Reference equations using segmented regressions for impulse oscillometry in healthy subjects aged 2.7–90 years

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Reference equations are presented for impulse oscillometry that can be applied across most of the lifespan (ages 2.7–90 years), thus avoiding the conflicting results often seen when two or more separate equations for different age ranges are used https://bit.ly/3LMwxqV

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Abstract

Background Published reference equations for impulse oscillometry (IOS) usually encompass a specific age group but not the entire lifespan. This may lead to discordant predicted values when two or more non-coincident equations can be applied to the same person, or when a person moves from one equation to the next non-convergent equation as he or she gets older. Thus, our aim was to provide a single reference equation for each IOS variable that could be applied from infancy to old age.

Methods This was an ambispective cross-sectional study in healthy nonsmokers, most of whom lived in Mexico City, who underwent IOS according to international standards. A multivariate piecewise linear regression, also known as segmented regression, was used to obtain reference equations for each IOS variable.

Results In a population of 830 subjects (54.0% female) aged 2.7 to 90 years (54.8% children ⩽12 years), segmented regression estimated two breakpoints for age in almost all IOS variables, except for R5−R20 in which only one breakpoint was detected. With this approach, multivariate regressions including sex, age, height and body mass index as independent variables were constructed, and coefficients for calculating predicted value, lower and upper limits of normal, percentage of predicted and z-score were obtained.

Conclusions Our study provides IOS reference equations that include the major determinants of lung function, *i.e.* sex, age, height and body mass index, that can be easily implemented for subjects of almost any age.

Introduction

The impulse oscillometry (IOS) system evaluates respiratory mechanics through small pressure oscillations superimposed on normal tidal breathing, allowing the equipment to estimate respiratory system impedance (Z) and its two components, resistance (R) and reactance (X). In recent decades, IOS has gained much attention because it is a noninvasive and simple-to-perform technique, so it can easily be carried out in subjects of any age. IOS provides insights about location (central or peripheral airways) and nature (increased frictional resistance to air flow and/or altered tissue elastance/inertance) of lung abnormalities [1]. Thus, IOS complements other tests of respiratory mechanics for the diagnosis and monitoring of diseases such as asthma, COPD and interstitial lung diseases, and it has been considered even more sensitive than spirometry for detecting subtle initial changes in disease [2–6]. Moreover, the manufacturing industry continuously introduces more portable and less expensive IOS apparatuses to the market, so this technology is becoming more affordable. Unfortunately, standardisation of IOS technical and interpretative strategies is still ongoing. An important issue limiting the clinical application of IOS is the relative lack of validated reference equations, especially in adults. For instance, in its last consensus, the European Respiratory Society (ERS) Task Force on Oscillometry Research listed seven oscillometry reference equations, most of them obtained in Caucasian subjects, and only one of them was carried out in subjects aged 45–91 years [7]. In addition to this scarcity of reference values, an additional problem arises when two or more reference equations are needed to cover the entire age range of a particular population. Because each equation is mathematically constructed only for a certain age range, it is not uncommon that 1) equations overlap in some age ranges but give different results, *i.e.* a person can have several predicted values; or 2) equations do not converge, *i.e.* a person has a sudden change in predicted value when moving from one equation to the other as he or she gets older. Although this problem is not new and occurs during the interpretation of other pulmonary function tests (PFTs), it clearly emphasises that the best reference equation needs to be a single equation covering the full lifespan [8]. Therefore, the objective of the present study was to provide a single equation to calculate reference values for each IOS variable in a population of healthy subjects ranging from 2.7 to 90 years of age. In this population, raw values of all IOS variables showed a large and progressive change during childhood, followed by a relative stabilisation after adolescence; therefore, we decided to use multivariate piecewise linear regression, also known as segmented regression, to account for these inflection points of lung function observed across the lifespan.

