Chapter 18
Lung Function at Age 18–25 Years: A Comparison of Different Reference Value Systems

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Abstract The anthropometrical data of the Caucasian population have significantly changed within the last five decades. The European Community for Coal and Steel (ECCS) assumes a plateau phase and recommends the entry of 25 years old for calculation of reference values in this age range. The question arises if the commonly used reference recommendations for lung function of the ECCS can still be accepted. In the present study standardized spirometric lung function tests were performed by pneumotachography, recording lung volumes and flows (MasterScreen Pneumo, CareFusion, Höchberg) in asymptomatic nonsmoking subjects (202 females, 201 males), aged between 18 and 26, according to the ATS/ERS criteria. The results were compared with the reference recommendations of ECCS, SAPALDIA, LuftiBus, and Bochum (only males). All absolute lung function values showed a correlation ($p < 0.05$) with height. With respect to FVC and FEV_1, SAPALDIA and Bochum reference values were comparable and close to a 100 (range 97.6–101.4) %pred, whereas both ECCS and LuftiBus showed higher values (range 103.6–109.9%pred). The FEV_1/FVC ratio was close to a 100 (range 97.6–101.7) %pred in all reference systems, whereas flows showed a wide variability between the reference systems (77.1–114.6%pred), single flows (e.g., 96.9–114.2%pred for MEF_{50}) and males/females (males: 93.6–114.6%pred; females: 77.1–107.9%pred). We conclude that SAPALDIA reference values for FVC and FEV_1 should be used, as they better represent lung function in the age group. ECCS and LuftiBus reference values are appreciably (4–10%) lower. Differences between reference systems were less important for the FEV_1/FVC ratio and lung flows.

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M. Pokorski (ed.), *Respiratory Regulation - Clinical Advances*,
Advances in Experimental Medicine and Biology 755, DOI 10.1007/978-94-007-4546-9_18,

Keywords Anthropometry • Lung function • Spirometry • Gender • Reference values

18.1 Introduction

The anthropometrical data of young adults have significantly changed within the last five decades, with increasing body height and body mass index. Therefore, the question arises whether the commonly used reference values of ventilatory lung function testing of the European Community for Coal and Steel (ECCS) (Quanjer 1983; Quanjer et al. 1993), or reference values from other studies are still valid today. ECCS values were erected by consensus in the 1960s and 1970s by local reference values from subjects with a limited range of age and body height. In practice, the measured values of young adults are classified by relating them to references, which are calculated for the age of 25 years in subjects aged 18–25, based on the assumption of a plateau phase of lung function in young adults (Sherrill et al. 1989; Robbins et al. 1995). In the last decades, several new reference studies were published, finding higher values for lung function parameters (ATS 1991, 1995; Brandli et al. 1996; Hankinson et al. 1999; Kuster et al. 2008; Roca et al. 1986), but could not commonly replace the former recommendations (Crapo et al. 1981; Enright et al. 1993; Knudson et al. 1983). Concerning the present reference values, the issue of alterations in lung function during the transition from childhood to adolescence and adulthood is an unsolved problem and needs to be studied further. The question if there is a plateau phase in lung function parameters is discussed controversially in the literature (Sherrill et al. 1989, 1992; Enjeti et al. 1978; Robbins et al. 1995; van Pelt et al. 1994). Difficulties arise from the fact that in adolescence height as the main parameter is changing (age or weight are potentially secondary parameters), later on height is nearly fixed and only age is changing. Furthermore, there are reasons to assume different variability in lung function parameters due to height in adolescence or later on, and in age with growing height and BMI. ECCS acts on the assumption of a plateau phase between 18 and 25 years of age. A complete set of parameters is available only from the ‘historic’ ECCS recommendations (Quanjer 1983; Quanjer et al. 1993).

The European Task Force on standardization of lung function testing has recently published a series of comprehensive recommendations for lung function testing and interpretation (Miller et al. 2005a, b; Pellegrino et al. 2005). However, the problems in evaluating the lower limit of normal (LLN), the limited age range and the concept in handling the transition from adolescence to adults were not addressed. Current investigations try to describe lung function parameters from preschool children to senescence in one continuous formula taking into account a peak value in early adolescents (Stanojevic et al. 2008). In a group of healthy young adults, 18–26 years of age, we examined if the ECCS reference recommendations still can be accepted in daily routine measurements in that special age group. Furthermore, we compared the results to the references values of the SAPALDIA and LuftiBus studies (Brandli et al. 1996; Kuster et al. 2008), and the set of ‘Bochum reference values’ for healthy non-smoking males (Marek et al. 2009).

