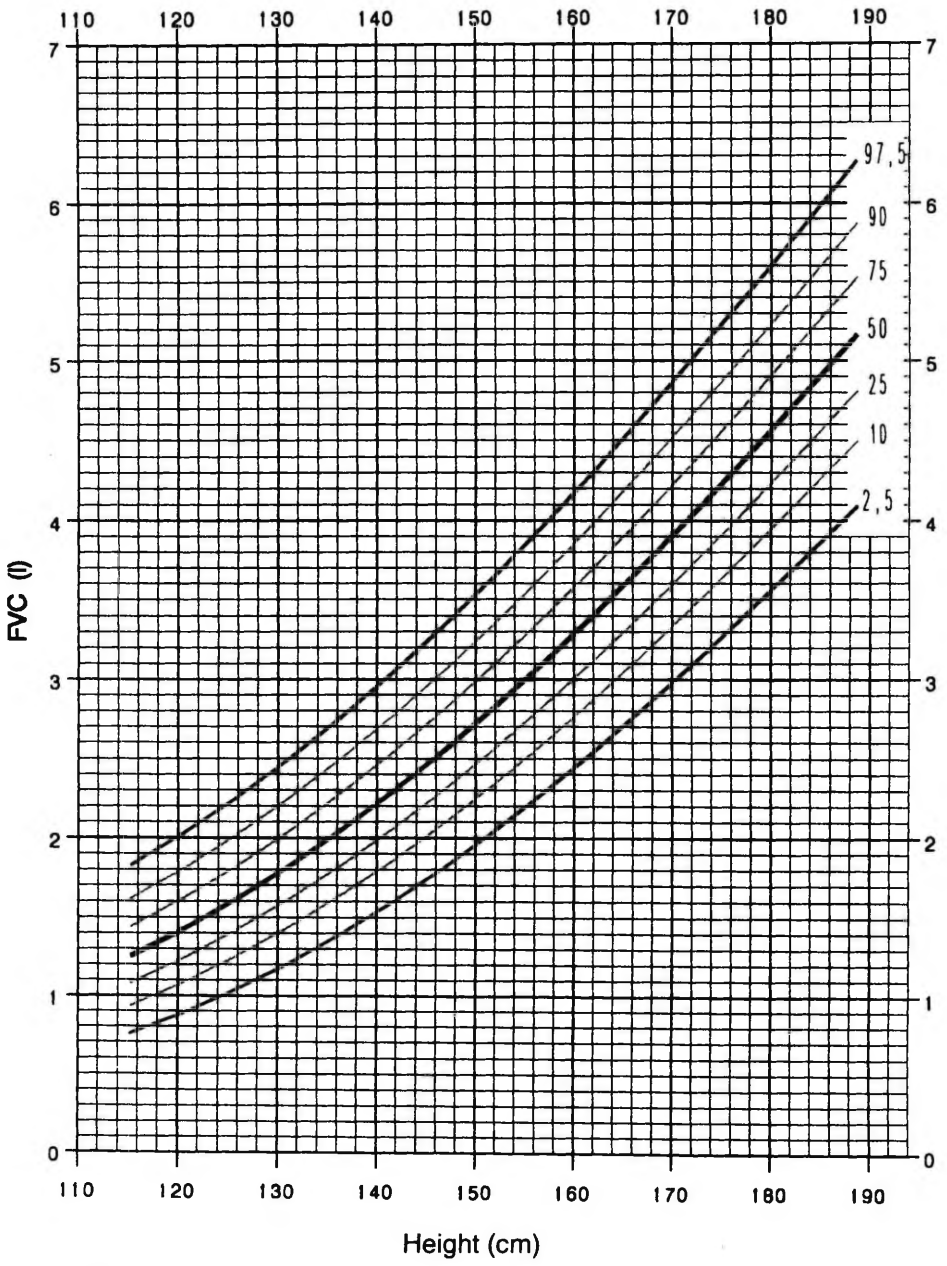


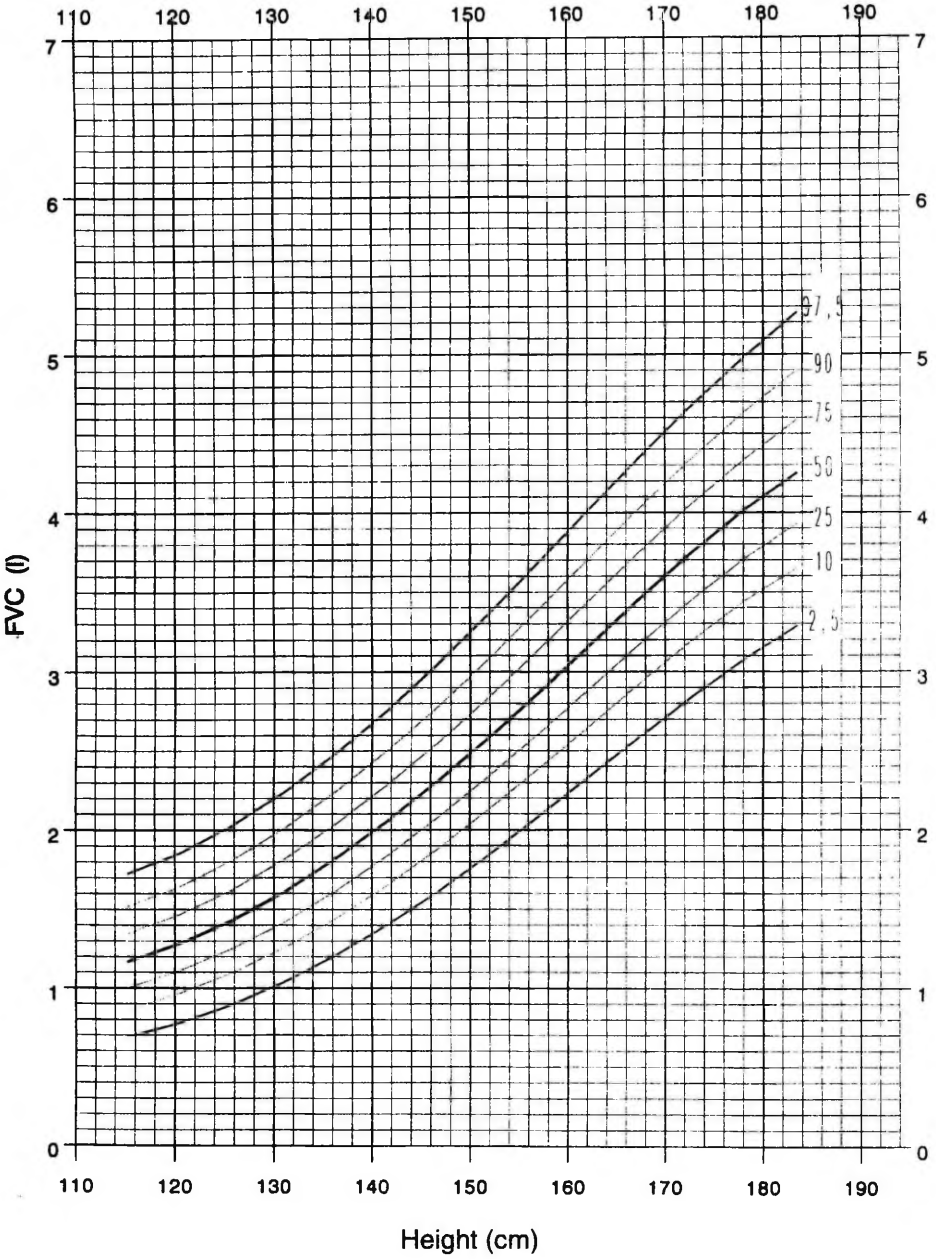
Figure 11. Residuals (actual ln FVC — predicted ln FVC) versus age in girls (n=643).

The corresponding nomograms using standing height were also produced, which show the 2.5th, 10th, 25th, 50th, 75th, 90th and 97.5th percentiles (Appendices 1–6).

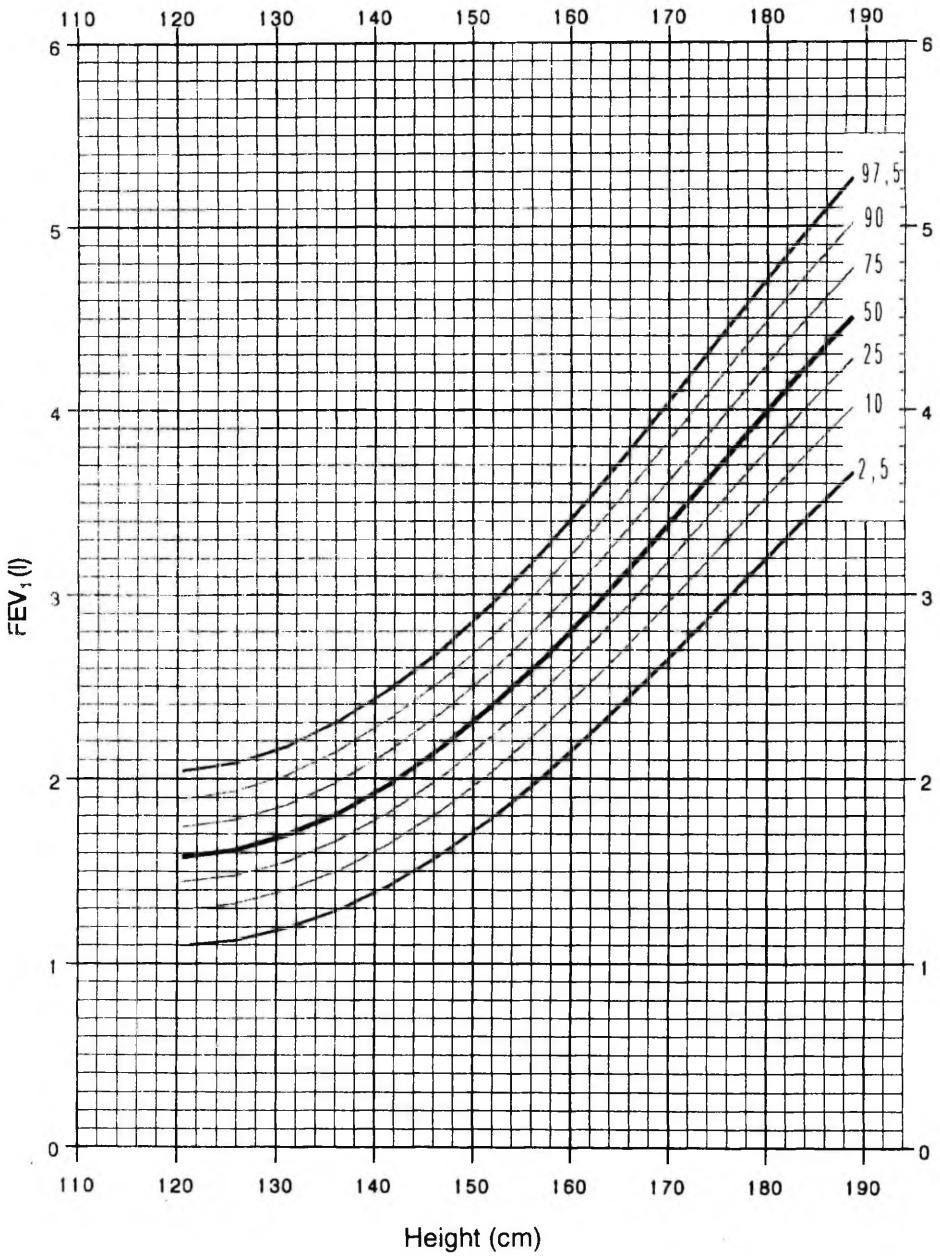
With respect to the FEV_1/FVC ratio, it turned out to be a very stable measurement that remains almost unchanged between the different age and height groups. Therefore, this ratio appears to be unrelated to the anthropometric data and age. The median value for FEV_1/FVC was 86.3% for boys and 89.5% for girls. For these individuals, the 2.5th percentile was 77.5% for girls and 71.5% for boys. These values can be used as quick reference values regardless of the age and height of the child.



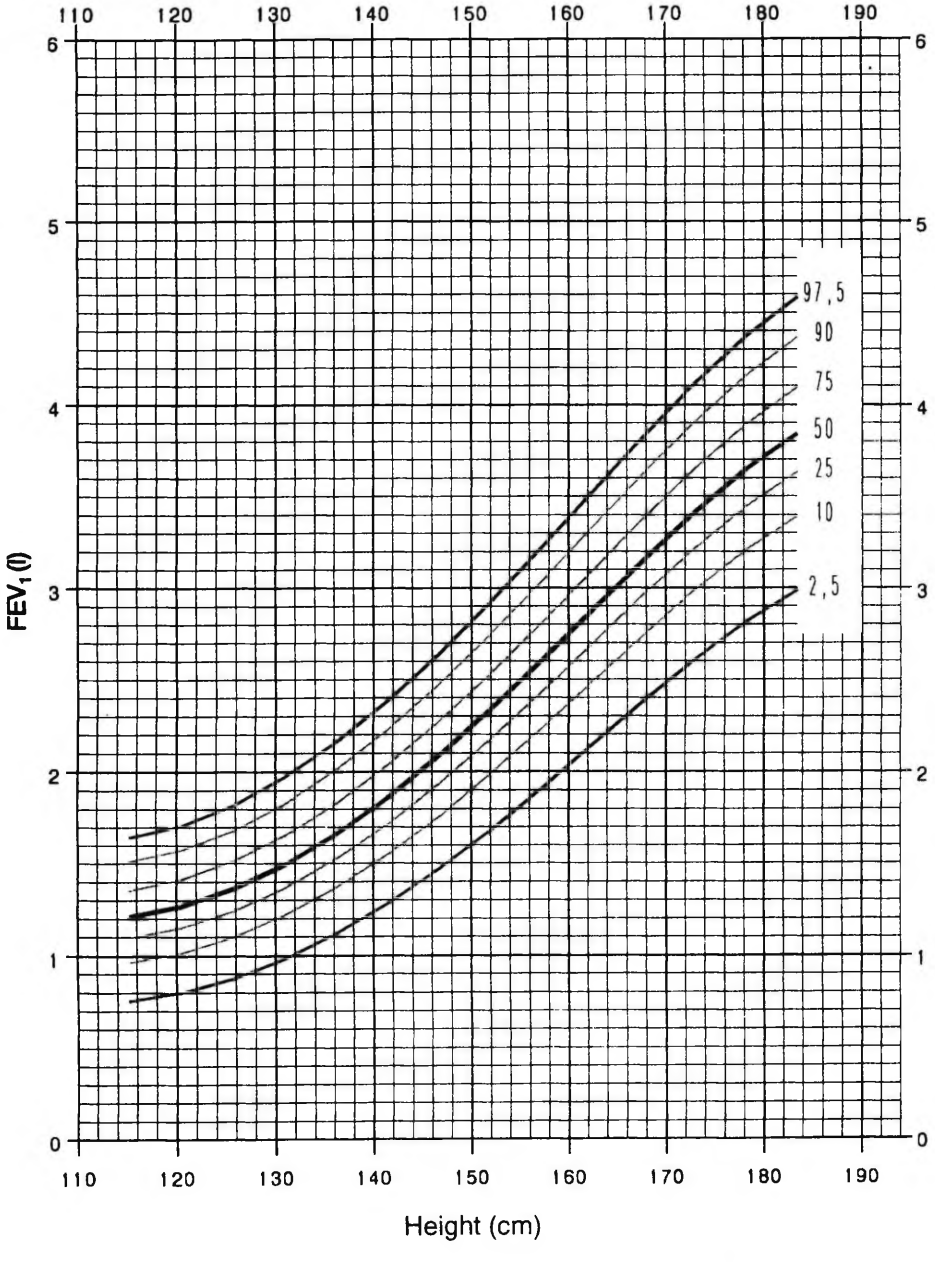
Appendix 1. Percentile curves of forced vital capacity in boys.