Materials and methods

Study design and population

This was a cross-sectional study that integrated three previously reported populations as well as a prospectively recruited population. The first report included 283 children (54.1% female) aged 2.7–15.4 years recruited in 2011 [9], the second included 224 children (52.2% female) aged 4.0–12.4 years recruited during 2014–2015 [10] and the third included 132 adults (48.5% female) aged 20–74 years recruited in 2018 [11]. Finally, the prospectively recruited population comprised 191 volunteers aged >14 years. Similar devices were used in all subjects (MS-IOS, Jaeger, CareFusion, San Diego, CA, USA). Almost all subjects lived in the metropolitan area of Mexico City and all were considered to be Mexican mestizos. The inclusion criteria for all subjects included the absence of any chronic respiratory disease or of any acute respiratory morbidity in the past 15 days, the lack of regular exposure to biomass or tobacco smoke (<100 cigarettes during the lifetime), and no data suggestive of sleep apnoea/hypopnoea syndrome or gastro-oesophageal reflux. Participants with thoracic surgery or major comorbidities were excluded, and those occasional participants who were unable to produce an adequate IOS measurement or who refused to continue with the test were eliminated from the study.

All procedures were conducted in accordance with the amended Declaration of Helsinki and all protocols were approved by the corresponding institutional review boards. The latter unpublished prospective study received approval number C43-17 from the Research Committee and Ethics in Research Committee of the Instituto Nacional de Enfermedades Respiratorias. Written informed consent was obtained from all participants or, in the case of children, by their legal guardians.

IOS procedure

On the day of the study, after the standing height and weight were measured with medical-grade devices, an IOS test was performed using the MS-IOS digital system (Jaeger) calibrated on the same day for volume with a certified 3-L syringe at three different flows as well as linearity on a weekly basis; pressure was verified with a pressure resistance with a 0.2 kPa impedance, with maximal resistance variability of ±0.01 kPa and zero reactance. The procedure was performed while the subject was comfortably seated, with the head in a very slight "chin-up" position, using a nose clip, supporting the cheeks with his or her hands or, in the case of children, with cheeks supported by one of the researchers, and quietly breathing at tidal volume into the equipment's mouthpiece through an antibacterial filter. IOS manoeuvres, each lasting 30 s and performed at least 1 min apart, were performed until three acceptable measurements were obtained. Acceptability criteria of the recording included a lack of artefacts and a coherence of ⩾0.6 at 5 Hz and ⩾0.9 at 10 Hz. The final reported value was the mean of the three acceptable manoeuvres according to the 2003 ERS Task Force on Respiratory Impedance Measurements [12]. The IOS variables included were R and X at 5, 10, 15 and 20 Hz (R5, R10, R15 and R20, and X5, X10, X15 and X20, respectively), R5−R20, (R5−R20)/R5, resonance frequency (Fres) and area of reactance (AX). The response to bronchodilators was not explored.

Statistical analysis

Age, height, weight, body mass index (BMI) and IOS variables are described using medians and ranges after their stratification by age periods. The intra-measurement variability, *i.e.* the variability among the three IOS manoeuvres performed within a single session, was evaluated through the coefficient of variation (CV) calculated as 100×SD/|mean|. Because at certain Hz, reactances have near-zero values, those few subjects whose final reactance was zero were excluded from CV computations.

For each IOS parameter (dependent variable), a single equation was calculated by adjusting for sex (woman=0, man=1), age in years, the inverse of height in cm and the inverse of BMI in $kg \cdot m^{-2}$ as independent variables. The inverse transformation of height and BMI values was performed to obtain a better adjustment in the final model. Through assessment of the variance inflation factor, we corroborated the lack of collinearity between BMI and height. In all IOS variables, it was evident that when plotted against age, at least two inflexion points of IOS values existed at approximately ages 7 and 17 years. To account for these breakpoints, piecewise linear regression was used. To this end, the package *segmented* from the R software (v4.1.2; www.r-project.org) was used to estimate the piecewise models with two breakpoints for age. The initial guess for these breakpoints were at ages 7 and 17 years old, but the final breakpoints incorporated into the equations were estimated for each IOS variable by the R package through an interactive procedure and using the Bayesian Information Criterion to select the best model. Graphical representation of the final models was performed with scatter plots for IOS variables *versus* age, height or BMI, including the smoothed predicted values (local polynomial regression, locally estimated scatterplot smoothing (LOESS) method).