18.2 Methods

The study was performed in conformity with the Declaration of Helsinki of the World Medical Association and the protocol was approved by a local Ethics Committee. Lung function was examined using pneumotachography for recording static lung volumes and parameters from the forced flow-volume-loops in 403 asymptomatic non-smoking Caucasian females and males, aged 18–26 years. Subjects were without diseases of the lung, heart or other organs with influence on lung function.

18.2.1 References for Lung Function in Children and Adults

The commonly accepted reference values for children were published in 1987 by Zapletal et al. (1987) for 3–16 years old boys and girls. In Europe reference values of the ECCS were published in 1983, and in 1993 in revised version (Quanjer 1983; Quanjer et al. 1993). In the 1990s, the SAPALDIA study was published by Brandli et al. (1996 and 2000), and recently in the LuftiBus study by Kuster et al. (2008). Reference value for FEV_1 for males of 180 cm body height and children and adolescents between 3 and 18 years of age with a final height of 180 cm along with the corresponding lower limit of normal (LLN) and the differences between predicted values and LLN are graphically presented in Fig. 18.1. The differences between Zapletal et al. (1987) reference values for an 18 years old adolescent of 180 cm height and other reference definitions for adults of 180 cm height range from 100 to 400 ml.

18.2.2 Anthropometric Data

The body height of males, recruited in the cross sectional study did not correlate with age, height = 0.126·age + 185.3 cm (r^2 = 0.001). As observed in males, body height did not correlate with age in females, height = 0.113·age + 166.7 cm (r^2 = 0.001) either. In both males and females, BMI showed a tendency to increase with age, BMI = 0.307·age + 16.8 (r^2 = 0.036) and BMI = 0.452·height + 11.5 (r^2 = 0.097), respectively (Table 18.1).

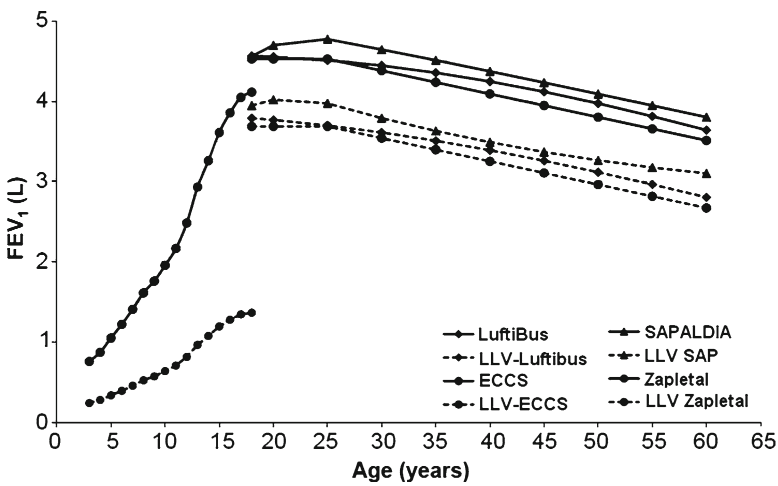

Fig. 18.1 Correlation of reference values for FEV_1 with age from Zapletal for boys and adolescents and from ECCS, SAPALDIA, and LuftiBus study for males of 180 cm in height

Table 18.1 Anthropometrical data for the male and female participants

	Males (n = 201)		Females (n = 202)	
	Mean ± SD	Min-Max	Mean ± SD	Min-Max
Age (yr)	22.9 ± 2.0	20.1–26.2	21.7 ± 1.9	21.1–26.2
Height (cm)	182.0 ± 6.9	164.2–206.1	169.0 ± 6.8	152.2–187.3
Weight (kg)	78.8 ± 11.1	55.3–110.6	61.8 ± 8.9	48.3–107.4
BMI (kg/m^2)	23.8 ± 2.1	20.4–32.7	21.7 ± 2.8	16.2–37.0

18.2.3 Lung Function Measurements

A minimum of three lung function measurements were recorded. The investigations included static and dynamic lung volumes and maximal expiratory flows, using MasterScreen Pneumo systems (CareFusion, Höchberg). All tests were performed according to the recommendations of the ATS/ERS Task Force on lung function testing (Wanger et al. 2005) and compared with the reference formulas of the ECCS (Quanjer et al. 1993). Only those measurements were accepted where the expiratory time (TE) exceeded 4 s, the variation of end-expiratory flow was below 25 ml/s and no cough disturbed the expiratory phase.

