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Spirometric reference values for children and adolescents from Kazakhstan

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Abstract

Background: Spirometric parameters are influenced by several factors and many reference data are available in the literature. However, no spirometric data are available for children and adolescents from Central Asia.

Aim: The study aimed to calculate spirometric reference curves on the basis of anthropometry, ethnicity (Kazakh vs. Russian) and living environment (urban vs. rural).

Subjects and methods: Spirometry (FEV1, FVC and FEF25–75%) was performed and anthropometric measurements taken for 1926 male and 1967 female Kazakh children aged 7–18 years.

Results: Height explained almost all the variance of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) for both sexes, while age and inspiratory circumference contributed slightly to the prediction. Moreover, FVC and FEV1 were greater in Russians than in Kazakhs and ethnicity did enter the prediction model for these parameters. The living environment had a marginal effect on spirometry. In fact, forced expiratory flow 25–75% (FEF25–75%) was slightly higher in urban than in rural females, FVC was slightly higher in rural than in urban males, while FEV1 was not affected. Finally, among several spirometric equations available in the literature, those performing better in our children were obtained in developed countries.

Conclusion: Anthropometry was the most important predictor of spirometry. Age and ethnicity were also predictors, while the contribution of the living environment was more limited.

Keywords: *Children, spirometry, Kazakhstan, ethnicity, living environment*

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Introduction

Spirometry, i.e. the measurement of airflow during maximal forced expiration, is a non-invasive technique for assessing lung function. The spirometric parameters most commonly employed are forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1). The prediction of FVC and FEV1 from equations based on gender, age and height is commonly employed to obtain reference values for evaluating lung function (Parma et al. 1996; Coultas et al. 1998; Mohamed et al. 2002). Other anthropometric parameters such as body mass index (BMI) may slightly improve the accuracy of the prediction (Marcus et al. 1988). Moreover, spirometric values are influenced by genetic factors, ethnic characteristics (American Thoracic Society 1991; Hankinson et al. 1999) environmental pollution, physical activity, altitude (Forastiere et al. 1994; MacAuley et al. 1999; Fiori et al. 2000; Havryk et al. 2002) and to a minor extent by nutritional and socio-economical factors (Harik-Khan et al. 2004; Raju et al. 2005), which are normally not included in spirometric reference curves. The transition between childhood and adolescence makes the relation between anthropometry and lung function more complicated than in adults (Knudson et al. 1983; Quanjer et al. 1995) and renders necessary the use of population-specific equations (Hellmann and Goren 1999).

No spirometric data are presently available for children and adolescents from Central Asia. As part of the Kazakhstan Health and Nutrition Examination Survey (KHAN-ES) (Facchini et al., in press), we performed spirometry in a large sample of children and adolescents with the aim of calculating reference curves on the basis of anthropometry, ethnicity (Russian vs. Kazakh) and living environment (urban vs. rural). This calculation and the comparison of our prediction model with those available in the literature may be useful for clinical purposes in a multiethnic country undergoing a rapid modernization process and could add information about lung function in developing countries.

Methods

Study design

Kazakhstan is a multiethnic country, where Kazakhs and Russians represent today about 80% of the population with consistent minorities of other ethnic groups (the main ones are Ukrainians, Germans and Uzbeks) (Bhavna 2004). Kazakhs have been rapidly increasing after independence (122% from 1989 to 1999) and a complete description of the demographic trend of the last century was published recently (Masanov 2002). Moreover, the ethnic characteristics of Kazakhs are well described in the literature (Facchini and Fiori 2000).

The measurement of lung function was one of the aims of KHAN-ES, a cross-sectional study of children and adolescents living in urban and rural areas of Kazakhstan. Male and female children of the two major ethnic groups of Kazakhstan, i.e. Kazakhs and Russians, were studied between 2002 and 2004. They were aged 7–18 years and resided either in Almaty or in Chilik. Almaty (1 200 000 inhabitants) is the biggest city in Kazakhstan, and is at an altitude of about 600–950 m. Chilik is a village of about 20 000 inhabitants located 150 km north-east from Almaty at an altitude of 600 m and is very distant from other urban centres. Because Chilik did not meet the demographic criteria of 'urban area' defined by the United States Department of Agriculture (US Department of Agriculture 2005) we classified its environment as 'rural'. Almaty is made up of six urban districts and at the time of the study had nearly 180 000 students aged 7–18 years, attending about 230 schools. Only 20 schools of three different districts agreed to participate in KHAN-ES, so our Almaty sample must be considered a convenience sample. In Chilik, about 5000 students aged 7–18 years attended 15 different schools, 11 of which agreed to participate in KHAN-ES. We recruited about 50 children (from 40 to 65) for every combination of gender (male vs. female), environment (Almaty vs. Chilik), ethnic group (Kazakh vs. Russian) and age group (7–18 years), for a total of 4808 children. The number of subjects was lower only at the extremes (7 and 18 years). We selected a random sample of school classes for each year of age from 7 to 18 years and an almost equal number of Russian and Kazakh children of both sexes for each class. The overall participation rate was about 1.5% in Almaty and 50% in Chilik. Age was calculated as the difference between the day of the visit and birthday, and was therefore decimal.

General exclusion criteria from KHAN-ES were mental impairment, having a sibling already enrolled into the study, unknown ethnic origin, and different ethnic origin of parents. Specific exclusion criteria for the present analysis were: (1) present smoking ($\geq$4 cigarettes/week); (2) previous smoking ($\geq$4 cigarettes/week within 12 months of spirometry); (3) presence of respiratory symptoms at the time of spirometry; (4) use of respiratory drugs; (5) chronic respiratory disease (e.g. asthma), cardiovascular disease or past history of other respiratory pathologies (violation of these criteria led to the exclusion of 608 children); (6) lack of data needed for analysis ($n = 299$); and (7) transcription errors ($n = 10$).

The above data were self-reported in a questionnaire compiled by the children (e.g. for smoking habits) or their parents. On the basis of the data of Gold et al. (1996), slight or occasional smokers (from 1 to 3 cigarettes/week, $n = 9$), sometimes considered as non-smokers (e.g. National Cancer Institute 2001) were included in the analysis. However, their exclusion from statistical analysis did not modify the results (data not shown). Because of the high number of subjects it was not possible to employ more accurate indicators of cigarette smoking such as cotinine in saliva or urine (Simoni et al. 2006). Therefore, the influence of environmental passive smoking was not considered in this study.