Comparison with other refence equations

To visually compare our results with previously published reference equations, we obtained relevant information from two recent publications [7, 13] and performed a search in PubMed using the search strategy (impulse oscillometry[ti] OR IOS[ti]) AND (reference values[ti] OR equation[ti]), limiting the search to works published from January 2018 to July 2022. These equations were applied to our study population according to each equation's limits of sex, age or anthropometric variables, and the obtained predicted values were plotted using LOESS regressions. Some published equations were excluded because they gave extremely different results for some IOS variables or because the reported values did not coincide with the frequencies (Hz) measured in the present study [14–16].

Results

We studied 830 subjects aged 2.7 to 90 years; 448 (54%) were female, 232 (28.0%) were overweight (BMI $\geqslant$25 to <30 $kg \cdot m^{-2}$) and 17 (2.0%) were obese (BMI $\geqslant$30 $kg \cdot m^{-2}$). The general characteristics of the study participants, stratified by age groups, are shown in table 1. The raw values and intra-measurement CV of IOS variables are summarised in supplementary table S1 and supplementary figure S1.

In almost all IOS variables, the segmented regression models estimated two breakpoints for age (these breakpoints were different for each IOS variable) (supplementary table S2); thus, three different reference

TABLE 1 Characteristics of the study population (n=830) according to age groups

Age, years	Subjects, n (male:female)	Height, cm	Weight, kg	BMI, $kg \cdot m^{-2}$
3.5 (2.7–4)	37 (17:20)	97 (86–108)	15 (13–19)	16.1 (13.9–19.3)
4.7 (>4–5)	44 (20:24)	106 (99–114)	18 (14–26)	15.9 (13.1–20.5)
5.5 (>5–6)	61 (29:32)	112 (101–127)	20 (15–37)	15.8 (13.1–24.3)
6.5 (>6–7)	41 (23:18)	118 (108–128)	22 (17–40)	15.7 (13.8–24.7)
7.6 (>7–8)	40 (20:20)	123 (111–135)	24 (19–42)	16.4 (13.2–22.7)
8.6 (>8–9)	57 (29:28)	128 (114–146)	28 (19–47)	16.9 (13.7–27.7)
9.6 (>9–10)	58 (21:37)	135 (121–150)	33 (23–57)	18.3 (14.9–27.2)
10.6 (>10–11)	56 (20:36)	140 (128–157)	34 (24–65)	18.4 (14.5–27.2)
11.6 (>11–12)	61 (32:29)	144 (131–161)	39 (28–66)	18.8 (14.6–26.9)
15 (>12–20)	56 (29:27)	158 (134–180)	54 (33–90)	20.7 (16.0–29.5)
24 (>20–30)	62 (28:34)	163 (150–185)	68 (46–94)	25.3 (17.6–29.8)
35 (>30–40)	54 (30:24)	164 (149–183)	70 (50–88)	26.1 (20.3–29.8)
45 (>40–50)	64 (25:39)	160 (146–185)	70 (52–96)	27.3 (19.4–31.6)
55 (>50–60)	56 (22:34)	155 (134–176)	66 (45–98)	26.9 (19.0–41.3)
65 (>60–70)	43 (20:23)	158 (142–175)	69 (51–89)	27.6 (20.4–31.0)
75.5 (>70–90)	40 (17:23)	158 (145–180)	68 (49–91)	28.3 (20.2–34.7)

Data correspond to median (minimum–maximum), unless otherwise stated. BMI: body mass index.