18.2.4 Data Analysis

The results were presented as means ± SD. Using Fisher's paired *t*-test, mean values were proofed to be significantly different from the reference values of ECCS, SAPALDIA- or LuftiBus values. A $p < 0.05$ was considered statistically significant. Linear regression analysis was performed for age, body height and BMI. Exponential or logarithmic functions did not show a close correlation to age. Therefore, the results from the simple linear regression analysis were presented. The mean values in %predicted according to the ECCS, SAPALDIA, LuftiBus and the Bochum reference formulas of spirometric parameters were compared.

18.3 Results

18.3.1 Correlations of Lung Function Parameters with Age and Height

No noticeable correlation between age and investigated respiratory parameters (VC, FVC, FEV_1, FEV_1%FVC, PEF, $MEF_{75,50,25}$) was found in the investigated age range of 18–26 years (Table 18.2, Fig. 18.2). Lung function parameter values increased with body height (Table 18.3). The most important parameters VC_{IN}, FVC, and FEV_1 were significantly correlated in both gender groups (Fig. 18.3).

18.3.2 Lung Function Parameters Compared with ECCS, LuftiBus, SAPALDIA, and Bochum Reference Values in Males

Values of lung function parameters in the group of young adult males were higher than predicted (Table 18.4). Most of them were 104.0 ± 7.4% of the reference values predicted by ECCS, 106.2 ± 8.6% by LuftiBus, and 106.1 ± 8.2% by SAPALDIA references. Lung function parameters of young adult males closely correlated with Bochum reference values. The mean value obtained from all parameters investigated was 98.0 ± 7.8%pred. The lowest values were obtained according to Bochum values for PEF (93.6 ± 15.7%pred), and the highest for MEF_{25} (103.5 ± 30.1%pred).

Table 18.2 Correlation of lung function parameters and age

	Males (n = 201)		Females (n = 202)	
	Regression equations	Coefficient of determination	Regression equations	Coefficient of determination
VC_{IN} (%pred)	y = –0.002x + 5.987	$r^2 < 0.011^{n.s.}$	y = –0.009x + 4.329	$r^2 < 0.011^{n.s.}$
FVC (%pred)	y = 0.007x + 5.663	$r^2 < 0.021^{n.s.}$	y = –0.006x + 4.276	$r^2 < 0.011^{n.s.}$
FEV_1 (%pred)	y = 0.001x + 4.936	$r^2 < 0.011^{n.s.}$	y = –0.024x + 4.086	$r^2 = 0.028^{n.s.}$
$FEV_1\%VC_{IN}$	y = –0.243x + 112.9	$r^2 = 0.021^{n.s.}$	y = –0.699x + 118.8	$r^2 = 0.011^{n.s.}$
PEF (%pred)	y = 0.159x + 7.102	$r^2 = 0.028^{n.s.}$	y = –0.057x + 8.491	$r^2 = 0.008^{n.s.}$
MEF_{75} (%pred)	y = 0.217x + 4.281	$r^2 = 0.050^{n.s.}$	y = –0.076x + 7.999	$r^2 = 0.014^{n.s.}$
MEF_{50} (%pred)	y = –0.003x + 6.230	$r^2 < 0.021^{n.s.}$	y = –0.039x + 5.370	$r^2 = 0.006^{n.s.}$
MEF_{25} (%pred)	y = 0.004x + 3.619	$r^2 = 0.007^{n.s.}$	y = –0.066x + 3.634	$r^2 = 0.042^{n.s.}$