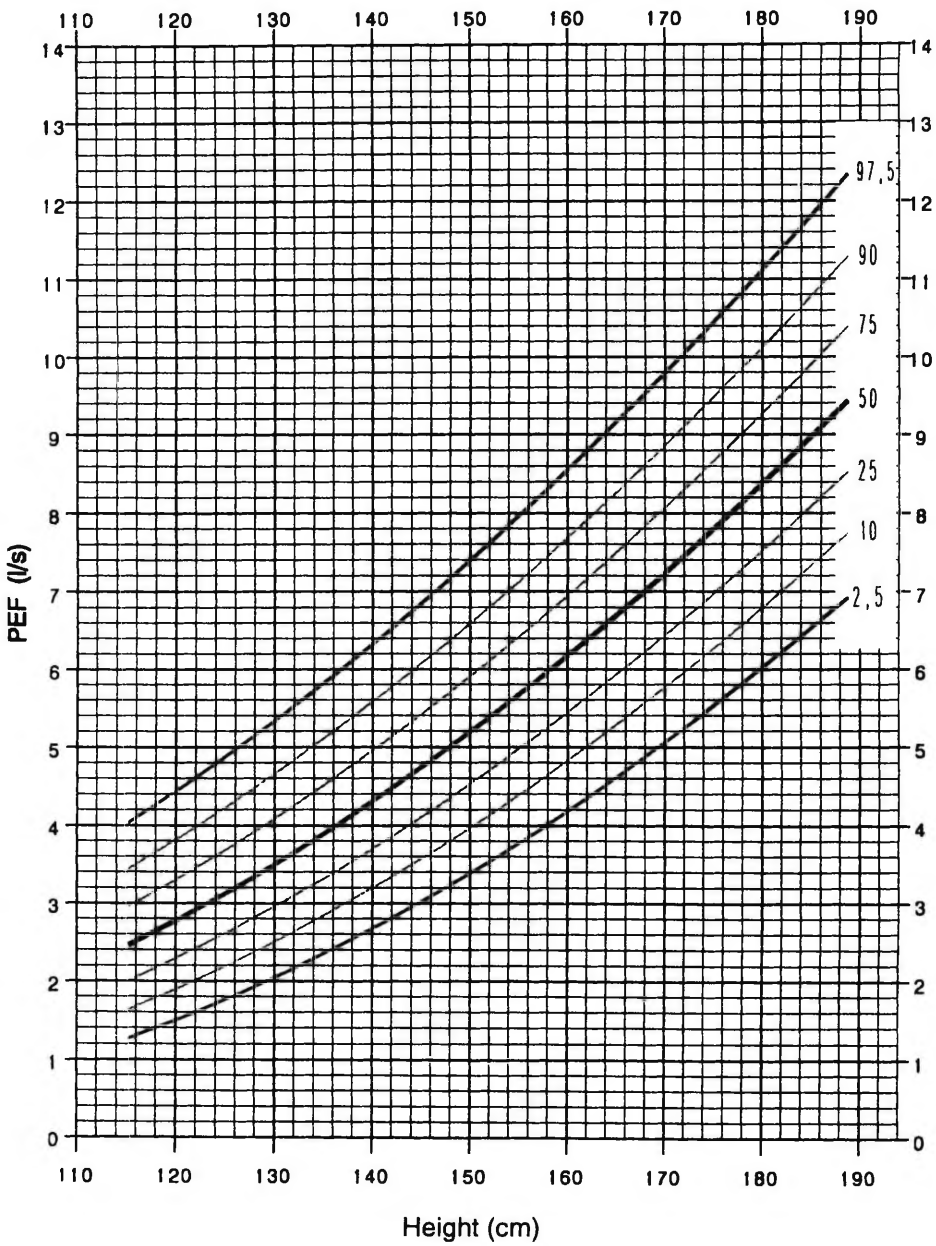
Appendix 2. Percentile curves of forced vital capacity in girls.



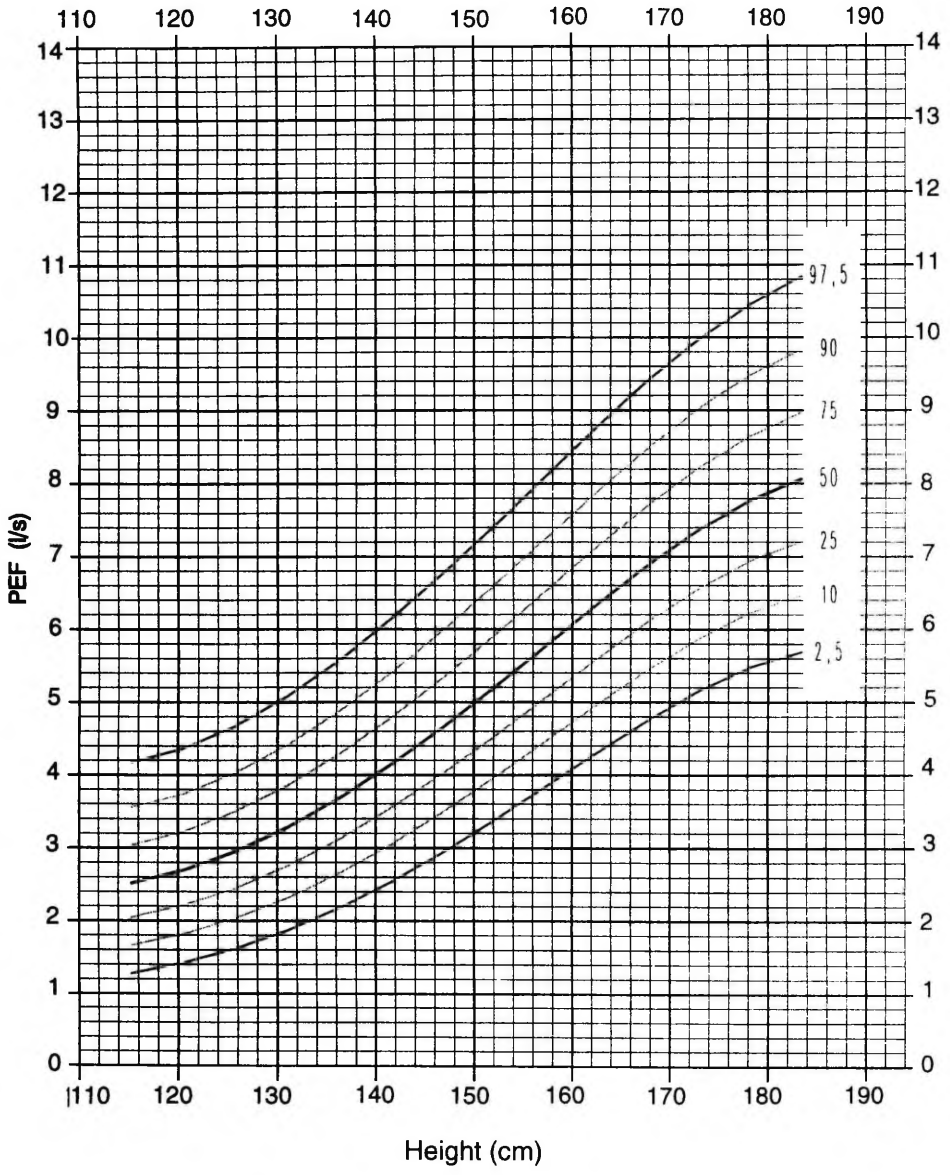
Appendix 3. Percentile curves of forced expiratory volume in 1 sec in boys.



Appendix 4. Percentile curves of forced expiratory volume in 1 sec in girls.



Appendix 5. Percentile curves of peak expiratory flow in boys.



Appendix 6. Percentile curves of peak expiratory flow in girls.

6. DISCUSSION

6.1. Effects of gender and anthropometric parameters on lung function

Growth spurts in standing height and lung function parameters took place from 11 to 13 years in girls and from 13 to 15 years in boys (I). Until the age of 11 the differences in lung function between two genders were non-significant, except for FVC and PEF being higher in boys. As girls entered the growth spurt two years earlier than boys, then female flow values were higher at the ages of 12 and 13, but not FVC and FEV_1. After the age of 14 FVC, FEV_1 and PEF values were higher in boys, and the slopes of the increase with age were much steeper for boys than for girls. When we plotted the mean values of different lung function variables as the function of height (II), there was a sudden change in lung function in each sex which appeared to coincide with the pubertal growth spurt (i.e. between 150.0 and 159.9 cm in girls and 160.0 and 169.9 cm in boys). It was in line with the observations of others (Rosenthal *et al.,* 1993).

Determination of flows, corrected for lung size is very important especially in children and adolescents because it enables us to compare the values in growing subjects of various age, height, and lung size (Zapletal *et al.,* 1987). Our finding of superior airflow per unit lung volume in girls (paper II) confirms the suggestion that younger girls have wider airways than boys. Several authors (Leeder *et al.,* 1977; Wall *et al.,* 1982; Rosenthal *et al.*, 1993) have suggested that until shortly after puberty girls have greater volume-adjusted flows than boys, but that boys may catch up in their late adolescence. In our sample, FEF_{50}/FVC, and FEF_{75}/FVC continued to be higher in girls until late adolescence, which accords with the findings of others (Schwartz *et al.,* 1988).

Some authors have not found any significant differences in lung performance between boys and girls (Michaelson *et al.,* 1978; Bellon *et al.,* 1982), but most of the authors have. Even though gender differences are much greater during the puberty and thereafter than during the early growth phase, the separation by gender in determining the reference values would help to keep the confidence limits of these values narrower throughout life and to achieve more reliable follow-up tracking of individual functional growth and development (Polgar, 1990).

It has been demonstrated in longitudinal studies (DeGroodt *et al.,* 1986; Jaeger-Denavit and Alphonse, 1990; Borsboom *et al.*, 1993; Geithner *et al.,* 1999) that the adolescent growth spurt affects first the long bones and, therefore, standing height, preceding the time of peak growth velocity of thoracic dimensions and lung function indices. Therefore, the use of sitting height as the reference variable in the prediction equations for lung parameters would be more exact because trunk development might be more closely associated to lung de-

velopment (Schrader *et al.*, 1984; DeGroodt *et al.*, 1986; Rahman *et al.*, 1990). As the lung is contained in the thorax, it seems plausible that the changes in thoracic dimensions will also have a bearing on the development of lung parameters (DeGroodt *et al.*, 1988). Our cross-sectional study could not show the time lag between growth spurts of standing height and thoracic dimensions (II). Thoracic dimensions were usually greater in boys than in girls of the same height, except for the height range of 150.0–164.9 cm, where also most of the lung function variables were larger in girls.

DeGroodt with co-authors (1988) showed that during the pubertal growth spurt the thorax changes not only in size but also in shape, and that is accompanied by alterations in size and subdivisions of the total lung capacity. A six-year follow-up study of adolescents whose ages ranged between 11.5 and 18.5 showed that thoracic width in females hardly changed during the study, whilst thoracic height clearly increased. In boys, thoracic height increased twice as fast as thoracic width. Thus, there was a relative elongation of the thorax (DeGroodt *et al.*, 1988). Unfortunately, the authors did not report any data on changes in standing or sitting height of their subjects. As we did not measure thoracic height in our cross-sectional study, it remains unclear how thoracic width is related to thoracic height in our data, and what pattern would the ratio thoracic width / sitting height follow in a longitudinal study. We found that in boys between the heights 165.0–174.9 cm the ratio of chest width to sitting height is significantly greater than in other height groups, whereas in girls this ratio is constant over the whole height range. This difference may contribute to the continuing divergence of male and female lung function (FVC, PEF) after puberty.

All anthropometric parameters showed positive correlations with lung function data. A stronger association was observed between lung function parameters and sitting height in boys, whereas standing height was the best predictor in girls. After controlling for age and standing height, the partial correlation coefficients between thoracic parameters and spirometric indices were mostly higher in boys. Inclusion of sitting height and thoracic parameters in the regression models eliminated the significance of the sex variable (zero for females and one for males) for FEF_{25}, FEF_{50}, FEF_{75} and FEF_{25-75}, yet the continued significance of the sex variable for FVC, FEV_1 and PEF indicated that some sex differences in lung function exist even after adjustment for thoracic frame size. This finding agrees quite well with that of another group of researchers, who found that after standardisation for height, FVC and FEV_1 were 14 to 19% higher in men than in women (Jacobs *et al.*, 1992). Standardisation for sitting height, leg height, elbow breadth, and biacromial diameter combined reduced these differences to 13–16%.

6.2. Influence of respiratory complaints and diseases on lung function (III)

There were 16.1% of boys and 15.5% of girls who gave affirmative answers to one or more questions about their respiratory symptoms. 1.8% of boys and 1.0% of girls had been diagnosed as having asthma by a doctor. In a recent study, the prevalence of asthma was 2.9% in 11–12-year-old Estonians, what was two to three times lower than in a study in Sweden, but similar to what was reported in Poland (2.9%). Twelve-month prevalence of respiratory symptoms, such as wheezing, breast tightness and breathlessness, nocturnal cough, and exercise-induced cough was reported in 5–7% of the Estonian children in the same study (Riikjärv *et al.*, 1995). Unfortunately, we were unable to compare these results with our data because we defined the summary variable "respiratory problems" as positive if at least one symptom had been reported. In studies using analysis similar to our one, point prevalence of respiratory symptoms and illnesses was 43.2% in 7–11-year-old Italians (Pistelli *et al.*, 1992), 32% in 6–12-year-old children from the Netherlands (Cuijpers *et al.*, 1994) and 6.0% in 8–10-year-old Danes (Mostgaard *et al.*, 1997).

When we compared the lung function in healthy children and in children with some respiratory disease or symptom, our results demonstrated the presence of reduced forced expiratory flow values in symptomatic girls, suggesting a probable underdiagnosis of asthma in Estonia. Too low number of asthmatics in our study population did not afford making separate analysis for effects of doctor-diagnosed asthma. Others have found even more severe impairment of lung function in known asthmatics than in symptomatic non-asthmatic children (Mostgaard *et al.*, 1997).

Several research teams have evaluated the relative sensitivity of the various spirometric parameters to separate children with a positive history of respiratory symptoms from those without these symptoms. The differences between two groups of children were found in FEV_1 (Pistelli *et al.*, 1992; Weiss *et al.*, 1992; Borsboom *et al.*, 1993; Rona and Chinn, 1993; Cuijpers *et al.*, 1994; Gold *et al.*, 1994), and/or in forced expiratory flows (Higgins and Keller, 1973; Bellon *et al.*, 1982; Pistelli *et al.*, 1992; Weiss *et al.*, 1992; Borsboom *et al.*, 1993; Rona and Chinn, 1993; Cuijpers *et al.*, 1994; Gold *et al.*, 1994; Mostgaard *et al.*, 1997; Droste *et al.*, 1999). FVC has often been found not to be affected by respiratory symptoms (Pistelli *et al.*, 1992; Weiss *et al.*, 1992; Rona and Chinn, 1993; Mostgaard *et al.*, 1997; Droste *et al.*, 1999), which accords with our findings. Although in our study the group with respiratory problems was more heterogeneous, the results can to some extent confirm the suggestion that asthma is more prevalent in boys, but in girls it is more severe as measured by the level of lung function (Weiss *et al.*, 1992).

Several epidemiological studies from different countries show that the prevalence of symptoms of asthma in children has increased in recent years

(Anderson *et al.,* 1994; Peat *et al.,* 1994; Venn *et al.,* 1998). It is important to ascertain whether these changes indicate a true increase in the incidence of asthma or a decrease in the underrecognition of asthma. Therefore, repeated surveys incorporating more objective data are needed before firm conclusions can be drawn (Magnus and Jaakkola, 1997). However, Peat with co-workers (1994) found about a twofold increase in airway hyperresponsiveness and current asthma, so their findings seem to show that the increase is real. As in Estonia the criteria for diagnosing asthma have traditionally been narrower than in many western countries, the underdiagnosis when compared to other countries, could at least in part explain the low prevalence of diagnosed asthma in Estonia (Riikjärv *et al.,* 1995). Therefore, we decided to exclude all children with some respiratory symptoms from our healthy subjects' group, even when they did not have a doctor-diagnosed asthma or any other illnesses.

Fifty-two boys (7.6%) and 14 girls (1.8%) from our whole study group reported smoking more than one cigarette per week. Even higher prevalence of smoking among Estonian schoolchildren has been found in the academic year 1997/98 (Suurorg, 1999). This study used questionnaires and showed that 7.8% of 6^{th} grade pupils and 25.8% of 9^{th} grade pupils were smokers (smoked one or more cigarettes per week). Our study may underreport smoking to some extent because we asked the smoking status directly from the child. When comparing lung function in boys who were smokers and who were not, we often found mean values in height groups to be greater in smokers. The smokers were also older than non-smokers of the same height group. Forty-six male smokers had no and only six smokers had respiratory problems, suggesting that boys with complaints connected with the respiratory system had avoided smoking.

The definition states that a healthy child has "no more than incidental smoking experience" (Taussig *et al.,* 1980). There are differences in excluding smokers in studies of lung function in children. For example, one group excluded all children who had admitted ever smoking even one cigarette (Asher *et al.,* 1987). The others excluded those who had reported smoking at least eight cigarettes per week (DeGroodt *et al.,* 1986), whereas the third group found that regression equations in schoolchildren with and without exclusion of the children who had ever smoked, were identical (Coultas *et al.,* 1988). We excluded children who reported smoking more than one cigarette per week, even if they were probably too young and smoked too little to develop a diminished lung function.

6.3. Lung function data in comparison with reference values from the literature

The comparison of results from a new study with existing reference studies is difficult when authors do not have access to the raw data from the previous studies and are only able to compare their data with earlier equations. Such comparisons are limited because they cannot account for differences in the distributions of the independent and dependent variables. We also have to control several other potential sources of interstudy differences, such as sample selection, exclusion rate, and technical differences (Crapo *et al.,* 1999). The ideal way to address ethnic differences would be to make ethnic comparisons part of a single study in which the study design is constant and procedures can be controlled and uniformly applied to both groups. Unfortunately, such studies are quite exceptional.

When comparing our data of 1,170 healthy non-smoking children with reference values from the literature, the ethnically and geographically closest group was that from Finland studied by Koillinen and co-authors. They presented logarithmic regression equations for FVC, FEV_1, $FEV_{0.5}$, PEF, and FEF_{50} based on data from 199 healthy children from one town (Koillinen *et al.,* 1998). Unfortunately, they did not include residual standard deviations into the tables and variance could be assessed only using their lower limits of normal as "% predicted".

We used standardised residuals (SR) in the comparison and in 43 equations out of 60 analysed by us, the mean SR was different from zero. SRs were often significantly related to age, suggesting the underestimation of lung function status on one and the overestimation on the other end of the age range. Several equations were meant only for very narrow age ranges, so that different sets were needed to cover our whole sample. When comparing with four sets of equations dealing with whole age range, our mean data were between those of Koillinen *et al.* (1998) and Quanjer *et al.* (1995) on one side and those of Kristufek *et al.* (1987) on the other.