TABLE 2 Reference equations for respiratory system resistances, measured by impulse oscillometry at 5, 10, 15 and 20 Hz

	First age range	Second age range	Third age range	t-test	p-value
R5, kPa/(L·s^{-1})					
Apply to ages (years):	2.70–7.36	7.37–19.10	19.11–90.0		
Coefficients					
Intercept	0.446389	0.2235	−0.28559	3.255	0.0012
Sex, 0=female, 1=male	−0.015418	−0.015418	−0.015418	−2.055	0.0402
Age, years	−0.054965	−0.024709	0.0019316	−6.082	<0.001
Height, cm	100.379581	100.379581	100.379581	9.227	<0.001
BMI, kg·m^{-2}	−2.606237	−2.606237	−2.606237	−4.565	<0.001
RMSE	0.143	0.104	0.0724		
Adjusted R^2 (full model)	0.85				
R10, kPa/(L·s^{-1})					
Apply to ages (years):	2.70–7.41	7.42–18.41	18.42–90.0		
Coefficients					
Intercept	0.50774	0.25469	−0.17295	4.447	<0.001
Sex, 0=female, 1=male	−0.009279	−0.009279	−0.009279	−1.489	0.137
Age, years	−0.055993	−0.021886	0.0013355	−7.650	<0.001
Height, cm	75.927159	75.927159	75.927159	8.355	<0.001
BMI, kg·m^{-2}	−2.077629	−2.077629	−2.077629	−4.396	<0.001
RMSE	0.1194089	0.08344332	0.06282849		
Adjusted R^2 (full model)	0.8561				
R15, kPa/(L·s^{-1})					
Apply to ages (years):	2.70–7.54	7.55–18.78	18.79–90.0		
Coefficients					
Intercept	0.47706	0.21664	−0.14633	4.445	<0.001
Sex, 0=female, 1=male	−0.014106	−0.014106	−0.014106	−2.388	0.017
Age, years	−0.052626	−0.018149	0.0011729	−7.792	<0.001
Height, cm	64.43336	64.43336	64.43336	7.504	<0.001
BMI, kg·m^{-2}	−1.230043	−1.230043	−1.230043	−2.749	0.0061
RMSE	0.1114599	0.07949125	0.06028402		
Adjusted R^2 (full model)	0.844				
R20, kPa/(L·s^{-1})					
Apply to ages (years):	2.7–7.65	7.66–17.85	17.86–90.0		
Coefficients					
Intercept	0.467775	0.21954	−0.091009	4.457	<0.001
Sex, 0=female, 1=male	−0.02099	−0.02099	−0.02099	−3.636	<0.001
Age, years	−0.048658	−0.016263	0.0011237	−7.480	<0.001
Height, cm	54.515578	54.515578	54.515578	6.465	<0.001
BMI, kg·m^{-2}	−0.801186	−0.801186	−0.801186	−1.830	0.068
RMSE	0.11	0.0785	0.0566		
Adjusted R^2 (full model)	0.81				
R5−R20, kPa/(L·s^{-1})					
Apply to ages (years):	2.7–23.55	23.56–90.0			
Coefficients					
Intercept	0.013349	−0.18775		0.286	0.775
Sex, 0=female, 1=male	0.004813	0.004813		1.079	0.281
Age, years	−0.0075403	0.00099579		−6.314	<0.001
Height, cm	43.014247	43.014247		10.389	<0.001
BMI, kg·m^{-2}	−1.794838	−1.794838		−5.259	<0.001
RMSE	0.0739	0.0348			
Adjusted R^2 (full model)	0.64				
(R5−R20)/R5, %					
Apply to ages (years):	2.7–7.89	7.90–22.53	22.54–90.0		
Coefficients					
Intercept	0.767122	25.320322	−2.296038	0.079	0.9368
Sex, 0=female, 1=male	1.248248	1.248248	1.248248	2.113	0.035
Age, years	2.210981	−0.897019	0.175967	3.644	<0.001
Height, cm	3347.062139	3347.062139	3347.062139	4.342	<0.001
BMI, kg·m^{-2}	−251.389691	−251.389691	−251.389691	−5.605	<0.001