n.s. non-significant

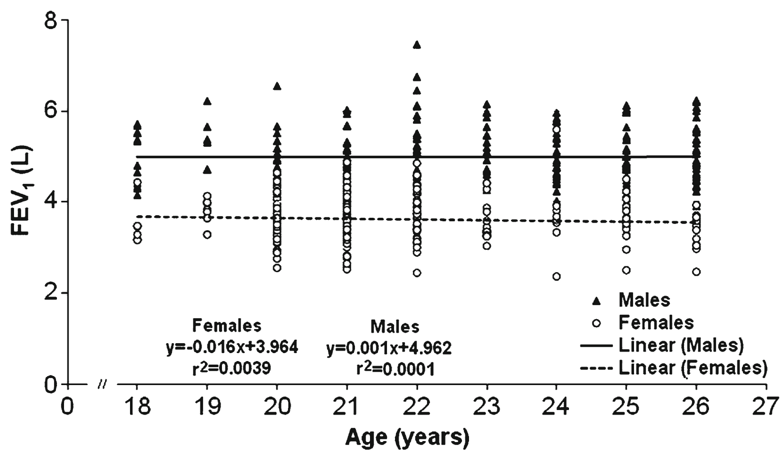

Fig. 18.2 Correlation of body height with age for non-smoking males (▲) and females (o)

Table 18.3 Correlation of lung function parameters and body height

	Males (n = 201)		Females (n = 202)	
	Regression equations	Coefficient of determination	Regression equations	Coefficient of determination
VC_{IN} (%pred)	y = 0.073x – 7.428	$r^2 = 0.382$**	y = 0.052x – 4.633	$r^2 = 0.356$**
FVC (%pred)	y = 0.071x – 7.136	$r^2 = 0.379$***	y = 0.056x – 5.250	$r^2 = 0.369$**
FEV_1 (%pred)	y = 0.048x – 3.835	$r^2 = 0.224$***	y = 0.039x – 3.054,	$r^2 = 0.2778$**
$FEV_1\%VC_{IN}$	y = 0.055x + 97.3	$r^2 > 0.021^{n.s.}$	y = –0.055x + 112.9	$r^2 < 0.021^{n.s.}$
PEF (%pred)	y = 0.047x – 0.614	$r^2 = 0.074^{n.s.}$	y = 0.072x – 2.321	$r^2 = 0.072^{n.s.}$
MEF_{75} (%pred)	y = 0.018x + 3.316	$r^2 = 0.011^{n.s.}$	y = 0.068x – 3.092	$r^2 = 0.062^{n.s.}$
MEF_{50} (%pred)	y = 0.021x + 1.014	$r^2 = 0.024^{n.s.}$	y = 0.023x + 2.019	$r^2 = 0.012^{n.s.}$
MEF_{25} (%pred)	y = 0.020x – 1.124	$r^2 = 0.053^{n.s.}$	y = 0.014x + 0.192	$r^2 = 0.014^{n.s.}$

n.s. non-significant

**p < 0.01, ***p < 0.001

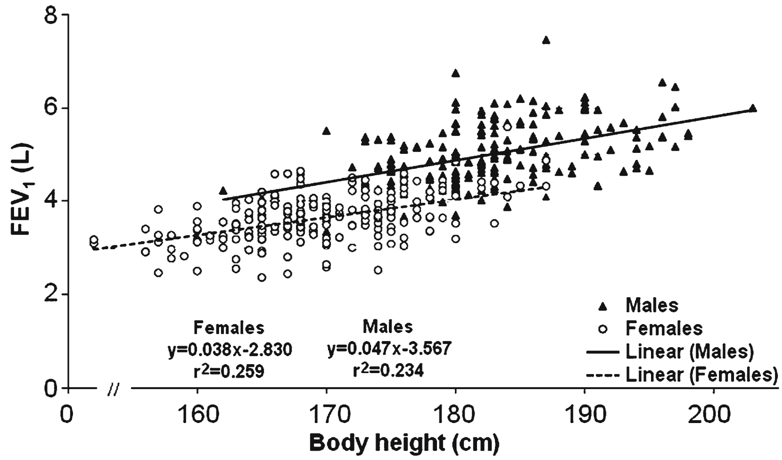

Fig. 18.3 Correlation of FEV_1 with body height for non-smoking males (▲) and females (o)

18.3.3 Lung Function Parameters Compared with ECCS, LuftiBus, and SAPALDIA Reference Values in Females

The values of spirometric lung function parameters in the group of younger females were up to 9.9% higher compared with the ECCS reference values in males, seen in Table 18.4. On average, the mean lung function parameters were 101.5 ± 3.64% of the reference values predicted by ECCS, 101.7 ± 6.1% by LuftiBus, and 98.5 ± 4.5% by SAPALDIA references.