Some differences can be explained by the use of different selection methods of the best flow-volume curve from amongst a set of curves. We used the envelope method recommended by ERS, i.e. the curves are superimposed from TLC to form a composite maximal curve, and the largest FVC is used to delineate the highest instantaneous flows at specified lung volumes (Quanjer *et al.,* 1993). ATS prefers to obtain maximum mid-expiratory flow and the instantaneous expiratory flows from the single curve that meets the acceptability criteria and gives the largest sum of FEV_1 and FVC (ATS. Standardization of spirometry, 1995). The authors of the reference values that we used for comparison mostly used the method recommended by ATS, except for Kristufek *et al.* (1987) who used the largest values for FEV_1 and VC, and forced expiratory flow values from the composite curve. In a study where eight different methods

of selecting the best curve were compared, the "ATS method" led to slightly lower average values and gave consistently poorer reproducibilities for forced expiratory flows than other methods (Schrader *et al.,* 1983). Our data of PEF and FEF_{50} were closer to Koillinen's reference values than those of Kristufek.

6.4. Reference values for Estonian children

We decided to determine the specific reference values for Estonian schoolchildren because no suitable set of equations could be found for our data.

Logarithmic transformations of lung function and independent variables are often used for achieving homoscedasticity (i.e. stabilising variance) and normalising distributions for regression analysis. We used logarithms to base e partly because of their use by most of the authors cited. However, base 10 could be equally used.

Standing or sitting height explained the highest proportion of the variation in lung function. Age has been found to be a very important determinant of lung function in children older than 11–12 years (Burrows *et al.,* 1983; Kristufek *et al.,* 1987; Quanjer *et al.,* 1995; Nysom *et al.,* 1997). Therefore, we included age in equations because of quite wide age range of studied children. Sitting height was a better determinant of lung function in boys, therefore we presented also equations using SH. However, this variable may be less popular for routine use.

The amount of the variance explained in our models suggests that the distribution of FVC, FEV_1, and PEF could be accurately described in our population using age and anthropometric variables (R^2 values were 86–91%, 86–89% and 74–82%, respectively). R^2 values for other flows were much lower. When compared to published equations, our R^2 values are similar or even higher than other groups have presented. For example, in equations for FVC and FEV_1 the R^2 was between 66 and 74% (Hellmann and Goren, 1999), 60 and 65% (Pistelli *et al.,* 1992), and 62 and 65% (Haby *et al.,* 1994). The last two papers used one equation for boys and girls, with sex as a dummy variable.

Our reference equations fitted better for boys than for girls (R^2 values were always higher in male than in female equations). The same conclusion was drawn in several other studies (Coultas *et al.,* 1988; Koillinen *et al.,* 1998). Also, correlation coefficients were found to be smaller in adults than in adolescent boys (Dickman *et al.,* 1971). The possible reason given was: "Perhaps adults and adolescent girls varied widely in their willingness to exert maximal physical effort". We could also conclude that boys aged between 10 and 17 are the best contingent to make competition in blowing "higher and bigger mountains" on a flow-volume scale.

To examine how well the models predict values of the dependent variable for individuals, we checked whether the residuals had a Normal distribution and

that the models were with equally good fit throughout the range of values of the dependent variable (Altman, 1991).

It may be argued that the use of logarithms and cubic values makes the predictive equations difficult to apply in medical practice, especially when non-automatised devices are used to measure lung function parameters. For this reason, the percentile curves were developed for those parameters whose overall variance in our population was better explained by the multiple regression equations, as several other groups have done (Shamssain, 1991; Chen-Mok and Bangdiwala, 1997). With these plots, the physician does not have to go through difficult calculations and has an instrument similar to the paediatric growth charts he or she has already accustomed to using. Percentile plots allow the interpreter to judge the normality or abnormality of the results of an individual patient in terms of the frequency of occurrence of similar results in the reference population. Normality or abnormality of a given result cannot, however, be determined completely by an arbitrary cutoff level. All results must be interpreted in the light of clinical history (Margolis and Montoya, 1997; Castile, 1998). The 1991 ATS statement recommends setting the lower limit of the normal range at the fifth percentile, several authors (Connett *et al.*, 1994; Mueller and Eigen, 1994; Sovijärvi, 1994) have used the 2.5^{th} percentile as also we did.

Our findings agree with those of previous studies in children, in which FEV_1/FVC ratio was not related to anthropometric measurements and female values were higher than male ones (Higgins and Keller, 1973; Schwartz *et al.*, 1988; Rahman *et al.*, 1990; Connett *et al.*, 1994; Quanjer *et al.*, 1995; Hyatt *et al.*, 1997). We presented values of the 50^{th} and the 2.5^{th} percentile for this parameter in both sexes.

Some of the spirometric parameters presented here, such as FEF_{50}, FEF_{75} and FEF_{25-75} are said to be of little practical use because of their high intra- and interindividual variability (Strachan, 1989; Glindmeyer *et al.*, 1995). In a recent textbook of pulmonary diseases the average and instantaneous flows are not discussed at all because they should be used only to assist in decision making if the primary indices (FVC, FEV_1, FEV_1/FVC) are close to the lower limits of their normal ranges (Crapo, 1998). However, as stated earlier, several studies have shown that flow variables are sensitive in detecting mild obstruction or differentiating between healthy children and those with respiratory problems. Therefore, we included a complete list of reference values, so that the users would not mix regression equations from different studies.

7. CONCLUSIONS

1) Our study established gender differences in the lung function variables when comparing boys and girls of the same age and also of the same height. Differences were more considerable in older children whose pubertal growth spurt had already started. Very similar patterns in the increase of sitting height, thoracic dimensions, and lung function parameters, and elimination of the sex variable from some regression models, when these anthropometric parameters were included, suggest that some differences in the lung function between boys and girls of the same height may be explained by differences in the thoracic size.

2) 16.1% of boys and 15.5% of girls reported at least one respiratory complaint. When we compared their lung function indices with those of healthy children, we found decreased forced expiratory flow values in girls with respiratory problems. Considering the possible underdiagnosis of asthma in Estonia, we decided to exclude all children with complaints from the group of healthy children.

3) When comparing our lung function data of 1,170 healthy non-smoking schoolchildren with seven sets of reference equations from the literature, no set appeared to fit in with our data. Some dealt with a very narrow age range, some presented equations for only one or two variables and over half of the equations gave reference values that differed significantly from our mean values. We conclude that different reference equations can give very different reference values and choosing between them is difficult.

4) Logarithmic reference equations and percentile growth charts were determined for Estonian children aged 6 to 18 years. The models included standing height and age as independent variables and the amount of the variance explained in our models was 74–91% for FVC, FEV_1, and PEF. Equations with sitting height as a predictor are useful for the accurate assessment of lung function results in adolescents and in situations where the measuring of standing height is not possible.

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EESTI KOOLILASTE HINGAMISFUNKTSIOONIST: seosed kehamõõtmete ja hingamiskaebustega ning dünaamiliste spirograafiliste näitajate normväärtused

Kokkuvõte

Laste välise hingamise funktsionaalsete uuringute alusel saab objektiivselt hinnata hingamiselundite eale vastavat arengut, haiguslikke muutusi ja ravi efektiivsust. Eestis tehakse laste spirograafilisi uuringuid ainult suuremates keskustes. See võib olla üheks põhjuseks, miks Eestis diagnoositakse hingamiskaebustega lastel vähe astmat, mille tõttu võib mõnikord jääda saamata ka adekvaatne ravi (Riikjärv jt.,1995).

Laste hingamisfunktsiooni näitajad suurenevad koos lapse vanuse ja pikkuse kasvuga. Näitajate tõus ei ole kogu aeg ühtlane, puberteedi ajal on see järsem ja tüdrukud saavutavad väärtuste platoo varem kui poisid. Kestevuuringutes on näidatud, et puberteedieaegsed kasvuspurdid on erinevatel näitajatel eri ajal, nii võivad rindkere mõõdud ja kopsude ruumalad jõuda kasvuspurti 6–12 kuud hiljem kui pikkuskasv (DeGroodt jt., 1986; Jaeger-Denavit ja Alphonse, 1990; Borsboom jt., 1993). Sama pikkusega poiste ja tüdrukute välise hingamise näitajate erinevused tulevadki selgemalt esile puberteedi alguses, võib-olla on nende erinevuste üheks põhjuseks kehatüve ja rindkere mõõtude lahknevused.

Forsseeritud hingamise voolu-mahu lingult saadud näitajate hindamiseks tuleb neid võrrelda isikule vastavate normväärtustega. Normväärtuste arvutamise valemid on koostatud suure hulga tervete laste vanuse, kehamõõtmete ja voolu-mahu lingult saadud andmete põhjal. Nn. terve lapse kriteeriumid (Taussig jt., 1980), mida enamik autoreid on kasutanud, ei määratle täpselt, kui palju ja millised kaebused võivad olla lapsel elu jooksul olnud, et teda hingamissüsteemi poolest saaks veel terveks pidada.

Viimastel aastakümnetel on avaldatud rohkesti laste välise hingamise näitajate normiarvutusvalemeid, mis sageli võivad anda üsna erisuguseid tulemusi. Lahknevused võivad olla tingitud uuritavate populatsiooni valikust, uuringumetoodika erinevustest, uuritud kontingendi etnilistest iseärasustest ja ka muudest põhjustest. Et välise hingamise näitajate normväärtuste eeskirjade leidmine on väga suuremahuline töö, siis soovitatakse uuritavate kontingendile sobivate normide leidmiseks võrrelda mingil hulgal tervetel lastel mõõdetud näitajaid eri autorite esitatutega ja valida kõige lähedasemate tulemustega regressioonivalemite komplekt. Oluliste erinevuste korral koostada normväärtuste arvutamise valemid oma mõõtmistulemuste põhjal (Quanjer jt., 1989).

Uurimuse eesmärgid

1. Selgitada, kas poiste ja tüdrukute välise hingamise funktsionaalsete näitajate lahknevus võib olla seletatav kehatüve pikkuse ja rindkere mõõtmete erinevustega.

2. Analüüsida tervete laste ja hingamiselunditepoolsete kaebustega laste hingamise funktsionaalset seisundit.

3. Võrrelda tervete mittesuitsetavate laste voolu-mahu lingu näitajaid mitmesuguste kirjanduses avaldatud normväärtustega.

4. Leida sobivaimad normiarvutusvalemid Eesti koolilaste dünaamiliste spirograafiliste näitajate hindamiseks.

Uuritavad ja meetodid

Uurimuses osales 1455 last kaheksast Eesti koolist, neist 646 Tartust, 168 Antslast, 370 Tallinnast ja 271 Harjumaalt. Iga laps täitis koos vanematega ankeedi, kus märgiti põetud haigused ja vastati küsimustele, kas lapsel on olnud sageli (kokku üle 3 kuu aastas) köha, õhupuudustunnet ja hingamisel kiuneid või vilinaid. Kui laps oli põdenud kroonilist hingamiselundite haigust või tal oli vähemalt üks hingamissüsteemiga seotud kaebus, arvasime ta positiivse anamneesiga laste hulka. Vastasel juhul oli laps terve. Laste suitsetamisharjumused saime teada eraldi küsitlusena.

Kõigil lastel mõõtsime pikkuse, istepikkuse, kolm rindkere mõõtu ja kehamassi ning registreerisime forsseeritud hingamise voolu-mahu lingud spiroanalüsaatoriga Pneumoscreen II (Erich JAEGER GmbH). Iga laps sooritas vähemalt kolm forsseeritud välja- ja sissehingamist, analüsaator analüüsis registreeritud voolu-mahu lingusid katmismeetodil. Käesolevas töös võtsime vaatluse alla järgmised näitajad: forsseeritud vitaalkapatsiteedi (FVC), forsseeritud ekspiratoorse sekundimahu (FEV_1), ekspiratoorse tippvoolu (PEF), forsseeritud ekspiratoorsed voolud, kui välja oli hingatud 25, 50 ja 75% FVC-st (FEF_{25}, FEF_{50} ja FEF_{75}) ning keskekspiratoorse voolu (FEF_{25-75}).

Andmete töötlemisel kasutasime programmipaketti *Statistica for Windows 5.0.*

Uurimuse peamised tulemused

Spirograafiliste näitajate suurenemine laste kasvades ei olnud ühtlane protsess. Keskmiste hingamisnäitajate järsem tõus oli nähtav samaaegselt pikkuskasvu spurdiga: tüdrukutel 11. ja 13., poistel 13. ja 15. eluaasta vahel. Samalaadsed

hingamisnäitajate kasvuspurdid olid täheldatavad 150–160 cm pikkusevahemikus tüdrukutel ja 160–170 cm pikkusevahemikus poistel. Istepikkusel ja rindkere mõõtudel olid suurimad tõusud samades vanuse- ja pikkusevahemikes, seega meie läbilõikeuuring ei näidanud ajalist nihet pikkuskasvu ja kehatüve mõõtmete ning spiromeetriliste näitajate kasvuspurtide vahel.

Enne näitajate järsemat muutust olid soolised erinevused kopsude funktsioonis suhteliselt väikesed, ainult FVC ja PEF olid poistel oluliselt suuremad. Et tüdrukute kiirem kasv algas varem, ületasid vahepeal tüdrukute hingamisnäitajad poiste omi, ja kui poisid alustasid spurti, saavutasid jälle nende tulemused ülekaalu. Tüdrukutel korreleerusid spirograafilised näitajad kõige enam kehapikkusega, poistel istepikkusega, ilmselt seetõttu, et poistel muutusid puberteedi saabumisega kehaproportsioonid rohkem.

Kõikide laste andmeid koos analüüsides olid hingamisnäitajate regressioonanalüüsis olulisteks argumenttunnusteks pikkus ja sugu. Kui me lisasime mudelisse veel rindkere mõõtmed ja asendasime kehapikkuse istepikkusega, jäi sugu sageli oluliste argumenttunnuste hulgast välja. Ainult FVC, FEV_1 ja PEF olid poistel alati suuremad. Seega võime kokkuvõttes väita, et laste istepikkuse ja rindkere mõõtude kasv on väga sarnane hingamisparameetrite suurenemisega ja et kasvuspurdiga kaasnevad sama pikkusega poiste ja tüdrukute hingamise funktsionaalsete näitajate erinevused on osaliselt seletatavad kehatüve mõõtmete erinevustega.

Ankeetküsitluse andmetel olid 683 poisist 110 (16,1%) ja 772 tütarlapsest 120 (15,5%) positiivse anamneesiga, astma oli diagnoositud 12 poisil ja 8 tüdrukul. Hingamiskaebustega laste spirograafiliste näitajate võrdlemiseks tervete laste vastavate näitajatega kasutasime sammregressiooni, võimalikeks argumenttunnusteks olid vanus, pikkus ja anamnees. Anamnees valiti oluliseks tunnuseks tüdrukute õhuvoolude mudelites, poistel olulist erinevust kahe grupi hingamisfunktsiooni näitajate vahel ei olnud. Ka teised autorid on leidnud, et poistel esineb küll rohkem astmat, kuid astmast tingitud kopsufunktsiooni vähenemine on tütarlastel märgatavam (Weiss jt., 1992). Erinevuseks, võrreldes nende uuringutega on see, et käesolevas töös oli positiive anamneesiga rühm mitmekesisem kui ainult diagnoositud astmahaiged. Arvestades astma aladiagnoosimise võimalusega, pidasime õigeks kõik hingamiskaebustega lapsed tervete grupist välja jätta.

Sobivaima normväärtuse arvutamise valemi leidmiseks valisime kirjandusest seitsme autoritegrupi poolt aastatel 1987–1998 avaldatud valemite komplektid, kokku 30 valemit nii tüdrukutele kui ka poistele. Meie andmetest kasutasime tervete ja mittesuitsetavate laste (643 tüdrukut ja 527 poissi) voolu-mahu lingu näitajaid. Tegelike ja normväärtuste erinevuse hindamiseks leidsime standardiseeritud jäägid ja regressioonanalüüsiga hindasime nende sõltuvust laste vanusest. Et me ei leidnud ühe autoritegrupi valemite komplekti, mille standardiseeritud jäägid ei sõltuks uuritud laste vanusest ega erineks nullist, siis pi-

dasime põhjendatuks normiarvutusvalemite koostamise tervete Eesti laste andmete põhjal.

Välise hingamise funktsionaalsete näitajate hajuvus suurenes koos lapse pikkuskasvuga ja enamiku hingamisparameetrite jaotus erines oluliselt normaaljaotusest. Logaritmilise transformatsiooni teel saime muuta hajuvuse pikkusest sõltumatuks ja jaotuse lähedaseks normaaljaotusele. Normväärtuste esitamisel kasutasime järgnevat funktsiooni:

$$\ln y = a + b \cdot \ln H + c \cdot \ln A,$$

kus funktsioontunnus y on hingamisnäitaja, a, b ja c — regressioonikoefitsiendid, argumenttunnused H ja A — vastavalt uuritud lapse pikkus ja vanus.

Esitatud valemites on funktsioontunnusteks peamised voolu-mahu lingu näitajad ja argumenttunnusteks kehapikkus ja vanus. Arvestades eelpool mainitud tihedat seost poiste hingamisnäitajate ja istepikkuse vahel, koostasime kehapikkust arvesse võtvate valemitega paralleelselt välja ka need, milles argumenttunnuseks on istepikkus. Et raviarstidel oleks kergem hinnata lapse hingamissüsteemi arengut, konstrueerisime põhiliste välise hingamise näitajate kohta ka protsentiilse jaotusega kasvukõverad.