A total of 3893 children (1926 males and 1967 females) were thus available for the present analysis. The study was conducted in conformity with the declaration of Helsinki and the protocol was approved by the Scientific Committee of the Kazakh Academy of Sciences. As requested in the case of no greater than minimal risk, every boy/girl gave his/her written assent and at least one parent gave a written and signed informed permission to participate in the study if the child's age was lower than 18.00 years (Burns 2003). Otherwise (age between 18.00 and 18.49 years), the boy/girl himself/herself gave his/her signed informed consent.

Spirometry

FVC and FEV1 were assessed using a Vitalograph spirometer calibrated at least twice daily with a 3-L syringe (Vitalograph, Maids Moreton, Buckingham, UK) in medical rooms at school with a temperature between 20 and 25°C, without differences between Almaty and Chilik. The children performed at least three blows from the sitting position and the highest values of FVC and FEV1 were recorded (American Thoracic Society 1995; Arets et al. 2001). Forced Midexpiratory Flow FEF25–75% was calculated from the blow with the largest sum of FEV1 and FVC. Reproducibility of measurements was within the limits established by the American Thoracic Society and ATS/ERS (American Thoracic Society 1995; Miller et al. 2005).

Anthropometry

Weight, height, sitting height, chest circumference (maximal inspiratory or ICC, maximal expiratory or ECC, and resting or RCC), chest breadth, and chest depth were measured following the *Anthropometric Standardization Reference Manual* (Lohman et al. 1991). BMI was calculated as weight (kg)/height (m)^2. The per cent increase in chest circumference was calculated as $\Delta CC = [(ICC–ECC)/ECC] \times 100$.

Statistical analysis

Medians, 10th and 90th percentiles were calculated for every measurement, stratifying children for living environment and ethnicity. Spirometry prediction equations were developed using forward stepwise multiple regression. Anthropometric variables (see above), age (years, continuous), living environment (0 = urban; 1 = rural) and ethnic group (0 = Kazakh; 1 = Russian) were input in the model separately for males and females. A base-10 logarithm ($\log_{10}$) transformation of the outcome variables with the predictors modelled as linear was chosen because there was no increase in the explained variance when using $\log_{10}$-transformed predictors or polynomial transformations and after taking interactions into account. Multicollinearity was checked using variance inflation factors (VIF). Values of VIF >10 were taken as evidence of multicollinearity (Myers 1990). Standardized residual plots are also reported. The final prediction model was compared with several models available in the literature (Knudson et al. 1983; Lebecque et al. 1991; Rosenthal et al. 1993; Quanjer et al. 1995; Sirotkovic and Cvoriscec 1995; Parma et al. 1996; Hankinson et al. 1999; Ip et al. 2000; Kivastik and Kingisepp 2001; Golshan et al. 2003; Al-Riyami et al. 2004; Chinn et al. 2006) using median values of the difference between measured and predicted values and the difference between 5th and 95th percentiles (Tables I and II). Residual standard deviation (RSD) as goodness-of-fit test is also reported for all experimental models. It was calculated as SD of differences between observed and predicted values in a log-scale. Moreover, linear RSD (LRSD) was calculated as the SD of differences between observed and predicted spirometric values for all considered models in a linear scale. Finally, the statistic of Bland and Altman (1986) was applied to log-transformed variables to further investigate deviations from measured values. Statistical analysis was performed using SPSS 13.0 (SPSS, Chicago, USA).

Results

Prediction of FVC in males

Figure 1 give the distribution of age and gender and Table III gives the 10th, 50th and 90th percentiles of all measurements.

At stepwise regression, the best model for the prediction of $\log_{10}$-FVC in males was based on height ($R^2 = 0.792$), ICC (additional $R^2 = 0.019$), ethnic group (additional $R^2 = 0.009$) and age (additional $R^2 = 0.005$) ($p < 0.001$ for all predictors). Other anthropometric variables were correlated with FVC, but they were not included because of multicollinearity (data not shown). The final best fit model is reported in Table IV with total R^2 and RSD together with a simplified model taking into account only height and ethnicity. Residual graph (Figure 2A) did not show significant deviations from normality, heteroskedasticity or non-linearity.

Table I. The literature models used for comparisons for FVC. ln, natural logarithm; log, $\log_{10}$; M, male; F, female. In the Chinn and Quanjer models, height is expressed in metres and in the Parma model, defined only for males. Units for FVC are millilitres.

Author	Model (FVC) M/F
Al-Riyami et al. (2004)	M: $\ln(FVC) = -15.699 + 3.339\ln(height)$
Oman, 6–19 years	F: $\ln(FVC) = -14.955 + 3.170\ln(height)$
Chinn et al. (2006)	M: $\ln(FVC) = -1.422 + (1.495 + 0.0141Age)height$
UK, 7–20 years	F: $\ln(FVC) = -1.466 + (1.471 + 0.0145Age)height$
Golshan et al. (2003)	M: $FVC = -4.322 + 0.04202Height + 0.09678Age$
Iran, <21 years	F: $FVC = -3.223 + 0.03510Height + 0.06651Age$
Hankinson et al. (1999), USA	M: $FVC = -0.2584 - 0.20415Age + 0.010133Age^2 + 0.00018642Height^2$
Caucasian (<20 years M, <18 years F)	F: $FVC = 1.2082 + 0.05916Age + 0.00014815Height^2$
Ip et al. (2000)	M: $\ln(FVC) = -13.851 + 2.964\ln(Height)$
Hong Kong, 7–19 years	F: $\ln(FVC) = -13.270 + 2.835\ln(Height)$
Kivastik and Kingisepp (2001)	M: $\ln(FVC) = -10.583 + 2.106\ln(Height) + 0.435\ln(Age)$
Estonia, 6–18 years	F: $\ln(FVC) = -10.136 + 1.969\ln(Height) + 0.484\ln(Age)$
Quanjer et al. (1995)	M: $\ln(FVC) = -1.2782 + [1.3731 + 0.0164Age]Height$
Europe, 6–21 years	F: $\ln(FVC) = -1.4507 + [1.4800 + 0.0127Age]Height$
Rosenthal et al. (1993)	M < 162.6 cm: $FVC = 0.043 \cdot Height - 3.619$
UK, 4–19 years	M ≥ 162.6 cm: $FVC = 0.068 \cdot Height - 7.038$
	F < 152.6 cm: $FVC = 0.039 \cdot Height - 3.311$
	F ≥ 152.6 cm: $FVC = 0.045 \cdot Height - 3.881$
Sirotkovic and Cvoriscec (1995)	M: $FVC = -5.00129 + 0.04634Height + 0.07952Age$
Croatia, 6–18 years	F: $FVC = -3.37147 + 0.03296Height + 0.09170Age$
Knudson et al. (1983)	M 6–12 years: $FVC = -3.3756 + 0.0409Height$
USA, variable age range	M 12–25 years: $FVC = -6.8865 + 0.0590Height + 0.0739Age$
	F 6–11 years: $FVC = -3.7486 + 0.0430Height$
	F 12–20 years: $FVC = -4.4470 + 0.0416Height + 0.0699Age$
Lebecque et al. (1991)	M: $\log(FVC) = -0.8703 + 0.00881Height$
Canada, 5–18 years	F: $\log(FVC) = -0.9742 + 0.00938Height$
Parma et al. (1996)	M: $\ln(FVC) = 0.1796 - 0.049age + 0.003age^2 + 0.791\ln(weight) - 0.043BMI +$
Italy, 7–18 years	$12.060\ln(ICC) - 11.106 \times \ln(ECC) - 9.678delta\%$