Continued

TABLE 2 Continued

	First age range	Second age range	Third age range	t-test	p-value
RMSE	8.503653	8.599485	7.49395		
Adjusted R^2 (full model)	0.31				

For each oscillometry parameter, the predicted value and the lower limit of normal (LLN) and upper limit of normal (ULN) can be calculated applying the following formulas, according to the subjects' age:

- Predicted value=Intercept+(sex coefficient×sex[0 if female, 1 if male])+(age coefficient×age[in years])+(height coefficient×1/height[in cm])+(BMI coefficient×1/BMI[in $kg \cdot m^{-2}$])
- LLN=Predicted value–1.6449×RMSE
- ULN=Predicted value+1.6449×RMSE
- z-score=(Observed value–Predicted value)/RMSE.

R: respiratory resistance; BMI: body mass index; RMSE: root mean square error.

equations were estimated. The exception was R5–R20, for which only one age breakpoint was detected, and thus, only two reference equations were estimated. The coefficients corresponding to these reference equations, along with detailed instructions on how to solve them, can be found in table 2 (resistances) and table 3 (reactances, Fres and AX). The LOESS regression of the predicted values achieved good fitting for age (figures 1 and 2). Supplementary figures S2 and S3 illustrate fitting for height and BMI, respectively. The supplementary material includes a Microsoft Excel file designed to solve the present equations, either for an individual subject, with a printable report form, or for a database of up to 1000 subjects. In this file, the results for each IOS variable include predicted value, lower and upper limits of normal, percentage of predicted, z-score and, if a bronchodilator was used, percentage change, delta of percentage of predicted, and delta of z-scores of both measurements (pre- and post-bronchodilator). Finally, supplementary figure S4 shows the overlap of predicted data obtained with our equations and those obtained with international IOS reference equations [9, 11, 17–26]. All these equations had better agreement when plotted against age (supplementary figure S4) than when plotted against height (supplementary figure S5). Data pertaining to R5, X5 and AX had the best overlap.

Discussion

In this study, we provide IOS reference equations for subjects of almost any age. The equations incorporate the most influential variables for lung function (sex, height, age and BMI). We reason that our equations can be easily implemented in clinical practice.

Since its first description in 1956 [27], measurement of respiratory system impedance using small pulses of pressure/flow superimposed on tidal breathing has progressively evolved into the procedure currently known as IOS. Several different reference equations have been generated for IOS parameters in different populations. Nevertheless, none of these reference equations includes most of the lifespan. This is a major drawback because if a population is divided into two or more age periods (*e.g.* childhood and adulthood), the separate mathematical fits of these segments will not necessarily converge. For example, if our study population was divided into younger (<20 years old) and older (⩾20 years old) subjects and a separate mathematical fit (multiple linear regression) was applied to each age group, a 19-year-old man would have a predicted R5 value of 0.15 $kPa/(L \cdot s^{-1})$, as calculated by the first equation, but this value would rise to 0.21 $kPa/(L \cdot s^{-1})$ when he moves to the next equation after his 20th birthday (supplementary figure S6). Thus, it may be the case (and in fact, it often occurs with other PFTs [8, 28, 29]) that two or more reference equations can be applied to the same person, especially if he or she is transitioning between later childhood and young adulthood, which yields contrasting interpretations of the IOS results. Our reference equations circumvent this problem because each equation covers most of the lifespan.