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PUBLICATIONS

I

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Lung function in Estonian children: effect of sitting height

J. Kivastik and P.-H. Kingisepp

Institute of Physiology, University of Tartu, Tartu, Estonia

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Summary. The present analysis formed part of the population study of Estonian schoolchildren and was undertaken in order to examine the relationships between lung function variables, standing and sitting height. We measured forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), peak expiratory flow and forced expiratory flows when 50 and 75% of FVC had been exhaled, and anthropometric indices in 645 healthy schoolchildren, aged 6–18 years. The growth spurt in standing and sitting height occurred between the ages of 11 and 13 years in girls, and 13 and 15 years in boys. Growth spurts of lung parameters occurred during the same periods. FVC and FEV_1 showed close correlations (r=0·89–0·94) with all anthropometric parameters and age, whereas correlation coefficients for the flows were less close (r=0·65–0·88). In boys, correlations between sitting height and lung function variables were greater than those with standing height. Using stepwise regression analysis, in boys sitting height was selected in all lung function parameters, and in girls sitting height was never selected. We conclude that there is a very close correlation between sitting height and lung function variables. The use of sitting height in parallel with standing height in predicted values for Estonian schoolchildren would make the values more exact.

Key words: adolescents, growth, lung volume and flow, reference values, stature.

Introduction

Measurements of lung function are important for the evaluation of physical development and for the complete assessment of children and adolescents with respiratory diseases. Usually the measurements are compared with standards obtained from healthy individuals of similar age and height. Development of pulmonary function is then described by means of regression equations, usually employing sex, age and standing height as independent variables. Several standard values of lung function indices for Europeans of all ages have been established (Dickman *et al.*, 1971; Quanjer *et al.*, 1989; Pistelli *et al.*, 1992; Rosenthal *et al.*, 1993).

Correspondence: J. Kivastik, Institute of Physiology, University of Tartu, EE2400 Tartu, Estonia.

Many authors have recognized that within the age range 6–18 years the relationship between ventilatory function and stature is non-linear and cannot often be expressed by a single equation (Dickman *et al.*, 1971; Schrader *et al.*, 1984; Schwartz *et al.*, 1988; Sherrill *et al.*, 1992). During the pubertal growth spurt the anthropometric proportions change, and it is possible that the use of sitting height would be more appropriate than standing height, because lung and trunk development could be more closely associated with each (Schrader *et al.*, 1984; Degroodt *et al.*, 1986).

The present study was undertaken in order to examine the relationships between lung volume and flow, standing and sitting height in Estonian schoolchildren.

Subjects and methods

The study was undertaken at five different schools in Estonia between September 1992 and May 1993. A total of 760 schoolchildren were examined, and the parents of each child completed a questionnaire regarding respiratory symptoms or diseases that had occurred in their child. According to the recommendations (Taussig *et al.*, 1980) regarding the definition of a 'healthy' child (no present acute disease and no past or present chronic disease of the respiratory system; no systemic disease which is known to influence the respiratory system and general state of health) a group of boys (n=312) and girls (n=333) aged 6–18 years was selected for the analysis. The study was approved by the Ethics Committee of the University of Tartu.

Children in the age range 6 years–6 years 11 months were included in age group 6, those aged 7 years–7 years 11 months were included in age group 7, and so on. Body weight and standing height were measured in all subjects without wearing shoes. We measured standing height as the child stood erect, with heels close together and the arms hanging naturally at the sides. The external auditory meatus and the lower border of the orbit were in a plane parallel with the floor. Sitting height was measured, while the child was in an upright sitting position, from the vertex of the head to the base of the seat. Both heights were measured using the anthropometer and read to the nearest millimetre.

The spiroanalyser Pneumoscreen II ('Jaeger') was used to record the static and dynamic lung parameters. The measurement of flow was achieved by means of a pneumotachographical open system, and the volume was determined by electronic digital integration. The analyser was calibrated with a 1-l syringe each time the unit was switched on. The child was sitting during the test, and a noseclip was used. After inhaling as deeply as possible, the child was told to blow out as hard and as far as he or she was capable. The maximum envelope of at least three similar flow-volume loops was analysed. In this study we examined only one part of the recorded volume and flow values (expressed at body temperature, pressure and saturation): forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), peak expiratory flow (PEF), and forced expiratory flows when 50 and 75% of FVC had been exhaled (FEF_{50} and FEF_{75}).

DATA ANALYSIS

Descriptive data were treated by univariate analysis. Correlation coefficients were calculated for the anthropometric and lung function measurements. For the correlation analysis we arranged children into four groups for both sexes (Tables 1 and 2). Stepwise multiple regression was used to assess the effects of age, weight, standing and sitting height on parameters of lung function. Calculations were performed using the STATGRAPHICS computer program.

Results

The mean data for body weight, standing and sitting height are presented in Tables 1 and 2. The growth spurt, an important indicator of the onset of puberty, both in standing and sitting height, was from 11 to 13 years in girls, and from 13 to 15 years in boys. Values of different lung function variables according to age are presented in Figs 1 and 2. Mean values and standard deviations of FEV_1 were calculated from data for 250 boys and 237 girls, because the duration of forced expiration in some of the children, especially the younger ones was less than 1 s. Among the 6-year-old children there were only two boys and three girls who had a forced expiratory time period of more than 1 s; therefore means of FEV_1 in children of age 6 years are not presented.

The correlation matrices shown in Tables 3 and 4 indicate positive correlations of lung parameters with all anthropometric variables in both sexes. In most cases the correlation between lung parameters and both heights was higher in the group at the growth spurt (i.e. group II for girls and group III for boys) than before or after that time. Comparing the coefficients of correlation with different anthropometric parameters, sitting height often yielded the closest correlation with pulmonary volume and flow, especially in boys.

Table 1. Anthropometric data (boys)

Group	Age (years)	*n*	Standing height (cm)	Sitting height (cm)	Weight (kg)
I	6	21	114·2 (4·64)	63·3 (2·73)	19·9 (2·38)
	7	10	127·3 (3·30)	69·6 (1·59)	24·6 (2·47)
	8	23	132·9 (5·82)	71·4 (1·73)	28·2 (3·08)
	9	23	136·5 (4·94)	72·8 (3·01)	30·3 (3·71)
II	10	34	143·0 (5·30)	74·5 (2·55)	33·3 (4·28)
	11	16	146·4 (7·03)	75·8 (3·38)	37·4 (6·15)
	12	19	152·7 (6·95)	78·0 (3·08)	38·4 (5·80)
III	13	13	157·5 (4·06)	80·2 (2·80)	44·3 (6·43)
	14	48	170·9 (7·13)	86·5 (4·36)	55·7 (8·76)
	15	45	176·6 (7·37)	90·3 (3·83)	61·4 (9·86)
IV	16	30	177·7 (8·23)	90·9 (4·46)	62·4 (9·24)
	17	24	180·9 (6·27)	93·9 (3·13)	68·4 (8·18)
	18	6	183·2 (4·88)	92·7 (2·71)	71·2 (8·21)

Mean values are shown, with SD in parentheses.

Table 2. Anthropometric data (girls)

Group	Age (years)	*n*	Standing height (cm)	Sitting height (cm)	Weight (kg)
I	6	14	118·8 (5·42)	65·3 (3·08)	22·4 (2·42)
	7	16	124·9 (4·01)	66·3 (2·97)	22·9 (3·34)
	8	22	131·4 (5·53)	70·5 (3·24)	27·2 (3·36)
	9	22	138·4 (6·65)	73·4 (3·01)	30·4 (5·07)
	10	26	141·0 (5·02)	73·7 (2·60)	31·8 (4·50)
II	11	12	142·5 (5·67)	74·3 (2·98)	32·3 (4·12)
	12	13	151·0 (8·92)	78·7 (4·92)	40·3 (8·79)
	13	13	163·5 (8·08)	84·6 (3·21)	53·2 (7·27)
III	14	52	163·5 (4·96)	85·1 (3·01)	52·1 (7·04)
	15	54	165·0 (5·41)	86·8 (2·54)	55·6 (8·46)
IV	16	52	165·2 (5·50)	86·5 (2·50)	56·8 (9·02)
	17	30	166·1 (6·31)	86·9 (2·57)	57·5 (7·34)
	18	7	171·3 (3·92)	88·3 (1·86)	63·0 (12·0)

Mean values are shown, with SD in parentheses.

Stepwise regression analyses of FVC, FEV_1, PEF, FEF_{50} and FEF_{75} on age and anthropometric parameters were performed separately for boys and girls. Input variables were age, standing height, sitting height and weight, and the selected variables and coefficients of determination are presented in Table 5. In boys, sitting height was selected in all cases, whereas it was not selected in any cases in girls.

Discussion

The present analysis forms part of a population study to obtain reference values of pulmonary function for Estonian schoolchildren, as these have not been reported previously.

Several factors, such as age and anthropometric parameters, have been found to influence the normal lung function values in children and adolescents. It has been shown in previous longitudinal studies (DeGroodt *et al.*, 1986; Jaeger-Denavit & Alphonse, 1990; Borsboom *et al.*, 1993) that the growth spurt of the lung and of thoracic dimensions lags somewhat behind that for standing height. Borsboom *et al.* (1993) have reported that in boys the average peak growth rate for standing height occurred at the age of 13·8 years, whereas the peak growth rate for FVC occurred 0·8 years later, that for FEV_1 and PEF occurred 1·1 years later and that for FEF_{50} occurred 1·5 years later than the peak growth rate for height. Because the spurt of standing height takes place first, adolescents tend to have small lungs relative to their height at the start of puberty. The reverse is true at the end of puberty; the lungs then alter faster than height, and adolescents will tend to have large lungs for their stature. Therefore, the use of sitting height as the reference variable in the prediction equations for lung parameters would be more exact, because trunk development could be more closely associated with lung development (Schrader *et al.*, 1984; Degroodt *et al.*, 1986). Some authors have found a

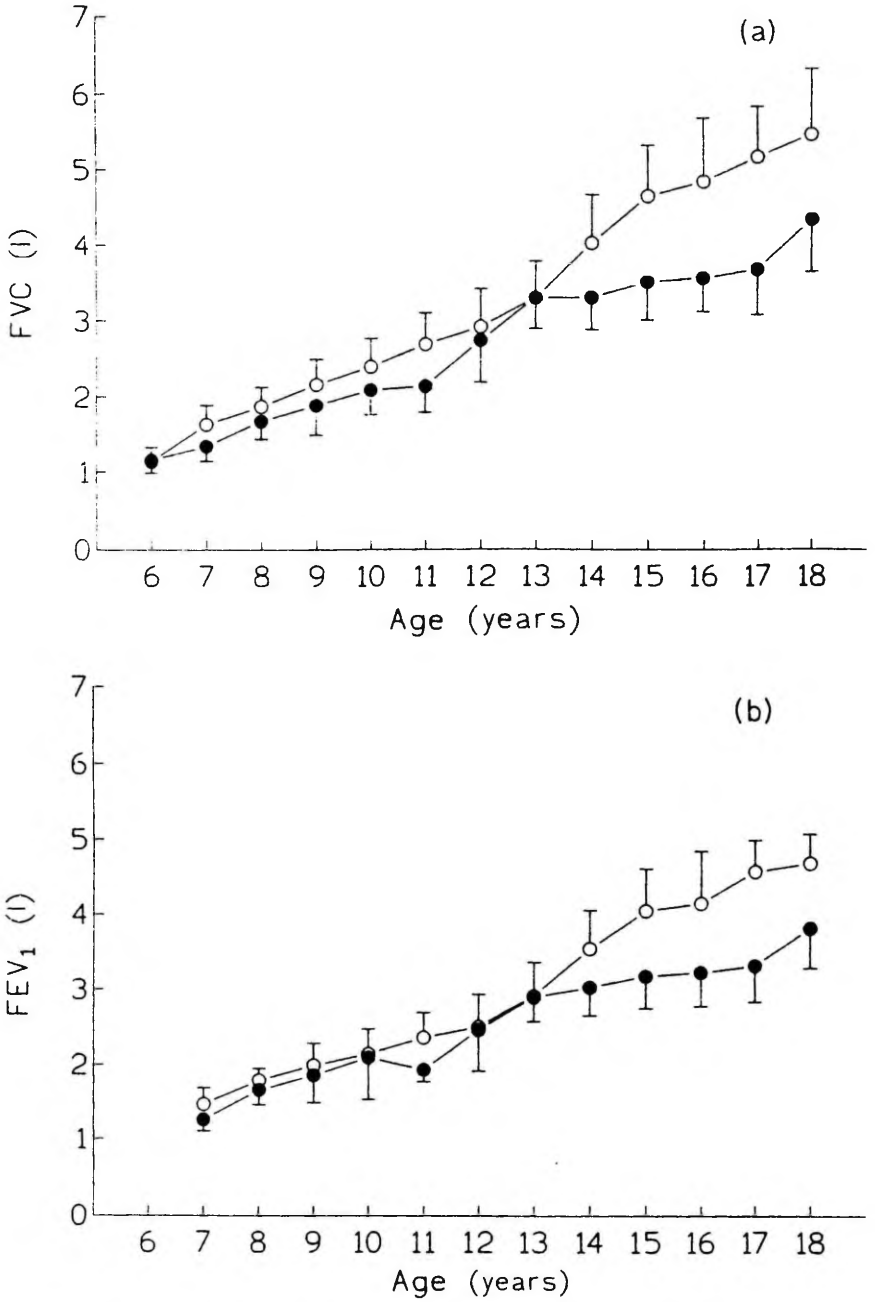

Fig. 1. Mean values and standard deviations (a) of forced vital capacity (FVC) and (b) of forced expiratory volume in 1 s (FEV_1) as a function of age in girls (solid circles) and boys (open circles).

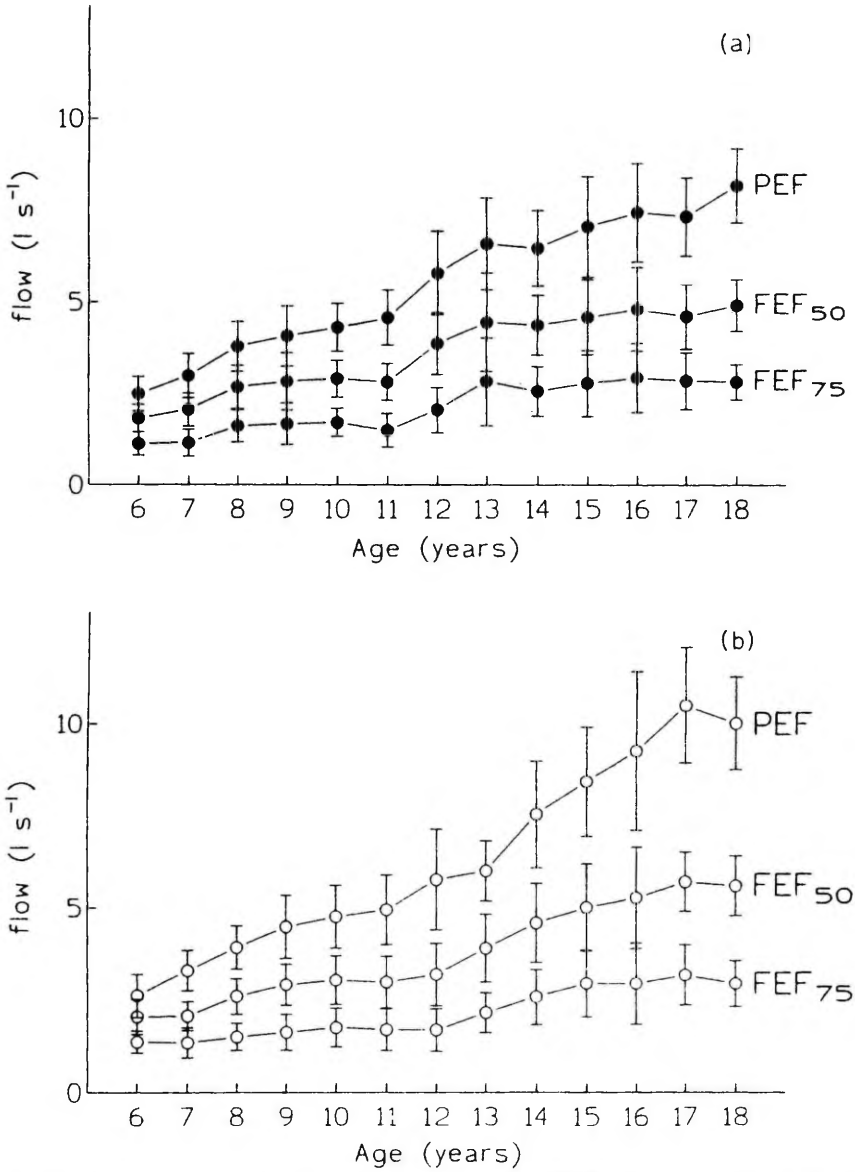

Fig. 2. Mean values and standard deviations of peak expiratory flow (PEF) and forced expiratory flows, when 50 and 75% of FVC had been exhaled (FEF_{50} and FEF_{75}) as a function of age (a) in girls and (b) in boys.

closer correlation between lung function variables and sitting height (Engström *et al.*, 1956; Rahman *et al.*, 1990), while others have found a closer correlation between these variables and standing height (Pistelli *et al.*, 1978; Hsu *et al.*, 1979; Wall *et al.*, 1982).