The mean (95% CI) FVC difference between Russians and Kazakhs was 0.314 (0.208–0.419).

The living environment did not contribute to the prediction and was therefore not inserted in the model. However, rural males had significantly but slightly higher values of FVC than urban ones [mean difference (95% CI) 0.128 (0.022–0.233), $p = 0.002$].

Prediction of FVC in females

At stepwise regression, the best model for the prediction of $\log_{10}$-FVC in females was based on height ($R^2 = 0.735$), ICC (additional $R^2 = 0.019$), ethnic group (additional $R^2 = 0.007$) and age (additional $R^2 = 0.005$) ($p < 0.001$ for all predictors). Other anthropometric variables were associated with FVC, but they were not included because of multicollinearity (data not shown). The final best fit model is reported in Table IV with total R^2 and RSD together with a simplified model taking into account only height and ethnicity. Residual graph (Figure 2B) did not show significant deviations from normality, heteroskedasticity or non-linearity.

Table II. The literature models used for comparisons for FEV1. ln, natural logarithm; log, $\log_{10}$; M, male; F, female. In the Chinn and Quanjers models, height is expressed in metres and in the Parma model, defined only for males. Units for FVC are millilitres.

Author	Model (FEV1) M/F
Al-Riyami et al. (2004)	M: $\ln(\text{FEV1}) = -14.83 + 3.135\ln(\text{height})$
Oman, 6–19 years	F: $\ln(\text{FEV1}) = -14.607 + 3.080\ \ln(\text{height})$
Chinn et al. (2006)	M: $\ln(\text{FEV1}) = -1.405 + [1.333 + 0.0174\text{Age}]\text{height}$
UK, 7–20 years	F: $\ln(\text{FEV1}) = -1.516 + [1.404 + 0.0163\text{Age}]\text{height}$
Golshan et al. (2003)	M: $\text{FEV1} = -3.683 + 0.03569\text{Height} + 0.09030\text{Age}$
Iran, <21 years	F: $\text{FEV1} = -2.732 + 0.02959\text{Height} + 0.06588\text{Age}$
Hankinson et al. (1999)	M: $\text{FEV1} = -0.7453 - 0.04106\text{Age} + 0.004477\text{Age}^2 + 0.00014098\text{Height}^2$
USA: Caucasian	F: $\text{FEV1} = -0.8710 + 0.06537\text{Age} + 0.00011496\text{Height}^2$
(<20 years M, <18 years F)	
Ip et al. (2000)	M: $\ln(\text{FEV1}) = -13.999 + 2.972\ln(\text{Height})$
Hong Kong, 7–19 years	F: $\ln(\text{FEV1}) = -13.392 + 2.843\ln(\text{Height})$
Kivastik and Kingisepp (2001)	M: $\ln(\text{FEV1}) = -11.554 + 2.371\ln(\text{Height}) + 0.234\ln(\text{Age})$
Estonia, 6–18 years	F: $\ln(\text{FEV1}) = -10.134 + 1.964\ln(\text{Height}) + 0.456\ln(\text{Age})$
Quanjer et al. (1995)	M: $\ln(\text{FEV1}) = -1.2933 + [1.2669 + 0.0174\text{Age}]\text{Height}$
Europe, 6–21 years	F: $\ln(\text{FEV1}) = -1.5974 + [1.5016 + 0.0119\text{Age}]\text{Height}$
Rosenthal et al. (1993)	$\text{M} < 162.6$ cm: $\text{FEV1} = 0.034 \cdot \text{Height} - 2.780$
UK, 4–19 years	$\text{M} \geq 162.6$ cm: $\text{FEV1} = 0.052 \cdot \text{Height} - 5.108$
	$\text{F} < 152.6$ cm: $\text{FEV1} = 0.033 \cdot \text{Height} - 2.734$
	$\text{F} \geq 152.6$ cm: $\text{FEV1} = 0.041 \cdot \text{Height} - 3.680$
Sirotkovic and Cvoriscec (1995)	M: $\text{FEV1} = -4.38161 + 0.04117\text{Height} + 0.07646\text{Age}$
Croatia, 6–18 years	F: $\text{FEV1} = -3.16798 + 0.03142\text{Height} + 0.08171\text{Age}$
Knudson et al. (1983)	M 6–12 years: $\text{FEV1} = -2.8142 + 0.0348\text{Height}$
USA, variable age range	M 12–25 years: $\text{FEV1} = -6.1181 + 0.0519\text{Height} + 0.0636\text{Age}$
	F 6–11 years: $\text{FEV1} = -2.7578 + 0.0336\text{Height}$
	F 12–20 years: $\text{FEV1} = -3.7622 + 0.0351\text{Height} + 0.0694\text{Age}$
Lebecque et al. (1991)	M: $\log(\text{FEV1}) = -0.8302 + 0.00825\text{Height}$
Canada, 5–18 years	F: $\log(\text{FEV1}) = -9389 + 0.00890\text{Height}$
Parma et al. (1996)	M: $\ln(\text{FEV1}) = 2.448 - 0.062\text{age} + 0.003\text{age}^2 + 0.768\ln(\text{weight}) -$
Italy, 7–18 years	$0.044\text{BMI} + 14.863\ln(\text{ICC}) - 14.044 \times \ln(\text{ECC}) - 12.440\text{delta\%}$

The mean (95% CI) FVC difference between Russians and Kazakhs was 0.203 (0.128–0.280).

The living environment did not contribute to the prediction and had no effect when added to the final equation ($p = \text{NS}$).