Recently, the Global Lung Initiative published multi-ethnic equations for spirometry, lung volumes and diffusing capacity of the lung for carbon monoxide (D_{LCO}) that can be applied from childhood to adulthood [8, 30, 31]. In these equations, the LMS method, which stands for location or skewness (L, lambda), mean value (M, mu) and scatter or coefficient of variation (S, sigma), was applied. Although this is an excellent mathematical approach for fitting the results obtained in spirometry, lung volumes or D_{LCO}, it is not fully applicable to IOS variables. This is because values obtained using the IOS technique are rather small or negative, which provokes the lack of convergence in some models and/or the impossibility of calculating some lower and upper limits of normal. Therefore, we decided to use piecewise linear regression models. These models differ from the classical multiple linear regression in that they consider potential breakpoints of one or more variables and make the proper adjustments to the equation in

TABLE 3 Reference equations for respiratory system reactances, measured by impulse oscillometry at 5, 10, 15 and 20 Hz, frequency of resonance and area of reactance

	First age range	Second age range	Third age range	t-test	p-value
X5, kPa/(L·s^{-1})					
Apply to ages (years):	2.7–5.29	5.30–18.68	18.69–90.0		
Coefficients					
Intercept	−0.089509	0.1172	0.19728	−1.067	0.286
Sex, 0=female, 1=male	0.009133	0.009133	0.009133	2.241	0.025
Age, years	0.043369	0.0043487	0.00006377	4.705	<0.001
Height, cm	−57.924822	−57.924822	−57.924822	−9.810	<0.001
BMI, kg·m^{-2}	1.090394	1.090394	1.090394	3.499	<0.001
RMSE	0.0922	0.0575	0.0408		
Adjusted R^2 (full model)	0.75				
X10, kPa/(L·s^{-1})					
Apply to ages (years):	2.7–4.79	4.80–17.77	17.78–90.0		
Coefficients					
Intercept	−0.074644	0.062574	0.14548	−1.067	0.2864
Sex, 0=female, 1=male	0.00594	0.00594	0.00594	1.872	0.0616
Age, years	0.032878	0.0042905	−0.00037304	3.383	<0.001
Height, cm	−37.396994	−37.396994	−37.396994	−8.132	<0.001
BMI, kg·m^{-2}	1.298675	1.298675	1.298675	5.346	<0.001
RMSE	0.08269942	0.0450797	0.03146344		
Adjusted R^2 (full model)	0.6482				
X15, kPa/(L·s^{-1})					
Apply to ages (years):	2.7–4.69	4.70–18.13	18.14–90.0		
Coefficients					
Intercept	−0.048396	0.099266	0.17472	−0.692	0.4894
Sex, 0=female, 1=male	−0.003995	−0.003995	−0.003995	−1.273	0.2035
Age, years	0.035226	0.0038081	−0.00035174	3.399	<0.001
Height, cm	−34.912858	−34.912858	−34.912858	−7.774	<0.001
BMI, kg·m^{-2}	1.229632	1.229632	1.229632	5.123	<0.001
RMSE	0.08089067	0.04453968	0.0326824		
Adjusted R^2 (full model)	0.6168				
X20, kPa/(L·s^{-1})					
Apply to ages (years):	2.70–5.29	5.30–20.99	21.0–90.0		
Coefficients					
Intercept	0.016911	0.1347	0.1774	0.342	0.732
Sex, 0=female, 1=male	−0.001806	−0.001806	−0.001806	−0.680	0.497
Age, years	0.024023	0.0017869	−0.0002462	4.091	<0.001
Height, cm	−28.29	−28.29	−28.29	−8.365	<0.001
BMI, kg·m^{-2}	1.01	1.01	1.01	4.923	<0.001
RMSE	0.0544	0.0351	0.0341		
Adjusted R^2 (full model)	0.57				
Fres, Hz					
Apply to ages (years):	2.70–9.69	9.70–20.98	20.99–90.0		
Coefficients					
Intercept	3.63228	7.518	1.2542	0.908	0.364
Sex, 0=female, 1=male	0.07493	0.07493	0.07493	0.312	0.755
Age, years	0.14349	−0.2571	0.041179	0.811	0.418
Height, cm	2781.55206	2781.55206	2781.55206	8.311	<0.001
BMI, kg·m^{-2}	−99.15807	−99.15807	−99.15807	−5.531	<0.001
RMSE	2.71	3.2	3.89		
Adjusted R^2 (full model)	0.49				
LN(AX), LN(kPa·L^{-1})					
Apply to ages (years):	2.70–6.98	6.99–23.21	23.22–90.0		
Coefficients					
Intercept	−3.42268	−2.367	−3.597	−5.594	<0.001
Sex, 0=female, 1=male	−0.06776	−0.06776	−0.06776	−1.872	0.062
Age, years	0.10429	−0.046624	0.0063497	2.289	0.022
Height, cm	544.962	544.962	544.962	11.532	<0.001
BMI, kg·m^{-2}	−18.97076	−18.97076	−18.97076	−6.839	<0.001