The fact that our study was cross-sectional rather than longitudinal possibly explains why a time lag between growth spurts of standing height and lung dimensions was not

Table 3. Correlation coefficients of FVC, FEV_1, PEF, FEF_{50} and FEF_{75} with age and anthropometric parameters in boys

	FVC	FEV_1	PEF	FEF_{50}	FEF_{75}
Age					
All*	0·92	0·89	0·87	0·79	0·65
I	0·86	0·56	0·78	0·61	0·30
II	0·45	0·41	0·37	NS	NS
III	0·59	0·62	0·52	0·35	0·38
IV	0·40	0·42	0·22	NS	NS
Standing height					
All	0·94	0·94	0·87	0·82	0·69
I	0·85	0·59	0·70	0·58	0·28
II	0·74	0·75	0·66	0·42	0·32
III	0·77	0·83	0·55	0·51	0·49
IV	0·55	0·62	0·29	0·31	0·19
Sitting height					
All	0·94	0·94	0·88	0·83	0·72
I	0·83	0·66	0·72	0·59	0·30
II	0·72	0·75	0·61	0·45	0·36
III	0·77	0·83	0·59	0·49	0·52
IV	0·56	0·67	0·43	0·37	0·26
Weight					
All	0·93	0·92	0·87	0·82	0·68
I	0·80	0·49	0·71	0·61	0·30
II	0·70	0·66	0·51	0·33	0·22
III	0·74	0·78	0·56	0·56	0·47
IV	0·60	0·55	0·32	0·19	NS

*Correlation analysis was performed in a group consisting of all boys ($n=312$), and in four age groups, except for correlation analysis of FEV_1, where the total number of boys was 250 (see text).

FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow; FEF_{50} and FEF_{75}, forced expiratory flows when 50 and 75% of FVC has been exhaled; NS, correlation not statistically significant ($P>0·05$).

observed in our data. The growth spurt in standing height in Estonian girls occurred between 11 and 13 years of age, while that in boys occurred between 13 and 15 years. Growth spurts in lung parameters took place during the same periods. As the growth spurt began earlier in girls, at the ages of 12 and 13 years girls showed higher sitting height and weight values and at the age of 13 years higher standing height values than boys of the same age (Tables 1 and 2). Teenage girls never had higher values of FVC and FEV_1 than boys of the same age, but this was the case for the values of PEF, FEF_{50} and FEF_{75} at the ages of 12 and 13 years (Figs 1 and 2).

FVC and FEV_1 showed very close correlations with all anthropometric parameters and age, while the correlation coefficients for the flows were less close. In general, the correlation coefficients calculated for girls were less than those for boys. When arranged into four age groups, the correlation between lung parameters and both heights was

Table 4. Correlation coefficients of FVC, FEV_1, PEF, FEF_{50} and FEF_{75} with age and anthropometric parameters in girls

	FVC	FEV_1	PEF	FEF_{50}	FEF_{75}
Age					
All*	0·89	0·82	0·84	0·73	0·62
I	0·76	0·65	0·71	0·55	0?43
II	0·71	0·66	0·63	0·57	0·57
III	0·23	0·17	0·21	NS	NS
IV	0·32	0·33	NS	NS	NS
Standing height					
All	0·92	0·88	0·85	0·79	0·68
I	0·83	0·62	0·72	0·60	0·41
II	0·89	0·90	0·75	0·75	0·71
III	0·50	0·58	0·33	0·35	0·33
IV	0·56	0·62	0·37	0·39	0·39
Sitting height					
All	0·90	0·86	0·84	0·78	0·68
I	0·78	0·54	0·67	0·55	0·43
II	0·88	0·88	0·71	0·69	0·65
III	0·39	0·53	0·31	0·35	0·35
IV	0·41	0·45	0·33	0·37	0·38
Weight					
All	0·89	0·83	0·80	0·74	0·60
I	0·75	0·57	0·64	0·52	0·37
II	0·86	0·81	0·54	0·57	0·63
III	0·56	0·51	0·25	0·22	NS
IV	0·46	0·44	0·30	0·32	NS

*Correlation analysis was performed in a group consisting of all girls (n=333), and in four age groups, except for correlation analysis of FEV_1, where the total number of girls was 237 (see text).

For definition of abbreviations, see footnote to Table 3.

higher in the group at the growth spurt stage than before or after that time. In boys, the correlation of lung function values with sitting height was often marginally greater than the correlation with standing height. In girls, standing height was usually a better predictor than sitting height (Tables 3 and 4).

Using stepwise regression analysis, the effects of age and anthropometric parameters were assessed (Table 5). Age, weight, standing and sitting height were all considered as independent variables. In boys, sitting height was selected in all lung function parameters, and in the equation for PEF sitting height was selected together with standing height. In girls, sitting height was never selected. The same results were obtained using stepwise regression analysis in different age groups (data not shown).

The relationship between sitting and standing height can be shown by the ratio of sitting to standing height. This ratio was about 0·55 in 6-year-old boys and girls, decreased to 0·518 in 13-year-old girls and to 0·506 in 14-year-old boys, and subsequently increased to 0·526 in girls and to 0·519 in boys (Fig. 3), as has also been reported in

Table 5. Stepwise regression analysis

Lung parameter	Sex	Variables selected	R^2
FVC	Boys	A, Sh, W	0·91
	Girls	A, H, W	0·87
FEV_1	Boys	A, Sh, W	0·91
	Girls	H, W	0·80
PEF	Boys	A, H, Sh, W	0·80
	Girls	A, H, W	0·75
FEF_{50}	Boys	Sh, W	0·69
	Girls	H, W	0·62
FEF_{75}	Boys	Sh	0·51
	Girls	H	0·46

R^2, coefficient of determination; A, age (years); H, standing height (cm); Sh, sitting height (cm); W, weight (kg).

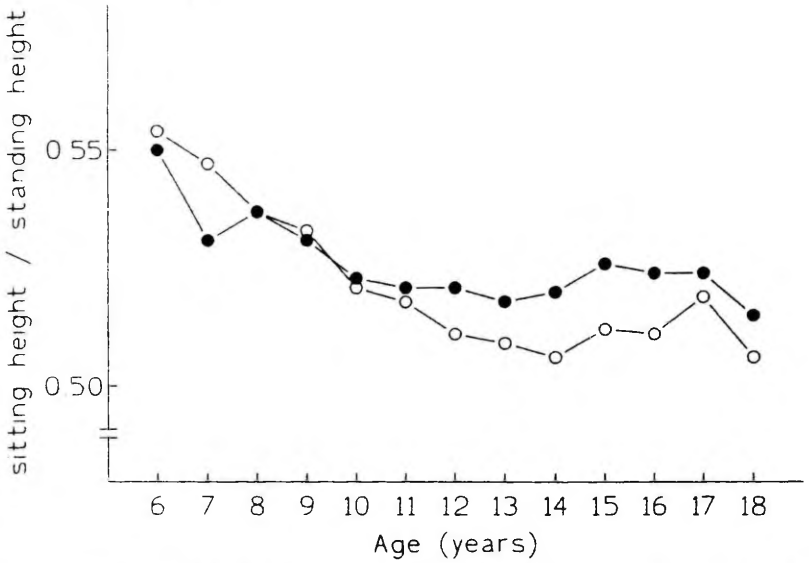

Fig. 3. Mean values of ratio of sitting height/standing height as a function of age in girls (solid circles) and boys (open circles).

Estonian schoolchildren in a previous anthropometric study (Silla & Teoste, 1989). In boys, the ratio showed a greater change, and leg length was longer than that in girls. Perhaps this was the reason why, in boys, the correlation between lung parameters and sitting height as a measure of trunk size was higher than in girls. Schwartz *et al.* have also reported that a substantial portion of the sex difference in pulmonary growth rates can be accounted for by differences in the increase in trunk length for the same standing height (Schwartz *et al.*, 1988).

We conclude that the correlations between sitting height and lung function variables are very close. The measurement of sitting height in the population sample in order to determine the predicted values for Estonian children and adolescents, and the use of sitting height in parallel with standing height would make the values more exact.

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II

J. Kivastik, P.-H. Kingisepp
Differences in lung function and
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Differences in lung function and chest dimensions in school-age girls and boys

J. Kivastik and P.-H. Kingisepp

Department of Physiology, University of Tartu, Tartu, Estonia

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Summary. The present analysis was undertaken to find out whether differences in the performance of the lungs of boys and girls of the same height are explicable by differences in thoracic size. We measured forced vital capacity (FVC), peak expiratory flow (PEF) and forced expiratory flows (FEFs), when 50% and 75% of FVC had been exhaled (FEF_{50}, FEF_{75}), and standing height, chest width and depth and biacromial diameter in 1187 schoolchildren aged 6–18 years. Thoracic dimensions were usually greater in boys than in girls of the same height, except for the height range of 150·0–164·9 cm. For this height range, the pulmonary function variables (PEF, FEF_{50}, FEF_{75} and PEF/FVC) were significantly higher in girls, and for FVC almost as high as the male values. For FEF_{50}/FVC and FEF_{75}/FVC, the female values were larger over the whole height range (115·0–184·9 cm), but even for these parameters the differences were greatest for the height range 150·0–164·9 cm. In conclusion, very similar growth patterns of lung function and thoracic parameters can suggest that differences in the lung function parameters of boys and girls of the same height may be explained by differences in the thorax size.

Key words: adolescents, anthropometry, children, growth, lung volumes and flows.

Introduction

Several investigations of spirometric variables in children have established that during puberty spirometric values exhibit a profound change, which often cannot be described by single equations (Schrader *et al.*, 1984; Schwartz *et al.*, 1988a; Sherrill *et al.*, 1992; Rosenthal *et al.*, 1993). Sex differences in lung function also emerge during puberty. It has been suggested that a complex relationship seems to exist between sex, anthropometric measures and age in predicting the lung function (Schwartz *et al.*, 1988b).

It was the aim of this study to analyse whether differences in the performance of the lungs of boys and girls of the same height may be explained by differences in thoracic size.

Correspondence: J. Kivastik, Department of Physiology, University of Tartu, EE2400 Tartu, Estonia.

Methods

SUBJECTS AND DATA COLLECTION

The study was carried out at eight different schools in Estonia from September 1992 to April 1995. A total of 1187 schoolchildren was examined. The parents of each pupil completed a questionnaire on previous respiratory symptoms or diseases in their child. This identified 95 boys and 114 girls with at least one respiratory symptom. The study was approved by the Ethics Committee of the University of Tartu.

Some of the data collected have been used for the assessment of the association between sitting height and lung function as described in a previous paper (Kivastik & Kingisepp, 1995). That description also includes the measurement of body weight, standing and sitting height of the children.

Chest dimensions were measured at the end of normal expiration on the standing subject by a large metal sliding caliper. Chest width (transverse chest diameter) and depth (anteroposterior chest diameter) were measured at the level of the fourth rib. Biacromial diameter was measured as the distance between the acromions.

A spiroanalyser Pneumoscreen II (Jaeger) was used to register static and dynamic lung parameters. Measurements of flow were made by a pneumotachographical, open system. Lung volumes were determined by electronic, digital integration of the flow signals. The analyser was calibrated with a 1-l syringe each time the equipment was switched on.

During the test, three to four children were watching the performance of the current test subject, to reduce the need for instructions when their turn came. The child was sitting during the test and a noseclip was used. After exhaling as fully as possible, each child was asked to breathe in to total lung capacity (TLC), subsequently blow out as hard and as fast as possible to residual volume, and then reinspire in a similar manner back to TLC. The maximum envelope of at least three correctly performed flow–volume loops was analysed and processed for calculation of forced vital capacity (FVC), peak expiratory flow (PEF) and forced expiratory flows when 50% and 75% of FVC had been exhaled (FEF_{50} and FEF_{75}) (all expressed at BTPS).

DATA ANALYSIS

The material was subdivided according to height into 5-cm classes (Table 1). Differences between class means for boys and girls were assessed for statistical significance using an unpaired Student's *t*-test. One-way ANOVA (Tukey HSD for unequal sample sizes) was performed to compare the mean values for each class.

Calculations were done with the STATISTICA computer program.

Results

None of the 95 boys (17·2% of the total of 552 boys) and 114 girls (18·0% of the total of 635 girls) with at least one respiratory symptom was affected by major thoracic, neuro-

Table 1. Data of volume-adjusted flows

Height group	Height range (cm)	No. of children		PEF/FVC (s^{-1})		FEF_{50}/FVC (s^{-1})		FEF_{75}/FVC (s^{-1})	
		Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys
1	<120	5	1	2·04 (0·40)	1·76	1·34 (0·20)	0·84	0·73 (0·20)	0·73
2	120–124·9	10	7	2·02 (0·59)	1·90 (0·38)	1·44 (0·37)	1·15 (0·31)	0·88 (0·28)*	0·61 (0·21)
3	125–129·9	25	25	2·20 (0·47)	1·96 (0·42)	1·49 (0·38)*	1·25 (0·29)	0·83 (0·25)*	0·65 (0·18)
4	130–134·9	30	46	2·05 (0·29)	2·02 (0·36)	1·37 (0·31)*	1·22 (0·25)	0·77 (0·26)	0·70 (0·22)
5	135–139·9	56	63	2·06 (0·30)*	1·93 (0·35)	1·40 (0·29)*	1·21 (0·29)	0·82 (0·25)*	0·68 (0·23)
6	140–144·9	47	51	2·00 (0·43)	1·98 (0·35)	1·30 (0·34)	1·19 (0·30)	0·75 (0·27)	0·65 (0·25)
7	145–149·9	44	52	1·97 (0·28)	1·87 (0·34)	1·27 (0·26)*	1·12 (0·30)	0·69 (0·21)*	0·59 (0·23)
8	150–154·9	38	36	2·08 (0·34)*	1·80 (0·25)	1·35 (0·28)*	1·10 (0·25)	0·77 (0·25)*	0·59 (0·19)
9	155–159·9	79	35	2·01 (0·35)*	1·82 (0·33)	1·28 (0·29)*	1·04 (0·22)	0·70 (0·25)*	0·53 (0·13)
10	160–164·9	118	30	2·03 (0·36)*	1·84 (0·42)	1·33 (0·32)*	1·10 (0·27)	0·80 (0·24)*	0·58 (0·22)
11	165–169·9	122	42	1·98 (0·31)	1·94 (0·30)	1·28 (0·26)*	1·12 (0·20)	0·77 (0·23)*	0·64 (0·19)
12	170–174·9	46	45	2·00 (0·36)	1·95 (0·45)	1·31 (0·31)*	1·12 (0·27)	0·81 (0·27)*	0·66 (0·22)
13	175–179·9	13	52	1·85 (0·26)	1·95 (0·33)	1·30 (0·33)	1·14 (0·24)	0·83 (0·31)*	0·63 (0·19)
14	180–184·9	2	37	1·85	1·83 (0·42)	1·10	1·08 (0·28)	0·81	0·62 (0·23)
15	>184·9	–	30	–	1·90 (0·31)	–	1·10 (0·25)	–	0·62 (0·19)

Mean values are shown with SD in parentheses.

*Significant difference between girls and boys ($P<0·05$, Student's unpaired t-test).

PEF, peak expiratory flow; FVC, forced vital capacity; FEF_{50} and FEF_{75}, forced expiratory flows, when 50% and 75% of FVC has been exhaled.

Table 2. Data of sitting height and ratio of chest width to sitting height

Height group	Height range (cm)	Sitting height (cm)		Chest width/sitting height	
		Girls	Boys	Girls	Boys
1	<120	64·0 (2·0)	66·2	0·291 (0·014)	0·313
2	120–124·9	65·2 (1·9)	67·2 (1·2)*	0·287 (0·016)	0·288 (0·014)
3	125–129·9	69·0 (1·8)	70·2 (1·7)*	0·279 (0·012)	0·284 (0·014)
4	130–134·9	71·4 (2·2)	71·1 (1·7)	0·277 (0·017)	0·286 (0·014)
5	135–139·9	73·0 (1·6)	73·3 (1·7)	0·275 (0·016)	0·287 (0·016)
6	140–144·9	75·4 (2·2)	75·1 (1·7)	0·283 (0·025)	0·288 (0·016)
7	145–149·9	77·7 (2·0)	77·0 (1·6)	0·278 (0·015)	0·291 (0·014)
8	150–154·9	80·9 (2·4)*	79·0 (2·0)	0·283 (0·018)	0·287 (0·019)
9	155–159·9	83·6 (2·4)*	80·4 (2·1)	0·282 (0·021)	0·290 (0·015)
10	160–164·9	85·6 (2·1)*	82·9 (2·1)	0·284 (0·017)	0·296 (0·017)
11	165–169·9	88·5 (2·3)*	86·1 (2·7)	0·282 (0·018)	0·301 (0·020)§
12	170–174·9	89·4 (2·0)	89·0 (2·5)	0·279 (0·019)	0·301 (0·020)§
13	175–179·9	91·2 (2·2)	91·1 (2·5)	0·284 (0·013)	0·298 (0·020)
14	180–184·9	92·2	93·9 (3·5)	0·280	0·294 (0·020)
15	>184·9	–	96·1 (2·7)	–	0·298 (0·021)

Mean values are shown with SD in parentheses.
*Significant difference between girls and boys ($P<0·05$, Student's unpaired t-test).
§Significant differences in boys between (1) group 11 vs. groups 3, 4, 5 and 8; (2) group 12 vs. groups 3, 4 and 5 ($P<0·01$, Tukey HSD for unequal sample sizes).

logical or systemic diseases. The prevalence of a history of respiratory symptoms in the two sexes did not differ significantly ($P=0·74$, Pearson χ^2 test). Differences in lung function between the groups of all subjects and subjects without respiratory symptoms were negligible. Therefore, we analysed the entire sampled population as one group.