Prediction of FEV1 in males

At stepwise regression, the best model for the prediction of $\log_{10}$-FEV1 in males was based on height ($R^2 = 0.788$), ICC (additional $R^2 = 0.018$), ethnic group (additional $R^2 = 0.004$) and age (additional $R^2 = 0.005$) ($p < 0.001$ for all predictors). Other anthropometric variables were not included because of multicollinearity (data not shown). The final best fit model is reported in Table IV with total R^2 and RSD together with a simplified model taking into account only height and ethnicity. Residual plots (Figure 2C) did not show significant deviations from normality, heteroskedasticity or non-linearity.

The mean FEV1 (95% CI) difference between Russians and Kazakhs was 0.227 (0.133–0.320).

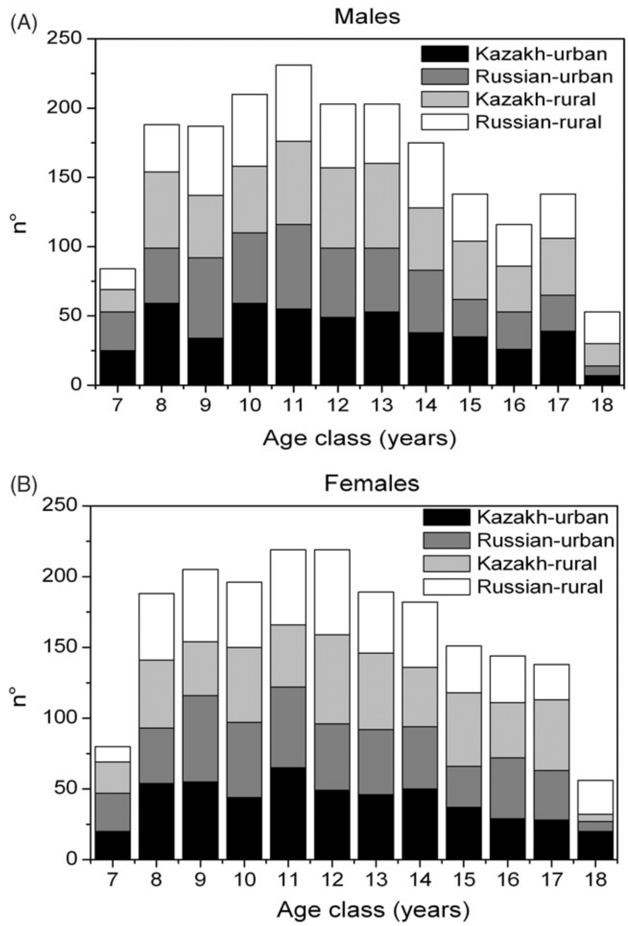


Figure 1. Distribution of children and adolescents with age for (A) males and (B) females.

The living environment did not contribute to the prediction and had no effect when added to the final equation ($p = \text{NS}$).

Prediction of FEV1 in females

At stepwise regression, the best model for the prediction of $\log_{10}$-FEV1 in females was based on height ($R^2 = 0.688$), ICC (additional $R^2 = 0.017$), ethnic group (additional $R^2 = 0.003$) and age (additional $R^2 = 0.004$) ($p < 0.001$ for all predictors). Other anthropometric variables were not included because of multicollinearity (data not shown). The final best fit model is reported in Table IV with total R^2 and RSD together with a simplified model taking into account only height and ethnicity. Residual plots (Figure 2D) did not show significant deviations from normality, heteroskedasticity or non-linearity.

The mean (95% CI) FEV1 difference between Russian and Kazakhs was 0.148 (0.080–0.218).

The living environment did not contribute to the prediction and had no effect when added to the final equation ($p = \text{NS}$).

Table III. Anthropometric and spirometric variables of the examined population. Medians with 10th and 90th percentiles are reported.

	Urban Kazakh	Urban Russian	Rural Kazakh	Rural Russian
Males	$n=479$	$n=466$	$n=520$	$n=461$
Age (mean ± SD)	11.9 ± 3.0 years	11.7 ± 2.9 years	12.2 ± 3.0 years	12.3 ± 3.0 years
Height (cm)	145.0 (125.0–173.0)	146.9 (126.2–174.7)	145.0 (123.6–172.2)	147.0 (126.0–173.0)
Weight (kg)	35.5 (25.0–58.0)	36.0 (24.0–61.0)	35.0 (23.0–57.0)	36.0 (24.0–60.0)
BMI (kg m^{-2})	16.9 (14.7–20.6)	16.9 (14.5–21.3)	16.6 (14.3–19.7)	17.1 (14.5–21.2)
Sitting height (cm)	76.0 (67.5–90.0)	76.0 (67.0–90.5)	76.4 (67.0–90.8)	76.6 (67.5–90.9)
ICC (cm)	73.5 (65.3–89.0)	74.0 (64.0–90.6)	74.5 (64.0–89.0)	74.0 (65.0–91.9)
ECC (cm)	65.0 (57.5–79.8)	65.5 (57.0–80.9)	65.0 (57.0–78.8)	65.0 (57.0–81.0)
NCC (cm)	67.0 (59.0–82.0)	67.0 (58.0–83.0)	67.0 (58.2–81.0)	67.0 (59.0–83.0)
Breadth (cm)	21.0 (18.0–25.1)	21.0 (17.8–25.6)	21.4 (18.8–25.4)	21.8 (18.8–26.5)
Depth (cm)	14.0 (12.3–16.5)	14.2 (12.0–17.0)	13.8 (12.2–16.0)	14.3 (12.6–17.3)
Waist circumference (cm)	57.0 (50.1–67.0)	58.0 (50.0–68.0)	57.0 (49.0–66.0)	56.0 (50.0–68.0)
ΔCC (%)	12.8 (8.6–16.1)	12.8 (8.4–16.4)	13.6 (10.5–16.8)	13.7 (10.9–16.9)
FEV1 (L)	2.3 (1.5–4.0)	2.4 (1.6–4.3)	2.3 (1.4–4.0)	2.5 (1.5–4.5)
FVC (L)	2.6 (1.7–4.4)	2.6 (1.8–4.7)	2.5 (1.6–4.5)	2.9 (1.8–5.2)
FEF25–75% (L s^{-1})	2.8 (1.6–5.0)	2.9 (1.7–5.1)	2.8 (1–7–4.9)	3.0 (1.6–5.4)
FEV1/FVC ratio	0.91 (0.76–0.99)	0.91 (0.80–0.99)	0.92 (0.79–1.00)	0.90 (0.73–0.99)
Females	$n=497$	$n=488$	$n=510$	$n=472$
Age (mean ± SD)	12.0 ± 3.0 years	11.9 ± 3.0 years	12.3 ± 3.0 years	12.2 ± 3.0 years
Height (cm)	149.0 (125.0–166.2)	149.0 (126.0–168.8)	148.3 (122.3–162.5)	148.0 (124.7–164.5)
Weight (kg)	38.0 (24.0–55.0)	37.0 (24.5–57.0)	37.0 (22.0–54.0)	37.0 (23.0–58.0)
BMI (kg m^{-2})	17.2 (14.5–20.9)	17.0 (14.3–21.5)	17.1 (14.1–21.3)	17.1 (14.0–22.1)
Sitting height (cm)	78.5 (67.0–88.5)	77.0 (67.0–88.7)	79.0 (66.0–87.7)	77.5 (66.7–88.3)
ICC (cm)	74.0 (63.0–85.6)	73.5 (64.0–88.0)	74.4 (63.0–86.0)	74.0 (63.0–87.0)
ECC (cm)	66.0 (56.0–76.8)	65.0 (55.8–79.0)	65.5 (55.0–76.0)	64.5 (54.8–77.2)
RCC (cm)	68.0 (57.0–79.0)	67.0 (57.0–81.0)	67.8 (56.5–78.0)	67.0 (56.0–80.0)
Breadth (cm)	21.0 (17.6–24.2)	20.7 (17.6–24.5)	21.3 (18.3–24.4)	21.5 (18.0–25.3)
Depth (cm)	13.8 (12.0–16.0)	14.0 (12.0–16.5)	13.6 (11.8–16.0)	14.0 (12.0–16.6)
Waist circumference (cm)	55.5 (48.2–64.0)	56.0 (48.5–66.0)	55.0 (48.0–63.0)	55.0 (48.0–64.3)
ΔCC (%)	12.3 (8.8–15.7)	12.8 (8.5–16.2)	13.7 (10.5–16.9)	14.0 (10.7–18.0)
FEV1 (L)	2.2 (1.4–3.4)	2.3 (1.5–3.6)	2.2 (1.3–3.3)	2.3 (1.5–3.5)
FVC (L)	2.5 (1.5–3.7)	2.6 (1.6–4.0)	2.5 (1.5–3.6)	2.7 (1.7–4.0)
FEF25–75% (L s^{-1})	2.8 (1.7–4.4)	2.9 (1.7–4.7)	2.6 (1.4–4.1)	2.7 (1.5–4.3)
FEV1/FVC ratio	0.93 (0.78–1.00)	0.94 (0.81–1.00)	0.94 (0.79–1.00)	0.91 (0.73–1.00)