18.3.4 Lung Function Parameters Compared with ECCS, LuftiBus, and SAPALDIA Reference Values for Both Genders

With respect to FVC and FEV_1, SAPALDIA and Bochum reference values were comparable and close to a 100 (range 97.6–101.4) %pred, whereas both ECCS and LuftiBus showed considerably higher values (range 103.6–109.9%pred). There was no main difference between males and females (Table 18.4). The FEV_1/FVC ratio was close to a 100 (range 97.6–101.7) %pred in all reference systems, whereas flows showed a wide variability between reference systems (77.1–114.6%pred), single flows (e.g., 96.9–114.2%pred for MEF_{50}) and males/females (males: 93.6–114.6%pred; females: 77.1–107.9%pred).

18.4 Discussion

The commonly accepted reference formulas of the ECCS (Quanjer 1983; Quanjer et al. 1993) for the assessment of ventilatory lung function measurements of Caucasians are limited in fulfilling the current requirements of lung function testing. As for all other reference recommendations, the handling of the transition from adolescence to adults is an unsolved problem. The formulas were compiled by the ECCS experts from different investigations and subsets of individuals in the 1970s and earlier. Meanwhile, anthropometrical parameters significantly altered, the population is getting higher especially in young adults, and technology has improved. The stringent definition of the lower limits of normal by subtracting 1.64·RSD with over age constant RSD has significant drawbacks for older and

Table 18.4 Lung function parameters in %pred of ECCS, LuftiBus, SAPALDIA, and Bochum in young adult males (n = 201)

	ECCS		LuftiBus		SAPALDIA		Bochum	
	Males	Females	Males	Females	Males	Females	Males	Females
VC_{IN} (%pred)	101.5 ± 11.1$^{n.s.}$	104.8 ± 12.2***	–	–	–	–	97.7 ± 11.0$^{n.s.}$	–
FVC (%pred)	105.8 ± 11.4***	109.9 ± 13.3***	106.5 ± 11.4***	105.7 ± 12.8***	99.5 ± 10.7$^{n.s.}$	99.1 ± 12.1$^{n.s.}$	97.6 ± 10.3$^{n.s.}$	–
FEV_1 (%pred)	107.4 ± 13.5***	103.6 ± 12.5***	106.9 ± 13.4***	105.1 ± 12.7***	101.9 ± 12.8**	99.8 ± 12.0$^{n.s.}$	99.5 ± 10.7$^{n.s.}$	–
FEV_1%VC_{IN}	101.4 ± 7.4$^{n.s.}$.	101.7 ± 7.8**	100.4 ± 7.2***	98.5 ± 7.72***	101.4 ± 7.23*	99.3 ± 7.77n.s.	97.6 ± 3.3*	–
PEF (%pred)	104.8 ± 17.3**	97.8 ± 15.1$^{n.s.}$	94.4 ± 15.6***	89.9 ± 13.9***	110.6 ± 18.1***	108.0 ± 16.7***	93.6 ± 15.6***	–
MEF_{75} (%pred)	105.0 ± 22.6**	99.3 ± 18.0$^{n.s.}$	106.7 ± 22.9***	97.8 ± 17.8$^{n.s.}$	107.3 ± 22.8***	101.4 ± 18.5$^{n.s.}$	97.5 ± 15.3$^{n.s.}$	–
MEF_{50} (%pred)	106.7 ± 24.9**	96.9 ± 19.6*	114.2 ± 26.6***	107.9 ± 21.8***	112.6 ± 26.2***	104.1 ± 21.1*	99.1 ± 23.1$^{n.s.}$	–
MEF_{25} (%pred)	101.6 ± 30.1$^{n.s.}$	98.0 ± 25.4$^{n.s.}$	114.6 ± 33.4***	107.2 ± 27.5***	109.1 ± 31.8***	77.1 ± 19.7$^{n.s.}$	103.1 ± 30.1$^{n.s.}$	–
Mean ± SD	**104.3 ± 7.4**	**101.5** ± 3.4	**106.2 ± 8.6**	**101.7** ± 6.1	**106.1 ± 8.2**	**98.4** ± 4.4	**98.0 ± 7.2**	–