Mean values of different lung function variables are presented in Figs 1 and 2. There was a sudden discontinuity in values in the girls between 150·0 and 159·9 cm and in the boys between 160·0 and 169·9 cm. In the children under 150·0 cm in height, FVC and PEF were significantly higher in boys than in girls. This was not seen for FEF_{50} and FEF_{75}. Between the heights of 150·0 cm and 164· 9 cm, when girls typically have their pubertal growth spurt, all female spirometric values were higher than male ones (except for FVC). After 165·0 cm, when boys are typically in their pubertal growth spurt, male FVC and PEF values were significantly higher than female values, the differences increasing with height. Again, the differences in FEF_{50} and FEF_{75} were not significant.

To examine the effects of sex on the dimensions of expiratory flow relative to lung volume, we divided PEF, FEF_{50} and FEF_{75} for each subject by his/her FVC. PEF/FVC and FEF_{50}/FVC in girls and FEF_{50}/FVC in boys were significantly negatively correlated with height (Table 1). All volume-adjusted flows were greater in girls than boys. For PEF/FVC however, the difference was significant only in the height range 150·0–154·9 cm. FEF_{50}/FVC and FEF_{75}/FVC continued to be higher in girls until late adolescence.

The mean data of sitting height and thoracic parameters by height groups are presented in Table 2 and Fig. 3. In children under 150·0 cm. there were mostly higher male values

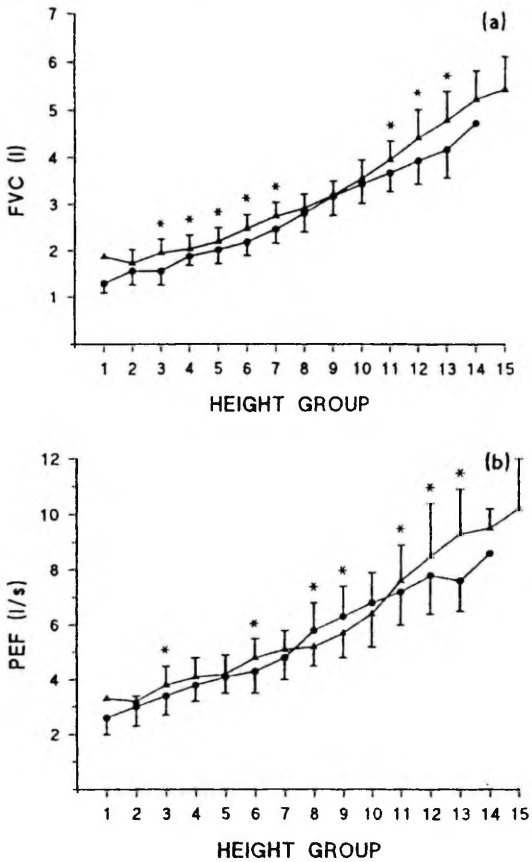

Fig. 1. Mean values and standard deviations of (a) forced vital capacity (FVC) and (b) peak expiratory flow (PEF) by height groups in girls (circles) and boys (triangles). *Significant difference between girls and boys ($P<0{\cdot}05$, Student's unpaired t-test).

for sitting height and all three thoracic size indices. Between heights of 150·0 and 164·9 cm, sitting height and biacromial diameter were significantly greater in girls; the differences in chest width and depth were not significant. For individuals taller than 165·0 cm, sitting height was greater in girls, but all thoracic dimensions were significantly higher in boys.

The ratio of chest width to sitting height helped us to decide if these two parameters had changed similarly. It was more or less constant in the girls irrespective of height. In the boys, the ratio was significantly greater for the height interval of 165·0–174·9 cm (Table 2).

Discussion

Several factors, such as age and anthropometric parameters, have been shown to influence the normal lung function values in children and adolescents. It has been

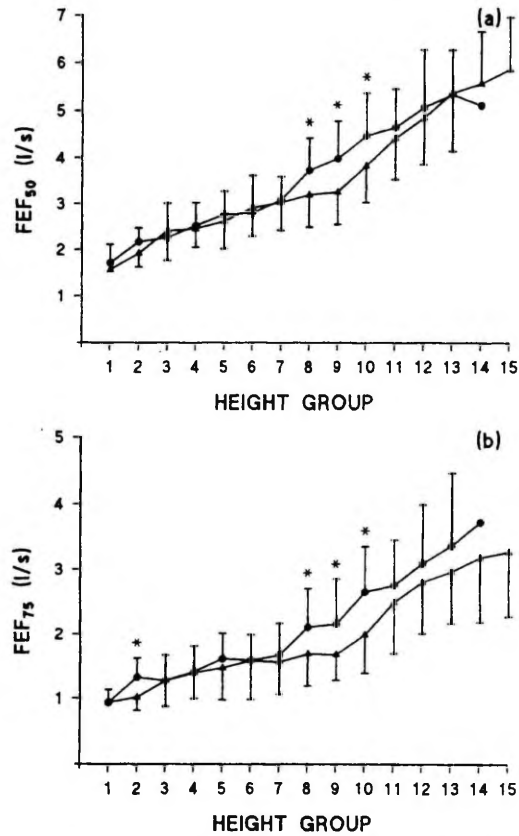

Fig. 2. Mean values and standard deviations of forced expiratory flows, when (a) 50% and (b) 75% of FVC has been exhaled (FEF_{50} and FEF_{75} respectively) by height groups in girls (circles) and boys (triangles). *Significant difference between girls and boys ($P<0{\cdot}05$, Student's unpaired t-test).

demonstrated in longitudinal studies (Degroodt *et al.*, 1986; Jaeger-Denavit & Alphonse, 1990; Borsboom *et al.*, 1993) that the growth spurts of the lung and of thoracic dimensions lag behind that of standing height. Therefore, the use of sitting height as the reference variable in the prediction equations for lung parameters would be more exact because trunk development might be more closely associated with lung development (Schrader *et al.*, 1984; Degroodt *et al.*, 1986; Kivastik & Kingisepp, 1995). As the lung is contained in the thorax, it seems plausible that the changes in thoracic dimensions will also have a bearing on the development of lung parameters (Degroodt *et al.*, 1988).

Some authors have not found any significant differences in lung performance between boys and girls (Michaelson *et al.*, 1978; Bellon *et al.*, 1982; Zapletal, 1982), but many have (Leeder *et al.*, 1977; Wall *et al.*, 1982; Schwartz *et al.*, 1988 a,b; Pistelli *et al.*, 1992; Rosenthal *et al.*, 1993). The purpose of our study was to find out whether the differences in the performance of the lungs of boys and girls of the same height might be explained by the differences in chest width and depth, and biacromial diameter.

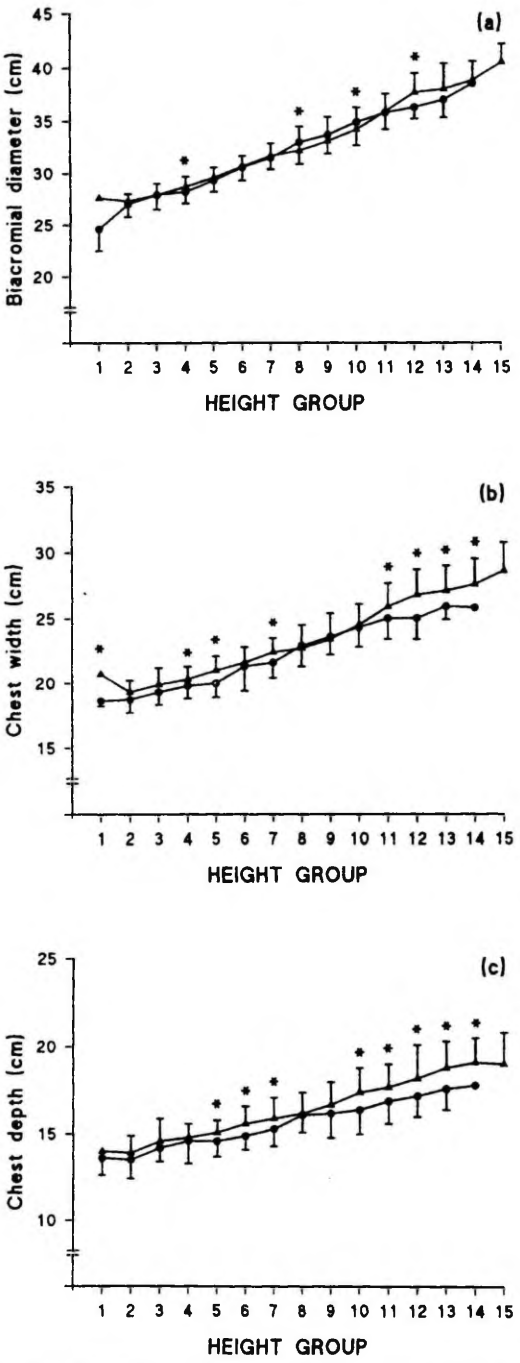

Fig. 3. Mean values and standard deviations of (a) biacromial diameter, (b) chest width and (c) chest depth by height groups in girls (circles)and boys (triangles). *Significant difference between girls and boys ($P<0{\cdot}05$, Student's unpaired t-test).

The sudden change in lung function in each sex that appeared to coincide with the pubertal growth spurt (i.e. between 150·0 cm and 159·9 cm in girls and 160·0 cm and 169·9 cm in boys) corresponds with the observations of Rosenthal *et al.* (1993). For the younger ages, the differences between the sexes for the various indices are also in agreement with previous reports, such as the compilation of reference values for lung function measurements (Quanjer *et al.*, 1989).

Determination of flows, corrected for lung size, is very important especially in children and adolescents, since, on this basis, it is possible to compare the values in growing subjects of various age, height and lung size (Zapletal *et al.*, 1982). In our data, PEF and FEF_{50} in girls and FEF_{50} in boys adjusted to FVC decreased significantly with increasing height. This decrease of volume-adjusted flows with an increase in body height has also been found by others (Leeder *et al.*, 1977; Zapletal *et al.*, 1982), whereas some authors have not seen it (Michaelson *et al.*, 1978; Bellon *et al.*, 1982). It has been suggested as being caused by the growth of the peripheral airways not proceeding at the same rate as the growth of the alveoli between the ages of 6 and 17 years.

Several authors (Wall *et al.*, 1982; Rosenthal *et al.*, 1993) have suggested that until shortly after puberty girls have greater volume-adjusted flows than boys but that boys may catch up in their late adolescence. In our sample, flows normalized by FVC were higher in girls than in boys, yet this difference in PEF/FVC was significant only in the height range 150·0–164·9 cm. FEF_{50}/FVC and FEF_{75}/FVC continued to be higher in girls until late adolescence, which accords with the findings of Schwartz *et al.* (1988b).

In a 6-year follow-up study of adolescents whose ages ranged between 11·5 and 18·5 years, Degroodt *et al.* (1988) showed that thoracic width in females hardly changed during the study, while thoracic height clearly increased. In boys, thoracic height increased twice as fast as thoracic width. Thus, there was a relative elongation of the thorax. Unfortunately, the authors did not report any data on the changes in standing or sitting height of their subjects. This finding of a relative elongation of the thorax was in contrast to the results of Openshaw *et al.* (1984) who found in a cross-sectional study that after the age of 10 years the diaphragm stays at about the same vertebral level at full lung inflation.

As we did not measure the thoracic height and our study was cross-sectional, unlike the study of Degroodt *et al.* (1988), it remains unclear how the thoracic width is related to thoracic height in our data, and what pattern the ratio of thoracic width to sitting height would follow in a longitudinal study. In our study, we found that, in boys between the heights of 165·0 cm and 174·9 cm, the ratio of chest width to sitting height is rather large, whereas in girls this ratio is constant over the whole height range (Table 2). This difference may contribute to the continuing divergence of boys' and girls' lung function (FVC, PEF) after puberty.

In conclusion, a very similar growth pattern of thoracic dimensions and lung function parameters suggests that differences in the lung function parameters between boys and girls of the same height may be explained by differences in thoracic size.

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III

J. Kivastik, P.-H. Kingisepp
Flow-volume loop parameters in healthy children and
in children with respiratory symptoms.
Eesti Arst 1999; 4: 291–294 (in Estonian).

Eesti Arst, 1999, 4, 291—294

TEOORIA JA PRAKTIKA

Voolu-mahu lingu näitajad tervetel ja hingamiskaebustega lastel

Jana Kivastik Peet-Henn Kingisepp

laste hingamisuuringud, voolu-mahu ling, hingamiselundite haigused

Äge hingamisteede infektsioon või kroonilise haiguse ägenemine toob endaga kaasa välise hingamise funktsionaalsete näitajate vähenemise võrreldes haiguseelse seisundiga. Pärast ägedate haigusnähtude möödumist (näiteks astma remissioonifaasis) enamik näitajaid tavaliselt taastub.

Paljudes uurimustes on püütud leida kopsude mahu või õhuvoolu näitajat, mille abil oleks võimalik eristada terveid ja anamneesis hingamiskaebusi esitanud lapsi, kuid ühtseid kriteeriume ei ole siiani leitud (1, 2, 3, 6, 7, 9, 11). Hingamiselundite funktsiooni hindamisel kasutatavate normväärtuste sobivuse kontrollimisel või uute leidmisel ei tohiks vaatlusalustel olla hingamiselundite haigusi, kasutusel on spetsiaalne terve lapse (*healthy child*) mõiste (10).

Käesoleva töö eesmärgiks seati hingamisfunktsiooni näitajate erinevuste hindamine tervetel ja hingamiskaebuste või krooniliste haigustega koolilastel.

Jana Kivastik, Peet-Henn Kingisepp — Tartu Ülikooli Füsioloogia Instituut

Uurimismaterjal ja -meetodid. Vaatlusalusteks oli 1455 last Eesti koolidest, neist 646 last Tartust, 168 Antslast, 370 Tallinnast ja 271 Harjumaalt. Iga laps täitis koos vanematega ankeedi, millele märkis põetud haigused ja vastas küsimustele selle kohta, kas lapsel on esinenud sageli (kokku üle kolme kuu aastas) köha, kas lapsel on esinenud õhupuudustunnet ägedate infektsioonidega seotult või füüsilisel pingutusel, kas lapsel on esinenud hingamisel kiuneid või vilinaid. Kui laps oli põdenud kroonilist hingamiselundite haigust või esines tal vähemalt üks hingamissüsteemiga seotud kaebus, arvasime ta "positiivse anamneesiga" laste hulka. Vastasel korral oli laps "negatiivse anamneesiga", s.t. terve.

Kõigil lastel mõõdeti pikkus ja kehakaal, seejärel registreeriti forsseeritud hingamise voolu-mahu lingud spiroanalüsaatoriga *Pneumoscreen* II (*Jaeger*). Uuringute ajal vaatlusalune istus, nina näpitsaga suletud. Iga laps sooritas vähemalt kolm forsseeritud välja- ja sissehingamist, analüsaator analüüsis registreeritud voolu-mahu lingusid katmismeetodil (*envelope method*).

Käesolevas töös võtsime vaatluse alla järgmised näitajad: forsseeritud vitaalkapatsiteedi (FVC), ekspiratoorse tippvoolu (PEF) ja forsseeritud ekspiratoorsed voolud, kui välja oli hingatud 25, 50 ja 75% FVC-st (FEF_{25}, FEF_{50} ja FEF_{75}). Metoodika ja nimetatud näitajate kohta vt. kirjandusallikad 4 ja 5.

Tunnuse "anamnees" (positiivne — 1, negatiivne — 0) olulisuse hindamiseks kasutasime sammregressiooni (*Statistica for Windows* 4.0).

Uurimistulemused. Tabelites 1 ja 2 on esitatud uuritute iseloomustus. 683 poeglapsest olid 110 (16,1%) ja 772 tütarlapsest 120 (15,5%) "positiivse anamneesiga". Haiguste ja hingamissüsteemi kaebuste esinemissagedus poeg- ja tütarlastel ei erinenud (P=0,75, χ^2-test). Astma diagnoos oli pandud 12 poeg- ja 8 tütarlapsele.

Sammregressiooni tulemused on esitatud tabelis 3, võimalikeks argumenttunnusteks olid vanus, pikkus ja anamnees. Erinevuste demonstreerimiseks on tervete ja "positiivse anamneesiga" tütarlaste FEF_{50} väärtused ning FEF_{50} regressioonijooned kehapikkuse suhtes esitatud joonisel.

Arutelu ja kokkuvõte. L. M. Taussigi ja kaasautorite järgi peetakse hingamisuuringutes last terveks, kui tal ei ole sel ajal ägedat ega ole kunagi olnud kroonilist hingamisteede haigust (näiteks astma), kui lapse anamneesis puuduvad rasked hingamissüsteemihaigused (näiteks destruktiivne pneumoonia, kaasasündinud arenguanomaaliad; ka rindkere operatsioonid) ja kui tal ei ole ka muid haigusi, mis võiksid mõjutada hingamissüsteemi (näiteks neuromuskulaarsed haigused) (10). Kui aga astma diagnoosi ei ole, kuid lapsel on esinenud kiunuvat hingamist ja sagedast köha, kas siis võib teda sellele definitsioonile vastavalt arvata terveks ja kaasata "tervete laste" rühma? Meie töö eesmärgiks oli leida, kas hingamissüsteemi haiguste ja/või kaebustega laste välise hingamise näitajad erinevad tervete laste omadest.

Vähemalt üks krooniline haigus või hingamissüsteemipoolne kaebus oli 16,1%-l poeglastest ja 15,5%-l tütarlastest, astma oli diagnoositud 1,8%-l poeg- ja 1,0%-l tü-

Tabel 1. Uuritud laste iseloomustus

Andmed	Tütarlapsed		Poeglapsed	
	keskmine (SD)	variatsioonniulatus	keskmine (SD)	variatsioonniulatus
Vanus, aastad	12,8 (3,4)	5—18	12,1 (3,2)	5—18
Pikkus, cm-tes	152,1 (15,4)	109—185	152,6 (19,6)	106—195
Kaal, kg-des	43,8 (14,5)	18—90	42,9 (16,4)	15—96

Märkus. SD on standardhälve.