Prediction of FEF25–75% and FEV1/FVC ratio

At stepwise regression, the best model for the prediction of $\log_{10}$-FEF25–75% in males had lower values of R^2 than for FVC and FEV1 (Table IV) and was based on height ($R^2=0.528$), ICC (additional $R^2=0.014$) and age (additional $R^2=0.004$). Neither ethnic group ($p=0.216$) nor the living environment ($p=0.466$) contributed to the model. In females, the same prediction was much less accurate (Table IV) and was based on height ($R^2=0.38$), ICC (additional $R^2=0.009$) and age (additional $R^2=0.003$). Moreover, the living environment (additional $R^2=0.004$) was highly significant with a negative coefficient ($p<0.001$). In other words, FEF25–75% was significantly higher in urban than rural females and ethnic group did not contribute to the model ($p=0.14$). Finally, in Table IV also simplified models with only height as predictor are reported. The FEV1/FVC ratio was not associated with height, age and other anthropometric variables. Moreover, the effect of living environment was also not significant. However, Kazakh males and females had slightly

Table IV. Best fit and simplified models with relative R^2 and RSD.

FVC – Males
Best fit model: $\log_{10}$-FVC = −0.729 + 0.00429 · height (cm) + 0.00526 · ICC (cm) + 0.0339 · ethnic group (1 = Russian; 0 = Kazakh) + 0.00991 · age (years)
$R^2 = 0.824$, RSD = 0.070
Simplified model: $\log_{10}$-FVC = −0.811 + 0.00830 · height (cm) + 0.0317 · ethnic group (1 = Russian; 0 = Kazakh)
$R^2 = 0.801$, RSD = 0.074
FVC – Females
Best fit model: $\log_{10}$-FVC = −0.710 + 0.00477 · height (cm) + 0.00407 · ICC (cm) + 0.0257 · ethnic group (1 = Russian; 0 = Kazakh) + 0.00744 · age (years)
$R^2 = 0.766$, RSD = 0.072
Simplified model: $\log_{10}$-FVC = −0.815 + 0.0082 · height (cm) + 0.0169 · ethnic group (1 = Russian; 0 = Kazakh)
$R^2 = 0.738$, RSD = 0.075
FEV1 – Males
Best fit model: $\log_{10}$-FEV1 = −0.782 + 0.00445 · height (cm) + 0.00506 · ICC (cm) + 0.0253 · ethnic group (1 = Russian; 0 = Kazakh) + 0.00892 · age (years)
$R^2 = 0.815$, RSD = 0.072
Simplified model: $\log_{10}$-FEV1 = −0.864 + 0.00844 · height (cm) + 0.023 · ethnic group (1 = Russian; 0 = Kazakh)
$R^2 = 0.793$, RSD = 0.076
FEV1 – Females
Best fit model: $\log_{10}$-FEV1 = −0.747 + 0.00496 · height (cm) + 0.00383 · ICC (cm) + 0.0190 · ethnic group (1 = Russian; 0 = Kazakh) + 0.00622 · age (years)
$R^2 = 0.712$, RSD = 0.081
Simplified model: $\log_{10}$-FEV1 = −0.832 + 0.008 · height (cm) + 0.0091 · ethnic group (1 = Russian; 0 = Kazakh)
$R^2 = 0.689$, RSD = 0.083
FEF25–75% – Males
Best fit model: $\log_{10}$-FEF25–75% = −0.616 + 0.00376 · height (cm) + 0.00515 · ICC (cm) + 0.0104 · age (years)
$R^2 = 0.545$, RSD = 0.128
Simplified model: $\log_{10}$-FEF25–75% = −0.703 + 0.00783 · height (cm)
$R^2 = 0.527$, RSD = 0.131
FEF25–75% – Females
Best fit model: $\log_{10}$-FEF25–75% = −0.515 + 0.00408 · height (cm) + 0.00364 · ICC (cm) + 0.00702 · age (years)-0.0273 · origin (0 = urban, 1 = rural)
$R^2 = 0.396$, RSD = 0.140
Simplified model: $\log_{10}$-FEF25–75% = −0.703 + 0.00783 · height (cm)
$R^2 = 0.381$, RSD = 0.142

higher values of FEV1/FVC ratio than Russians males ($p = 0.001$) and females ($p = 0.004$) (Mann–Whitney test).