n.s. non significant

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

smaller subjects. The most frequently used reference values in Europe include a plateau phase, which would be appropriate for only 63% of the subjects according to the data of Robbins et al. (1995) and Roca et al. (1986). Prediction equations with no plateau, as used by most pulmonary function laboratories in the USA, are only appropriate for 22% of the men aged 18–33 years in this study. Van Pelt et al. (1994) studying FEV_1 in a cross-sectional and longitudinal study in young adults, found a plateau phase or a period of continued lung growth when data were correlated to age. Today there is a consensus that FEV_1 in smokers declines earlier in smoking young adults, compared with non-smoking young adults (Robbins et al. 1995; van Pelt et al. 1994). Until now, we cannot conclude, that pulmonary function development in young adults reaches a plateau phase since we have performed a cross sectional study. In the relevant age range of 18 to about 33 years, longitudinal studies have shown either an ongoing lung growth or a decline in lung function parameters. Taking the mean values into account, the different slopes may compensate each other and result in a plateau, but this is only one explanation. Follow-up periods of 10 years, reported in the literature, are quite a long time, but do not cover the period from 17 to 45 years. More research is needed to get a final conclusion.

18.4.1 ECCS Reference Values Compared with LuftiBus and SAPALDIA Predictions

ECCS predicted values for FEV_1 in comparison to the LuftiBus-Study differ by about 200 ml in young adult males. For middle aged and older subjects differences are even smaller. The reference values of the SAPALDIA-Study are about 200 ml higher for young and middle aged males and about 300 ml for subjects older than 65 years. Values of LLN are largely similar in young subjects by ECCS and LuftiBus, LLN values for middle aged subjects are about 200 ml higher in the LuftiBus study. Despite the decrease of more than 1.5 l from 25 to 80 years of age, the difference between the predicted value and the 5th percentile is nearly constant over the whole range of age. In the original version of the SAPALDIA-Study, the value of the lower limit of normal approximates the predicted values with increasing age (Brandli et al. 1996). Due to a simplified mathematical model, with respect to the small number of older subjects, the authors newly computed the equations for the LLN (Brandli et al. 2000). Now the reference values and their LLN are almost parallel in the SAPALDIA-Study as we know from ECCS formulas.

18.4.2 Multicenter Study for New European Lung Function Recommendations

The need for a complete set of reference values, replacing the ECCS recommendations due to the altered structures of our population can be realized only with a great financial, material and personal engagement in a multi centre European research project. At least, 20,000 subjects have to be recruited from local registration offices. Only subjects with verified heath status and non-restricted cooperation in the measurement are allowed to be selected, whereas smokers and diseased subjects carefully have to be excluded from evaluation. In a comprehensive reference value project not only static and dynamic lung volumes and maximal flows should be studied, but also parameters of body plethysmography, diffusion testing and blood gas analysis should be studied with standardized and well calibrated devices. Recently, the European Respiratory Society established a task force for generation of new reference values of lung function with the aim of compiling current normals from early childhood to senescence. A set of sustained references across all ages will be derived from their investigations, solving the problems of overlaps from adolescence to adults. But for statistical reasons this procedure is highly problematic. In childhood the independent variables for lung function parameters are mainly height and weight, however, for adolescents and adults height, age and sex are determining. So, there is a discontinuity in the underlying mathematical models. Stanojevic et al. (2007, 2008) have published a reference values spanning from early childhood to senescence. This new approach should provides an elegant solution to a complex and longstanding problem of fitting age and height trends to all-age lung function data. These equations provide smoothly changing reference curves during periods of rapid growth and transition to produce a single reference across a wide age range (5–80 years) in Caucasians.

18.5 Conclusions

No correlation between age and body height was found in the age range of 18–26 years in males and females, whereas BMI slightly increases with age. However, in the small age range of investigation, lung function parameters did not correlate with age or BMI but the expected correlation to body height could be confirmed. According to our limited data, the recommendation of a plateau phase from ECCS entering an age of 25 years for calculation of reference values in the age range between 18 and 25 years can be supported. Static and dynamic parameters of younger adults were significantly higher than predicted by ECCS, SAPALDIA and LuftiBus study reference values. Between Zapletal references for adolescents and ECCS, SAPALDIA, and LuftiBus predictions a difference of 300–500 ml was found, which is not acceptable. Considering the increasing age and height of our population and the changes in working conditions, a comprehensive multi center study on lung function of Caucasians should be initiated by the international respiratory societies.

Conflicts of Interest: No conflicts of interest were declared in relation to this article.

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