Tabel 2. Laste arv vanuserühmades

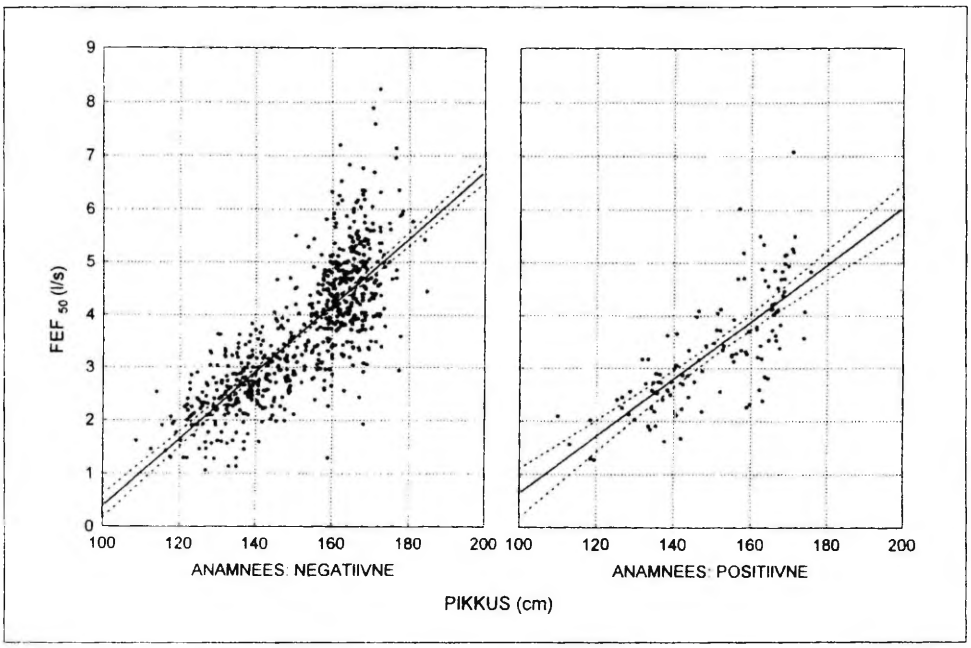
Vanus aastates	Tütarlapsed	Poeglapsed
5,0—6,9	17	22
7,0—8,9	95	88
9,0—10,9	149	189
11,0—12,9	127	111
13,0—14,9	121	119
15,0—16,9	164	100
17,0—18,9	99	54
Kokku	772	683

Tabel 3. Regressioonanalüüsi tulemused

Funktsioontunnus	Poeglapsed		Tütarlapsed	
	mudelisse lülitatud argumenttunnused*	R^2	mudelisse lülitatud argumenttunnused	R^2
FVC	A, H	0,88	A, H	0,84
PEF	A, H	0,77	A, H, AN	0,72
FEF_{25}	A, H	0,73	A, H, AN	0,67
FEF_{50}	A, H	0,66	A, H, AN	0,62
FEF_{75}	H	0,48	A, H	0,46

* Mudelisse lülitatud tunnuse regressioonikordaja olulisuse tõenäosus P<0,05.

Tähistused. FVC on forsseeritud vitaalkapatsiteet; PEF — ekspiratoorne tippvool; FEF_{25}, FEF_{50} ja FEF_{75} — forsseeritud ekspiratoorsed voolud, kui välja on hingatud 25, 50 ja 75% FVC-st; R^2 — determinatsioonikordaja; A — vanus aastates; H — pikkus sentimeetrites ja AN — anamnees (positiivne — 1, negatiivne — 0).



Joonis. FEF_{50} ja kehapikkuse hajuvusdiagrammid ning regressioonijooned tervetel (n=652) ja "positiivse anamneesiga" (n=120) tütarlastel. Katkendlike joontega on tähistatud regressioonisirgete usalduspiirkonnad 95% usaldusnivool. FEF_{50} on forsseeritud ekspiratoorne vool, kui välja on hingatud 50% forsseeritud vitaalkapatsiteedist.

tarlastest. M.-A. Riikjärve ja kaasautorite andmetel oli astmat 2,9%-l 11—12-aastastest Eesti lastest, mittespetsiifilisi hingamisteede haiguse sümptomeid leidsid nad 5—7%-l uurituist (8). Kahjuks ei saa nimetatud töös toodud sümptomite esinemist meie andmetega võrrelda, sest võtsime "positiivse anamneesiga" (s.t. vähemalt ühe kaebuse või haigusega) lapsed kõik kokku. Meie töös esitatuga sarnane sümptomite arvestus 7—11-aastastel Itaalia lastel (7) on andnud "positiivse anamneesi" esinemissageduseks 43,2% (siia hulka on arvatud ka hingamisteede infektsioon kaks nädalat enne uuringut) ja 8—10-aastastel Taani lastel 6,0% (6).

Kuigi poeg- ja tütarlastel oli hingamissüsteemi kaebusi peaaegu ühepalju, ei ole poeglastel ühegi hingamisfunktsiooni näitaja regressioonimudelisse valitud "anamneesi". Tütarlastel on "anamnees" oluliseks argumenttunnuseks ($P<0,05$) PEF, FEF_{25} ja FEF_{50} regressioonimudelis, mitte aga FVC ja FEF_{75} mudelis. Tervete ja "positiivse anamneesiga" laste vahelise erinevuse saime seega ainult tütarlaste forsseeritud väljahingamise alguse õhuvoolude väärtuste osas. Erinevate autorite töödes, milles on püütud leida "parimat" hingamisfunktsiooni näitajat, mis aitaks eristada terveid ja hingamiselundkonna kaebustega lapsi, on pakutud sellisteks näitajateks FEV_1 (2,

3, 7, 9, 11), PEF (7), FEF_{50} (1, 2, 6, 7), FEF_{75} (1, 6, 7), FEF_{25-75} (1, 3, 9, 11) ning FEF_{75-85} (9).

Samasuguselt käesoleva tööga on ka teised rühmad leidnud, et FVC on üks suurusi, mis hingamiskaebustega lastel ei erine tervete laste omast (6, 7, 9, 11). Leitud parima hingamisfunktsiooni näitaja seisukohalt on meie töö tulemused kõige rohkem sarnased R. Pistelli ja kaasautorite tulemustega, kuid kahjuks ei ole nende uuringus analüüsitud poeg- ja tütarlaste andmeid eraldi (7). Neid andmeid eraldi analüüsides leidsid G. J. Borsboom ja kaasautorid hingamisfunktsiooni näitajate vähenemise haigetel poeglastel, mitte aga tütarlastel (2).

Meie töö tulemused on lähedased S. T. Weissi jt. longitudinaalse uuringu järeldusele, mille kohaselt on astmast tingitud kopsufunktsiooni vähenemine tütarlastel märgatavam, kuigi poeglastel esineb astmat sagedamini (11). Erinevuseks nende uuringute vahel on see, et käesolevas töös oli "positiivse anamneesiga" rühm mitmekesisem kui ainult astmahaiged.

Kokkuvõtteks võib öelda, et kuigi meie andmeil ilmnes erinevus tervete ja "positiivse anamneesiga" laste vahel ainult tütarlaste õhuvoolu väärtuste osas, leiame, et töödes, milles võrreldakse tervete laste andmeid normväärtustega või ka haigete laste andmetega, tuleks tervete rühmast välja jätta need, kellel on anamneesis hingamissüsteemipoolsed kaebused, isegi siis, kui arsti diagnoos puudub.

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Summary

Flow-volume loop parameters in healthy children and in children with respiratory symptoms. The aim of the study was to investigate if impaired lung function could be demonstrated in symptomatic schoolchildren, even in the absence of diagnosed asthma. Spirometry and anthropometric measures were obtained from 1455 children (aged 5—18 years). 110 boys and 120 girls reported one or more asthma-like symptoms in the questionnaire. Only 12 boys and 8 girls of these children reported having asthma. Using stepwise regression analysis the reduced values in symptomatic girls were found in peak expiratory flow and forced expiratory flows, when 25 and 50% of forced vital capacity had been exhaled. Although in boys the differences between two groups were not found we suggest that symptomatic non-astmatics in such lung function studies where healthy children are needed, should be excluded.

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IV

J. Kivastik
Review: Paediatric reference values for spirometry.
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REVIEW

Paediatric reference values for spirometry

Jana Kivastik

Department of Physiology, University of Tartu, Tartu, Estonia
Received 30 January 1998; accepted 8 June 1998
Correspondence: J. Kivastik, 2 Näituse Str., Department of Physiology, University of Tartu, EE2400 Tartu, Estonia

Introduction

Several publications about standardization of pulmonary function tests, the reproducibility of results, calibration of equipment, instrument response and other engineering details have been published. Miller has called these considerations the 'hardware' of pulmonary function testing (Miller, 1986). Another aspect he has called 'software': what do the results mean? are they 'normal' or 'abnormal'? It is customary to establish this by comparing the test results with reference values (called also predicted or normal values). Polgar & Promadhat (1971) collected from the literature a great number of reference values (published in 1921–69) for various lung indices for children. They derived summary equations from previously published data and these equations were widely used. More recently about 50 publications from 1950 to 1986 were compiled in one report (Quanjer *et al.*, 1989); there were large discrepancies between various predictions. The purpose of this review is to summarize the paediatric reference values for lung function tests, published from 1987.

There have been several publications on reference values in the last 10 years; the present review concentrates on articles about lung volumes and forced ventilatory flows in school-age children. A brief description of the reference populations, the equipment used, measured parameters and the type of regression equations is given in Table 1; some aspects are discussed in more detail below.

Subjects

Definition of health

To define a 'normal' population from which reference standards can be derived it is useful to adopt the recommendations of the GAP Conference (Taussig *et al.*, 1980) on defining a 'healthy' child:

1 no present acute and no past or present chronic disease of the respiratory system;
2 no major respiratory disease such as congenital anomalies, destructive type of pneumonia, or thoracic surgery in the past medical history;
3 no systemic disease which directly or indirectly is known to influence the respiratory system and general state of health;
4 no more than incidental smoking experience;
5 no history of an upper respiratory tract infection during the previous 3 weeks.

Most of the authors have used these or similar inclusion criteria; in one study the degree of air pollution, outdoor and indoor temperature and indoor air humidity were also fixed (Kristufek *et al.*, 1987). One study group considered all children, including those with respiratory diseases, and afterwards analysed the effects of diseases (Pistelli *et al.*, 1992). Some differences can be found concerning children's smoking experience: for example, Asher *et al.* (1987) excluded those who had admitted ever smoking one or more cigarettes, but Coultas *et al.* (1988) did not exclude children who had reported smoking cigarettes. In some works data about smoking status were missing.

Table 1 Brief description of reference populations, methods and regression models reported in the literature on paediatric reference values for lung function parameters.

First author, year of publication	No. of children	Age and race of children	Selection criteria	Parameters studied and the device	Posture	Regression equations
Asher 1987	571	5–13 years, Polynesians and Europeans	Non-smoking healthy schoolchildren in New Zealand	VC, FVC, FRC, TLC (BP)	NS	Linear models with H as a predictor, separately for two ethnic groups
Azizi 1994	1098	7–12 years, Malay, Chinese and Indian origin	Non-smoking healthy schoolchildren in Malaysia	FVC, FEV_1, FEF_{25-75} (Vitalograph)	ST	Logarithmic models with H as a predictor, separately for each ethnic group
Berman 1994	191	11–18 years, Navajo Native Americans	Non-smoking healthy schoolchildren in USA, Arizona	FVC, FEV_1, FEV_3, FEF_{25-75}, PEF (Flowmate plus spirometer)	ST	Logarithmic models with H as a predictor
Chinn 1992	1682	6–12 years, Europeans	Healthy schoolchildren in England	FVC, FEV_1, FEF_{25-75}, FEF_{75-85} (Vitalograph)	NS	Logarithmic models with H and A as predictors
Connett 1994	1944	6–18 years, Chinese, Malay and Indian origin	Healthy schoolchildren in Singapore	FVC, FEV_1 (Jaeger pneumotachometer)	ST	Two logarithmic models over separate height ranges with H as a predictor for Chinese, correction factors for Malays and Indians
Coultas 1988	328	6–18 years, Hispanics	Healthy schoolchildren in USA, New Mexico	FVC, FEV_1, PEF, FEF_{25-75} (Stead–Wells spirometer)	SI	Logarithmic models with H as a predictor
Haby 1994	1278	8–11 years, Caucasians	Healthy schoolchildren in Australia	FVC, FEV_1, PEF, FEF_{25-75} (dry rolling seal spirometer)	ST	Multiple regression models with H, H^2, W and A as predictors
Koillinen 1998	199	5–17 years, Europeans	Non-smoking healthy schoolchildren in Finland	VC, FVC, FEV_1, $FEV_{0.5}$, PEF, MEF_{50} (MasterLab pneumospirometer)	NS	Logarithmic models with H as a predictor
Kristufek 1987	1024	6–81 years, Europeans (218 of them were 6–18 years)	Non-smoking healthy children and adults in Czechoslovakia	VC, FEV_1, RV, FRC, TLC, PEF, MEF_{50}, MEF_{25} (BP)	SI	Logarithmic models with H, W and A as predictors for the whole age range
Neukirch 1988	1007	10–19 years, Polynesian, European and Chinese origin	Non-smoking healthy schoolchildren in Tahiti	FVC, FEV_1, FEF_{25-75}, FEF_{25}, FEF_{50}, FEF_{75} (Spiromatic)	SI	Logarithmic models with H, W and A as predictors
Nysom 1997	348	13–24 years, Caucasians (176 of them were 13–18 years)	Non-smoking healthy adolescents and young adults in Denmark	FVC, FEV_1, FVC/FEV_1, TLC, transfer factor (Jaeger pneumotachometer)	NS	Customized equations (using equations from the literature and the Danish data)

Pistelli 1992	2176	7–11 years, Europeans	Schoolchildren in Italy	FVC, FEV_1, PEF, FEF_{25-75}, MEF_{50}, MEF_{25} (Biomedin water-sealed spirometer)	NS	Logarithmic models with H, BMI and A as predictors
Quanjer 1995	5861	6–21 years, Caucasians	Healthy schoolchildren and young adults in the Netherlands, Austria, UK, Spain and Italy	FVC, FEV_1, FEV_1/FVC (several devices)	SI	Logarithmic models with H–A interaction as predictor
Rahman 1990	588	12–19 years, Bengalees	Healthy schoolchildren in Bangladesh	FVC, FEV_1, PEF (Micro Medical Instr. spirometer)	ST	Multiple regression models with H, SH, W and A as predictors
Roizin 1993	471	7–14 years, European, Iraqi, North African, Indian, Yemenite and Georgian origin	Non-smoking healthy schoolchildren in Israel	FVC, FEV_1, FEV_1/FVC (Vitalograph)	NS	Linear models with H as a predictor for all ethnic groups
Rosenthal 1993	772	4–18 years, Caucasians	Healthy schoolchildren in England	FVC, FEV_1, PEF, MEF_{50}, MEF_{25}, PIF (OHIO spirometer)	NS	Two linear models over separate height ranges with H as a predictor; also separate models with SH as a predictor
Schwartz 1988 (a, b)	1963	6–20 years, white and black Americans	Non-smoking healthy children and teenagers in USA	FVC, FEV_1, FEV_3, PEF, FEF_{50}, FEF_{75}, MMEF (OHIO spirometer)	ST	Logarithmic models with H, SH, BMI, A and race as predictors
Shamssain 1988	796	6–19 years, Libyans	Non-smoking healthy schoolchildren in Libya	FVC, FEV_1, PEF, FEF_{25-75} (Vitalograph)	ST	Logarithmic regression models with H and A as predictors
Shamssain 1991	2000	6–19 years, Africans	Non-smoking healthy schoolchildren in Transkei	FVC, FEV_1, PEF, FEF_{25-75} (Vitalograph)	ST	Multiple regression models with H and A as predictors

VC, vital capacity; FVC, forced vital capacity; FEV_1 and FEV_3, forced expiratory volumes in 1 and 3 s; RV, residual volume; FRC, functional residual capacity; TLC, total lung capacity; PEF, peak expiratory flow; PIF, peak inspiratory flow; FEF_{25}, FEF_{50} and FEF_{75}, forced expiratory flows when 25%, 50% and 75% of FVC has been exhaled; MEF_{50} and MEF_{25}, maximal expiratory flows when 50% and 25% of FVC remains to be expired; MMEF (same as FEF_{25-75}), maximal mid-expiratory flow; FEF_{75-85}, forced late expiratory flow; BP, body plethysmograph; SI, sitting; ST, standing; NS, not stated; H, standing height; SH, sitting height; A, age; W, weight; BMI, body mass index.

Ethnic differences

Race has consistently been shown to be an important determinant of lung function. When compared with Caucasians, most other races usually show smaller lung volumes and lower forced expiratory flows, as found also by Asher *et al.* (1987), Azizi & Henry (1994), Chinn & Rona (1992), Connett *et al.* (1994), Neukirch *et al.* (1988), Rahman *et al.* (1990) and Roizin *et al.* (1993). Native American children have lung volumes and flows equivalent to or even larger than those of Caucasians (Berman *et al.*, 1994). The reason for these differences between ethnic groups is as yet unclear; they may be related to the body proportions and in particular a smaller ratio of sitting to standing height characteristic of the racial groups studied (Asher *et al.*, 1987; Connett *et al.*, 1994). The use of sitting height as an index of body size in prediction equations reduces but does not fully eliminate the observed differences between races. Ethnic differences in chest wall dimensions (Rahman *et al.*, 1990), environmental differences and socio-economic factors, racial differences in lung growth and maturation, different ages and heights when pubertal changes start (Connett *et al.*, 1994) – all these factors are also thought to be important in determining the lung function of ethnic groups.