Comparison with available equations

Table V gives the values of FVC and FEV1 predicted by the equations of Tables I and II. The data are given as 5th, 10th, 25th, 50th, 75th, 90th and 95th percentiles of the difference and as the difference between 95th and 5th percentiles (per cent variability or Δ). We also calculated the difference between the median measured and the best possible result if the experimental and theoretical model coincided: 100% (this statistic was called Dev50). Finally, the LRSD of the model was also reported. The model of Parma et al. (1996) was

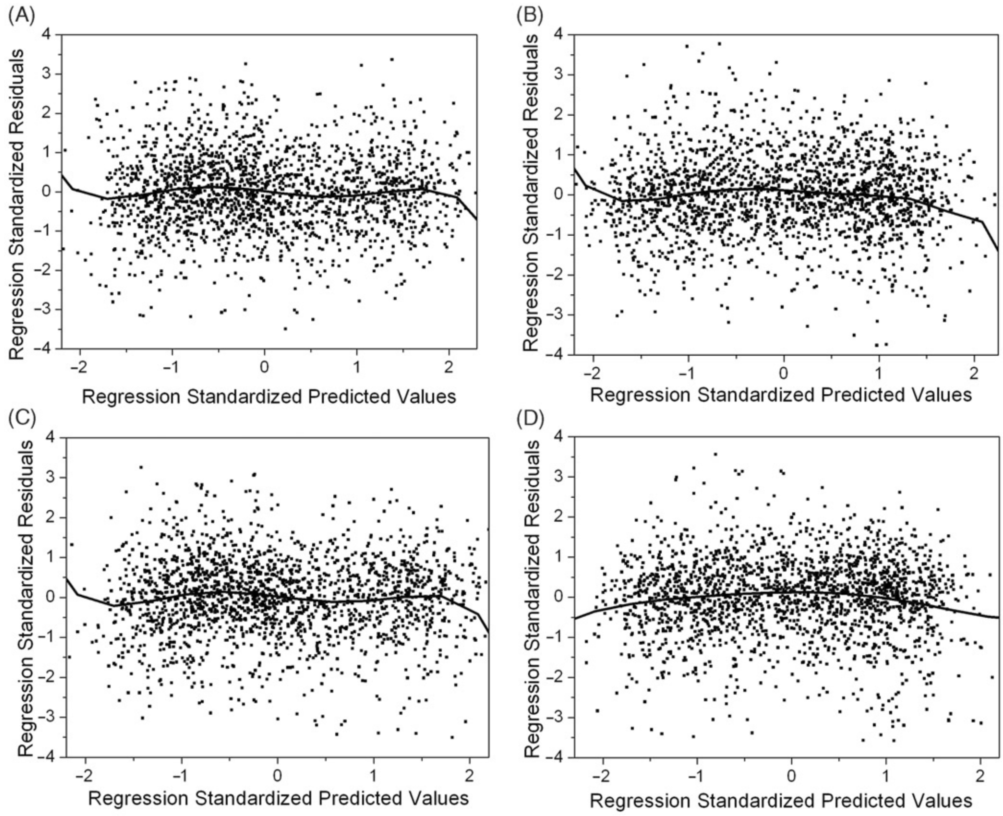


Figure 2. Standardized residuals as a function of standardized predicted values of best fit models for (A) male FVC, (B) female FVC, (C) male FEV1, and (D) female FEV1.

used only for FEV1, because of a probable error in the intercept of FVC (0.176, while one would expect a value between 1.5 and 2.5). As for FVC in males, some models had a value of Δ similar to our model (Chinn, Quanjer), but underestimated the median value. The Quanjer model also presented the lowest difference in LRSD value as compared to the experimental model. The Knudson model gave a good estimation of median values but had a higher variability (+3.1%) than the experimental model. As for FVC in females, several models had a variability similar to our model (Chinn, Golshan, Hankinson, Quanjer), while the Knudson and Lebeque models estimated the median better. Looking at LRSD, the Knudson model presented the lowest value as compared to the experimental model. As for FEV1 in males, the models of Parma and Quanjer provided a good estimate of both the median and variability with lowest LRSD (together with the Chinn model), very close to those of our model. Lastly, as for FEV1 in females, the Quanjer model had predictive power similar to our model and most models presented similar LRSD.

As an example, Figure 3 gives the Bland–Altman plots for the comparison of our model (FVC for males) with Knudson and Sirotkovic models. A non-linearity of the residual trend was slightly evident for Knudson model and dramatically evident for the Sirotkovic model. The Sirotkovic model tended in fact to underestimate FVC at lowest and highest values. Moreover, the residual mean and SD in the first comparison (0.0016 ± 0.03) were much lower than in the second comparison (0.024 ± 0.05).

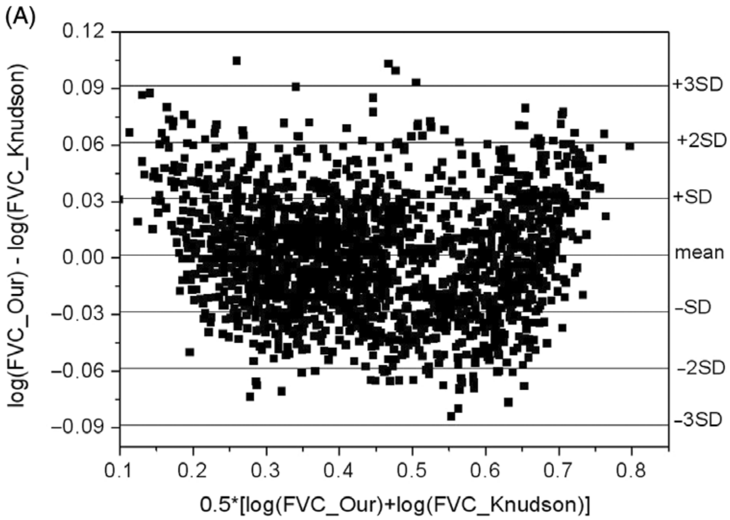
Table V. (A) Male FVC as% predicted; (B) female FVC as% predicted; (C) male FEV1 as% predicted; (D) female FEV1 as% predicted using all the models presented in Tables I and II. NA, not applicable. LRSD (linear residual standard deviation) is expressed in litres. Best fit and simplified models are taken from Table IV.

Model	5th	10th	25th	50th	75th	90th	95th	Dev50	Δ	LRSD
(A) *Male FVC as% predicted*										
Best fit	76.6	82.7	90.6	99.8	110.4	122.2	131.6	−0.2	55.0	0.499
Simplified	77.2	82.5	91.3	101.8	113.2	126.3	136.6	+1.8	59.4	0.548
Al-Riyami	78.6	83.6	93.3	104.8	118.6	133.3	143.2	+4.8	64.6	0.567
Chinn	73.3	77.8	86.7	96.6	107.6	119.8	129.1	−3.4	55.8	0.552
Golshan	71.3	76.0	84.6	95.2	107.5	120.5	131.4	−4.8	60.1	0.581
Hankinson	75.1	79.6	88.3	98.8	111.0	124.4	134.0	−1.2	58.9	0.558
Ip	81.8	86.2	96.0	107.2	120.1	134.3	144.6	+7.2	62.8	0.569
Kivastik	76.7	81.7	91.1	101.7	113.7	126.7	137.3	+1.7	60.6	0.557
Quanjer	72.8	77.5	86.4	96.2	106.9	119.0	127.8	−3.8	55.0	0.549
Rosenthal	74.7	79.7	88.7	99.1	110.9	123.8	133.4	−0.9	58.7	0.568
Sirotkovic	77.8	83.3	92.6	105.0	119.3	135.3	148.8	+5.0	71.0	0.580
Knudson	76.3	81.1	90.2	100.3	112.3	125.1	134.4	+0.3	58.1	0.553
Lebeque	77.1	81.5	91.2	101.4	113.2	127.2	136.6	+1.4	59.5	0.562
Parma	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
(B) *Female FVC as% predicted*										
Best fit	76.1	82.1	90.9	100.3	110.5	122.2	130.0	+0.3	53.9	0.442
Simplified	74.8	81.1	90.0	100.2	111.6	124.3	132.6	+0.2	57.8	0.473
Al-Riyami	80.1	86.3	96.0	107.6	120.7	133.9	144.4	+7.6	64.3	0.478
Chinn	72.5	77.9	86.0	95.9	106.7	118.9	127.6	−4.1	55.1	0.477
Golshan	71.3	76.5	85.1	94.9	105.4	117.4	125.7	−5.1	54.4	0.467
Hankinson	72.4	77.2	85.7	95.9	107.3	118.9	127.2	−4.1	54.8	0.474
Ip	79.6	85.9	94.6	106.4	118.0	131.1	141.3	+6.4	61.7	0.475
Kivastik	79.1	84.5	93.8	104.7	116.8	130.0	138.6	+4.7	59.5	0.466
Quanjer	72.6	78.1	86.4	96.5	107.1	119.7	127.8	−3.5	55.2	0.472
Rosenthal	76.0	81.4	90.7	101.9	113.2	125.9	136.2	+1.9	60.2	0.481
Sirotkovic	76.5	81.6	90.9	101.4	114.0	126.3	135.4	+1.4	58.9	0.469
Knudson	75.3	80.7	89.2	99.8	111.3	123.1	132.7	−0.2	57.4	0.465
Lebeque	73.6	79.6	88.5	99.1	110.6	122.7	132.5	−0.9	58.9	0.497
(C) *Male FEV1 as% predicted*										
Best fit	74.6	81.4	90.8	100.6	110.9	121.2	129.4	+0.6	54.8	0.455
Simplified	73.6	80.3	90.0	100.6	111.7	123.5	132.4	+0.6	58.8	0.490
Al-Riyami	80.0	87.2	97.4	108.9	122.0	135.6	147.3	+8.9	67.3	0.499
Chinn	75.1	81.2	91.5	101.7	113.4	124.4	133.5	+1.7	58.4	0.486
Golshan	71.1	77.6	86.9	97.0	109.4	121.6	130.4	−3.0	59.3	0.514
Hankinson	75.0	81.6	91.6	102.2	114.2	126.6	136.2	+2.2	61.2	0.493
Ip	78.7	86.0	95.8	107.1	119.8	132.1	143.1	+7.1	64.4	0.503
Kivastik	77.7	84.5	94.4	104.8	117.1	128.7	138.7	+4.8	61.0	0.502
Quanjer	73.9	80.1	90.3	100.2	112.1	122.5	132.5	+0.2	58.6	0.487
Rosenthal	79.0	85.4	96.2	107.4	119.7	132.5	142.6	+7.4	63.6	0.502
Sirotkovic	72.9	79.0	89.2	99.7	112.5	127.9	137.9	−0.3	65.0	0.512
Knudson	76.5	82.8	92.9	103.3	115.2	126.6	135.5	+3.3	59.0	0.492
Lebeque	73.8	79.5	89.8	99.9	111.8	123.7	132.4	−0.1	58.6	0.498
Parma	73.1	80.3	90.1	100.2	111.3	122.5	130.6	+0.2	57.5	0.479
(D) *Female FEV1 as% predicted*										
Best fit	71.6	79.1	90.6	101.6	111.9	123.0	132.0	+1.6	60.4	0.440
Simplified	71.4	80.0	91.2	102.4	114.4	126.3	133.8	+2.4	62.4	0.460
Al-Riyami	76.0	83.7	95.9	108.3	122.0	134.8	142.8	+8.3	66.8	0.462
Chinn	69.1	76.5	87.6	98.0	108.9	120.4	129.1	−2.0	60.0	0.467

(*continued*)

Table V. Continued.

Model	5th	10th	25th	50th	75th	90th	95th	Dev50	Δ	LRSD
Golshan	68.9	76.6	86.8	98.2	109.2	121.2	128.2	−1.8	59.3	0.454
Hankinson	68.5	76.6	86.9	98.2	109.3	121.1	128.2	−1.8	59.7	0.455
Ip	73.4	81.4	93.3	105.1	117.4	129.3	136.9	+5.1	63.5	0.459
Kivastik	73.4	81.7	92.8	105.0	116.5	129.1	136.2	+5.0	62.8	0.455
Quanjer	70.3	77.7	88.8	100.1	111.0	122.0	130.8	+0.1	60.5	0.459
Rosenthal	73.9	82.0	93.6	105.6	118.5	130.0	138.8	+5.6	60.2	0.460
Sirotkovic	68.4	76.1	86.5	98.0	109.5	121.5	128.9	−2.0	60.5	0.459
Knudson	72.7	80.2	91.8	103.4	115.1	126.7	134.4	+3.4	61.7	0.452
Lebeque	68.5	75.6	86.8	97.6	109.4	120.3	128.7	−2.4	60.2	0.476