Infants

Problems specific to lung function studies in infants are dealt with in the statement of the American Thoracic Society and European Respiratory Society (1993).

Methods

Reference values should derive from studies employing standardized procedures and equipment: the latest recommendations about standardization can be found in the official statements of the European Respiratory Society (Quanjer *et al.*, 1989, 1993) and the American Thoracic Society (1991, 1995).

Posture

Body position affects spirometric volumes, particularly forced vital capacity (FVC) and vital capacity (VC), which are 7–8% lower in the supine than in the standing position and 1–2% lower in the sitting than in the standing position (American Thoracic Society, 1991). The American Thoracic Society states that testing may be done in either the sitting or the standing position and it is necessary to indicate the position used (American Thoracic Society, 1995). The European Respiratory Society recommends making the measurements with the subject seated in an upright position (Quanjer *et al.*, 1993). The studies reviewed have made investigations in the standing or sitting position; some have not stated the posture.

Instrumentation and parameters measured

Volume changes of the lung have mostly been measured at the mouth, by means of different spirometers and pneumotachometers; two study groups have additionally used a whole-body plethysmograph (Asher *et al.*, 1987; Kristufek *et al.*, 1987).

Classical spirometry and flow–volume curve registration are the most widely used lung function tests in children, and several articles with the reference values for those tests were found. The most popular were FVC and forced expiratory volume in 1 s (FEV_1): at least one of these two parameters was represented in all reviewed papers. Instantaneous maximal expiratory flows were expressed in two different ways: FEF_{75} (forced expiratory flow when 75% of FVC had been exhaled) is the same as MEF_{25} (maximal expiratory flow when 25% of FVC remained to be expired). It is recommended that the latter index be used (Quanjer *et al.*, 1993).

The widespread and growing use of peak flow meters in clinical and epidemiological settings was the reason for the publication of a special supplement on peak expiratory flow (Lebowitz & Quanjer, 1997). An excellent review about reference values for residual volume, functional residual capacity and total lung capacity (in both children and adults) was published by Stocks & Quanjer (1995).

The best flow–volume curve

The preferred method of selection of the best flow–volume curve from amongst a set of maximal flow–volume curves is different in the European Respira-

tory Society and American Thoracic Society statements. The European Respiratory Society recommends the envelope method, i.e. the curves are superimposed from total capacity to form a composite maximal curve, and the largest FVC is used to delineate the highest instantaneous flows at specified lung volumes (Quanjer *et al.*, 1993). The American Thoracic Society prefers to obtain maximum mid-expiratory flow and the instantaneous expiratory flows from the single curve that meets the acceptability criteria and gives the largest sum of FEV_1 and FVC (American Thoracic Society, 1995). Authors of the reference values have mostly used the method recommended by the American Thoracic Society, while some have defined the best trial as that with the highest FEV_1 (Shamssain, 1991; Rosenthal *et al.*, 1993; Haby *et al.*, 1994), and one used the composite curve (Kristufek *et al.*, 1987).

Data analysis

Cross-sectional or longitudinal analysis

In this review I have included only cross-sectional studies. In the last 10 years there has been an explosion in the application of new analytical techniques for use with longitudinal data. A number of cross-sectional and longitudinal comparisons using these methods have also been performed. Material from the special American Thoracic Society–European Respiratory Society workshop on longitudinal analysis of pulmonary function data was published recently (Weiss *et al.*, 1996). Although the exact causes of the differences between cross-sectional and longitudinal analyses might be different for different investigations, it is clear that differences exist and that therefore longitudinal studies should be compared with longitudinally collected data, and cross-sectional studies should be compared with data collected cross-sectionally (Pattishall *et al.*, 1989).

Gender and independent variables

There is growing evidence that, after correcting for body size, girls have smaller lungs but higher expiratory flows than boys. It is recommended treating data from boys and girls separately (Quanjer *et al.*, 1989), as in all reviewed papers.

Body size of the subject is usually measured as standing height, although sitting height may be a useful predictor in certain circumstances (e.g. mixed ethnic origins, pubertal changes). Age as a variable is more important in prediction equations during adolescence than during the prepubertal period. Most authors have used standing height as the independent variable; some have also used age, weight, body mass index and sitting height.

Which regression model to use?

There is no agreement of how best to represent the relationship between a lung index and an independent variable. Apart from the power function and the exponential function, linear relationships can still be used in situations when the age range is small or when the population has been artificially partitioned into narrow age ranges (Quanjer *et al.*, 1989).

Most authors have used logarithmic equations, with only standing height or more parameters as predictors. Simple linear models were used by Asher *et al.* (1987), Roizin *et al.* (1993) and Rosenthal *et al.* (1993), whereas the last study group presented two models over separate height ranges (change of model at 152·5 cm in girls and 162·5 cm in boys) with the correcting factors for pubertal stage 15 cm above and below the discontinuity point. Some groups have published multiple regression models (Rahman *et al.*, 1990; Shamssain, 1991; Haby *et al.*, 1994).

Normality in statistical terms

The method of expressing results by percentage predicted (i.e. 100 × observed/predicted) may not be as inappropriate in children and adolescents as in adults owing to increased variability with increased height (heteroscedasticity). But the arbitrary level of abnormality for all tests such as 80% of predicted is not valid even in children, because there are differences among the various tests with respect to intersubject variation, resulting in a large standard deviation for many tests. For FEF_{25-75} and the instantaneous flows the lower limits of normal are closer to 50% of predicted; for example, Koillinen *et al.* (1998) have given the lower limit of normal for MEF_{50} in girls as 63% and in boys as 64%. Several other groups have also reported such cut-off percent-

ages for different parameters (Coultas *et al.*, 1988; Neukirch *et al.*, 1988; Pistelli *et al.*, 1992).

The second possibility (more often seen in reviewed papers) is to use the centile approach, when a lower 5 and upper 95 percentile (encompassing the 90% confidence interval) are obtained by calculating the predicted mean ± 1·64 × RSD (residual standard deviation). A practical disadvantage of the centile approach is that it is difficult to quantify the degree of abnormality. The recently recommended solution to this is to use the standardized residual, i.e. (observed – predicted) divided by the RSD from the regression line. This provides a dimensionless index, indicative of how far the observed value is removed from the predicted and thus the likelihood that such a value would be observed in a healthy population (Quanjer *et al.*, 1993; Stocks & Quanjer, 1995). Standardized residuals were used only by Nysom *et al.* (1997).

Effects of puberty

During recent years the potential effects of puberty on lung growth have been studied. The finding that no single linear or power curvilinear relationship correctly describes the relationship between forced ventilatory manoeuvres and height throughout childhood was first noted by Dickman *et al.* (1971). Sudden changes in both standing height and lung function take place during the adolescent growth spurt, but the lung growth appears to lag behind the increase in standing height (Degroodt *et al.*, 1986; Jaeger-Denavit & Alphonse, 1990; Borsboom *et al.*, 1993, 1996; Lebowitz & Sherrill, 1995). It is possible that the use of sitting height would be more appropriate than standing height, because lung and trunk development could be more closely associated with each other (Schrader *et al.*, 1984; Degroodt *et al.*, 1986; Kivastik & Kingisepp, 1995).

It is more likely that the true growth pattern is more accurately represented by multiple equations and discontinuous regression lines, but then care should be taken to avoid abrupt changes in the predicted values from one line to the other (Quanjer *et al.*, 1989); for example correction factors for pubertal stages can be used (Rosenthal *et al.*, 1993).

Quanjer with co-workers wished to assess whether, using original data rather than published equations, it was possible to describe spirometric data from childhood to adulthood, taking into account the adolescent growth spurt. The analysis comprised six studies from five different countries; data were collected from 1972 to 1985 (Quanjer *et al.*, 1995). Authors showed that adding an age–height interaction to the model of a lung index as an exponential function of standing height [ln volume = a + (b + cA)H] satisfactorily resolves the changing relationship between lung volume and anthropometric data occurring at the time of the adolescent growth spurt. They suggest that these rather simple equations can be applied to children and adolescents in the various regions within Europe.

Selection and use of equations

There is a fundamental difference of philosophy over the application of reference equations: the European ideal is for a set of standardized equations which would be applicable in all laboratories (Quanjer *et al.*, 1993), while the North American view is that each laboratory should choose equations from the literature which best suit that laboratory (American Thoracic Society, 1991).

Reference values should be chosen from a study which used the same techniques that will be employed and using a healthy population similar to the population being tested in that particular laboratory. This requires examining the population characteristics, such as age range as well as gender and race composition. After a reference standard is chosen, a small number of healthy children should be tested and the results should be compared with the chosen values from the literature (Quanjer *et al.*, 1989; Pattishall, 1990; Stocks & Quanjer, 1995).

Recent questionnaires have shown that, despite the large number of reference equations available in the literature, surprisingly few are actually used. Three studies accounted for 85% of the equations used for standard spirometric indices in adults (Ghio *et al.*, 1990); in paediatric patients the summary equations of Polgar & Promadhat (1971) were the most widely used – in 39 laboratories from 94 that had responded (Pattishall, 1990). Reference values were often chosen because they were available in the pulmonary function test equipment of the laboratories, rather than because they had been analysed and found to be the best for the local population. Only half of the centres were

Table 2 Comparison of the different reference values for forced vital capacity (FVC) for Europeans.

First author	Reference equation	Reference values in litres		
	Boys	H = 130 cm A = 8 years W = 27 kg	H = 150 cm A = 12 years W = 38 kg	H = 170 cm A = 16 years W = 55 kg
Asher	FVC = 0·045 × H − 3·76	2·09	2·99	– †
Chinn	ln FVC = −11·574 + 2·508 × ln H + 0·016 × ln A	1·96	2·81	–
Coultas	ln FVC = −6·6863 + 2·9247 × ln H	1·9	2·89	4·16
Haby	FVC = −0·261 + 0·000123 × H^2	1·82	–	–
Koillinen	ln FVC = −13·4611 + 2·9092 × ln H	2·01	3·05	4·39
Kristufek	ln FVC = 0·6801 × ln A + 0·5704 × ln W + 0·0077 × H − 0·0057 × W − 0·0234 × A − 3·3447	1·84	2·94	4·25
Neukirch	ln FVC = 3·095 + 0·013 × H + 0·029 × A + 0·005 × W	–	2·58	4·21
Nysom‡	ln FVC = (1·3731 + 0·0164 × A) × H − 1·3386	–	–	4·23
Quanjer‡	ln FVC = (1·3083 + 0·0186 × A) × H − 1·2217	1·96	2·93	4·52
Roizin	FVC = 0·04 × H − 3·68	1·52	2·32	–
Rosenthal	FVC = 0·0429 × H − 3·619, if H < 162·6 cm FVC = 0·0678 × H − 7·038, if H > 162·5 cm	1·96	2·82	4·49
	Girls	H = 130 cm A = 8 years W = 26 kg	H = 150 cm A = 12 years W = 42 kg	H = 165 cm A = 16 years W = 55 kg
Asher	FVC = 0·041 × H − 3·41	1·92	2·74	–
Chinn	ln FVC = −10·808 + 2·267 × ln H + 0·167 × ln A	1·78	2·63	–
Coultas	ln FVC = −6·1478 + 2·8016 × ln H	1·79	2·67	3·49
Haby	FVC = −0·261 + 0·000123 × H^2 − 0·147	1·67	–	–
Koillinen	ln FVC = −13·68 + 2·9423 × ln H	1·9	2·89	3·83
Kristufek	ln FVC = 0·6541 × ln A + 0·5584 × ln W + 0·0078 × H − 0·0063 × W − 0·0252 × A − 3·3036	1·69	2·75	3·61
Neukirch	ln FVC = 3·378 + 0·013 × H + 0·029 × A	–	2·92	3·98
Nysom‡	ln FVC = (1·48 + 0·0127 × A) × H − 1·4785	–	–	3·66
Quanjer‡	ln FVC = (1·5374 + 0·0129 × A) × H − 1·5371	1·81	2·52	3·34
Roizin	FVC = 0·05 × H − 4·42	2·08	3·08	–
Rosenthal	FVC = 0·03918 × H − 3·311, if H < 152·6 cm FVC = 0·04512 × H − 3·881, if H > 152·5 cm	1·78	2·57	3·56

FVC, forced vital capacity; H, standing height; A, age; W, weight.

†The missing value indicates that no child of that age was included in the reference population.

‡Height in meters in Nysom *et al.* (1997) and Quanjer *et al.* (1995).

correcting for ethnic differences, and then usually in the form of a fixed proportional reduction in Caucasian-based equations rather than by using population-specific regression equations, as endorsed by the GAP Conference Committee (Taussig *et al.*, 1980).

Nysom *et al.* (1997) have offered a different approach for selecting the best reference values that would span the age range from childhood to young adulthood. They used data from a local sample of healthy 13–24-year-olds to screen previously published reference equations; in adolescents (< 18 years) the equations of Quanjer *et al.* (1995) were chosen as they best fitted the Danish data. The parameters of these models were then customized by applying a correction factor to ensure an optimal fit, and the new residual standard deviations were also calculated. Customized models in adolescents and young adults could bridge the gap between the childhood and adulthood reference values, which often occurs at 18 years of age (Nysom *et al.*, 1997).

When comparing the reference values for FVC calculated by different authors' equations, 300–500-ml differences between the values are apparent (Table 2). The picture is a little less disturbing if we read carefully the paper by Roizin *et al.* (1993) and find that the FVC values for boys have to be higher than for girls (p. 908). I believe that their equations were printed incorrectly, and hope they have been corrected in later editions. But discrepancies still exist: for example, a 16-year-old girl's reference value for FVC would be 3·34 l according to Quanjer *et al.* (1995) and 3·98 l according to Neukirch *et al.* (1988).

Future research

There are several unsolved problems connected with paediatric reference values for lung function tests – changing relationship between anthropometric and lung parameters, effects of puberty, ethnic differences, use of different regression models, etc. – and further studies are needed to answer as many of the questions as possible. One option to help researchers is suggested by Quanjer *et al.* (1995), namely starting an international database to which study groups could submit their cross-sectional and longitudinal pulmonary function data, and making these data available for research purposes. This would often obviate the need for costly and time-consuming new studies as so much information is already available but not exploited (Quanjer *et al.*, 1995).

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CURRICULUM VITAE

Jana Kivastik

Citizenship:	Estonian
Born:	January 28, 1967 in Tallinn, Estonia
Marital status:	Married, two children
Address:	Department of Physiology, University of Tartu, Ravila 19, Tartu 50411
Telephone:	(27) 374 330
Fax:	(27) 374 332
E-mail:	jana.kivastik@ut.ee

Education

1974–1985	Tallinn Secondary School No. 37
1985–1992	University of Tartu, Faculty of Medicine
1992–1996	Department of Physiology, University of Tartu, postgraduate student

Special courses

1993	Two weeks at the Department of Clinical Physiology and Nuclear Medicine, University Hospital of Kuopio
1993	One month at the Lung Function Laboratory, Helsinki University Central Hospital
1994	International course "Academic pediatric skills symposium" held by the International Pediatric Research Foundation, Pühajärve
1994	One month at the Department of Physiology, University of Copenhagen
1998	One month in the University of Oxford, Oxford Colleges Hospitality Scheme for East European Scholars

Professional employment

1994–	Department of Physiology, University of Tartu, teaching assistant

Scientific work

Main research field: pulmonary function studies in children and young adults
28 scientific publications, nine presentations at international conferences
Member of the Estonian Physiological Society and the European Respiratory Society

CURRICULUM VITAE

Jana Kivastik

Kodakondsus:	Eesti
Sünniaeg- ja koht:	28. jaanuar 1967, Tallinn
Perekonnaseis:	abielus, 2 last
Aadress:	TÜ füsioloogia instituut, Ravila 19, Tartu 50411
Telefon:	(27) 374 330
Faks:	(27) 374 332
E-post:	jana.kivastik@ut.ee

Haridus

1974–1985	Tallinna 37. Keskkool
1985–1992	Tartu Ülikooli arstiteaduskond, pediaatria eriala
1992–1996	TÜ füsioloogia instituut, doktorantuur

Erialane enesetäiendus

1993	kaks nädalat Kuopio Ülikooli Kliiniku kliinilise füsioloogia ja nukleaarmeditsiini osakonnas
1993	üks kuu Helsingi Ülikooli Keskhaigla kopsufunktsiooni laboris
1994	International Pediatric Research Foundation'i korraldatud kursus "Academic pediatric skills symposium", Pühajärve
1994	üks kuu Kopenhaageni Ülikooli füsioloogia kateedris
1998	üks kuu Oxfordis, Avatud Eesti Fondi raamatukogude kasutamise stipendium (Oxford Colleges Hospitality Scheme)

Erialane teenistuskäik

1994–	TÜ füsioloogia instituudi assistent

Teadustöö

Peamine uurimisvaldkond: välise hingamise funktsionaalsed uuringud lastel ja noorukitel.
28 teaduspublikatsiooni, üheksa ettekannet rahvusvahelistel konverentsidel.
Eesti Füsioloogia Seltsi ja European Respiratory Society liige.

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