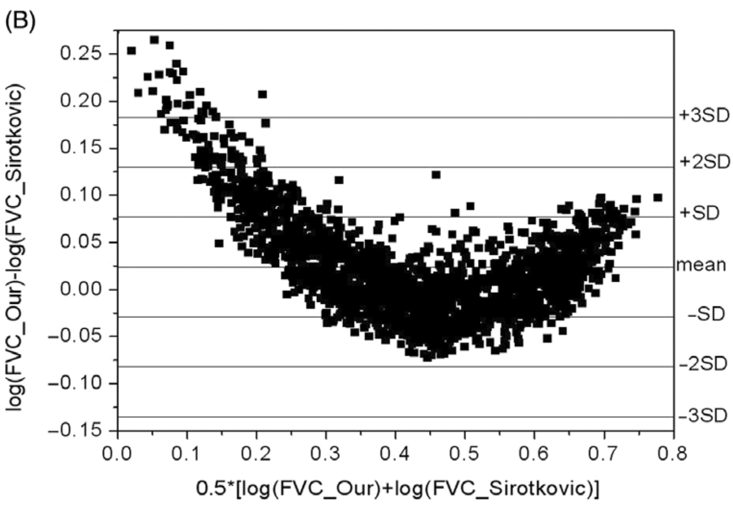


Figure 3. Bland–Altman graphs on logarithm for the comparisons between (A) our model and the Knudson model, and (B) our model and the Sirotkovic model using male FVC as an example.

Discussion

KHAN-ES was aimed at evaluating the contribution of the living environment to nutrition and health in children and adolescents living in Kazakhstan. KHAN-ES children also underwent spirometry, offering us the possibility to calculate spirometric reference curves for Kazakh children and adolescents also taking in account the living environment. While little data on adults are available in the literature (Fiori et al. 2000), this is the first study of spirometry in children from Central Asia. However, a limitation of KHAN-ES is that only children and adolescents attending school were studied, so that our results do not necessarily apply to all Kazakh children.

In our equations, height was the most important predictor of FVC and FEV1 and some anthropometric parameters such as ICC marginally improved the accuracy of the estimate. However, most anthropometric variables (weight, BMI, sitting height, waist circumference, expiratory and resting chest circumference, chest breadth, chest depth and also BMI) did not significantly contribute to the prediction or were excluded because of multicollinearity.

The contribution of age to the predictions was statistically significant inside the best fit models in the presence of standing height even if it marginally improved the model. More importantly, Russians had higher values of FVC and FEV1 – but not of FEF25–75% – than Kazakhs, and this is the first study to report this difference in Mongolian vs. Caucasian children. Another study (Crapo et al. 1999) performed in a sample with a limitated number of subjects with a greater variability in age did not find such an effect. A small but significant ethnic difference was evident also for the FEV1/FVC ratio. R^2 values found in our reference models for FEV1 and FVC (0.712−0.824) are perfectly in line with the literature, indicating that the most part of variance of these parameters was explained by predictor variables considered in this study. Finally, RSD of the models are also consistent with the literature, when logarithmic models for FVC and FEV1 have been considered (Quanjer et al. 1995; Ip et al. 2000; Kivastik and Kingisepp 2001; Al-Riyami et al. 2004).

This does not imply that other variables could be taken into consideration as predictor factors, like puberty onset, socio-economical status, nutritional status, genetic factors, environmental pollution and so on. However, it would be difficult to include them in reference curves available for current clinical practice. Further analyses of the KHAN data are in progress to evaluate the association between puberty, living environment, anthropometric variables, socio-economical factors and clinical variables.

Finally, simplified models taking into account only height and ethnicity were added, to simplify their use for clinical practice without measuring specific anthropometric values, such as ICC.

Prediction equations for FEF25–75% were less accurate because their R^2 were much lower than those for FVC and FEV1. A similar trend had been already observed by Parma et al. (1996), indicating that FEF25–75% needs further investigation and that other variables not considered in this study may be needed to improve prediction.

The effect of the living environment on spirometry requires a brief discussion. In fact, the influence of the living environment (urban vs. rural) on lung function has been poorly studied in the literature. KHAN-ES shows that the living environment in Kazakhstan has only a marginal influence on spirometric parameters. FEF25–75% was higher in urban than in rural females and FVC was higher in rural than urban male children. The living environment was not associated with FEV1 so that, at this stage of analysis, it is impossible to speculate about the environmental factors that could influence our results. However, they are in good agreement with those reported for Italy (Centanni et al. 2001), while the results from other developing countries are contrasting. In Nigeria, spirometric parameters of children were not associated with the living environment (Glew et al. 2004), while in Iran, urban children had a worse pulmonary function as compared with rural children (Asgari et al. 1998).

After defining a predictive model for FVC and FEV1, we compared it with the most recent models available in the literature (Tables I and II). As measures of accuracy, we used the median predicted for FVC and FEV1 (expected value = 100%), the difference between 95th and 5th percentiles and RSD. The best models were Knudson for FVC in both genders, Quanjer and Parma for male FEV1 and Quanjer for female FEV1, even if other models (Golshan, Hatkinson) gave acceptable results. In general, the best models were those developed in white Caucasians of developed countries (USA, Europe), while models developed in more selected populations were more prone to error.

To definitively and accurately compare experimental and literature models, we used Bland–Altman plots on a logarithmic scale. The difference between measured values of FVC and those predicted by the Knudson algorithm was uniformly distributed, with evidence of low bias (average difference near 0) and only a few points were above 3 SD (the Bland–Altman statistics employ a 2 SDs cut-off also because it calculates 95% limits of agreement from the standard error). With a less well performing model such as Sirotkovic, the differences between measured and predicted values had a non-linear trend and the average difference was clearly different from zero. As a general rule, the comparison of several models confirmed that the log transformation of spirometric values appears to be the most appropriate way of analysing such data.

In conclusion, while the living environment only slightly affected male FVC and female FEF 25.75%, spirometric prediction equations depended primarily on height (for FVC and FEV1 in both genders) with a modest but significant contribution from ICC and age. Moreover, Russians had higher values of FVC and FEV1 than Kazakhs and ethnic group was maintained in prediction equations. Lastly, a statistical approach based on the calculation of% predicted values and Bland–Altman graph is proposed to compare experimental spirometric reference curves with literature models. In our case, models that better predicted FVC/FEV1 were those defined on white Caucasians of developed countries.

Competing interests

All the authors declare that they have no conflicts of interest.

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