Continued

TABLE 3 Continued

	First age range	Second age range	Third age range	t-test	p-value
RMSE	0.366	0.461	0.621		
Adjusted R^2 (full model)	0.66				

For each oscillometry parameter, excepting AX, the predicted value and the lower limit of normal (LLN) and upper limit of normal (ULN) can be calculated applying the following formulas, using the coefficients corresponding to the subjects' age:

- Predicted value=Intercept+(sex coefficient×sex[0 if female, 1 if male])+(age coefficient×age[in years])+(height coefficient×1/height[in cm])+(BMI coefficient×1/BMI[in kg·m^{-2}])
- LLN=Predicted value–1.6449×RMSE
- ULN=Predicted value+1.6449×RMSE
- z-score=(Observed value–Predicted value)/RMSE.

For AX, the formulas to apply are as follows:

- Predicted value=EXP[Intercept+(sex coefficient×sex[0 if female, 1 if male])+(age coefficient×age[in years])+(height coefficient×1/height[in cm])+(BMI coefficient×1/BMI[in kg·m^{-2}])]
- LLN=EXP[LN(Predicted value)–1.6449×RMSE]
- ULN=EXP[LN(Predicted value)+1.6449×RMSE]
- z-score=[LN(Observed value)–LN(Predicted value)]/RMSE.

In the latter formulas for AX, the term EXP refers to the number *e*, also known as Euler's number, raised to the power obtained from the rest of the formula, and LN refers to the natural logarithm.

X: respiratory reactance; BMI: body mass index; RMSE: root mean square error; Fres: frequency of resonance; AX: area of reactance.

each of the segments delimited by such breakpoints. An advantage of the piecewise regression is that it is less complex to implement than the LMS method [32–34], and that sex is included in the models, so a single set of equations can be used for both sexes.

As can be seen in figures 1 and 2, all IOS variables showed contrasting differences between children and adults, with a sharp decline (resistances, Fres and AX) or rise (reactances) as age increases during childhood, followed by a relatively flat trend afterwards. This changing trend between children and adults was also observed in R5−R20 and (R5−R20)/R5. The sharp decline in IOS resistances during childhood is in line with the previously described behaviour of airway resistance measured by body plethysmography [35], and it is probably due to the increase in airway calibre as stature increases. On the other hand, the gradual increase in resistances during adulthood may be due to the progressive loss of elastin within the lung parenchyma [36], with the consequent decrease in lung elastic recoil and diminished airway calibre due to the loss of airway tethering. The behaviour of (R5−R20)/R5, an index that supposedly represents small airway resistance, might be due to the interplay between the above-mentioned factors (airway calibre, elastic recoil) and some unknown factor(s) added by BMI. In fact, table 2 shows that the only IOS variable in which BMI had more influence than height and age was indeed (R5−R20)/R5, *i.e.* in this variable, BMI had the highest absolute t-value. The reasoning for the use and interpretation of the R5 minus R20 difference and the (R5−R20)/R5 ratio is as follows. Each small pressure wave sent by the IOS equipment rapidly reaches the entire respiratory system and provokes a minuscule tissue expansion. Then, due to the elastic and inertial recoil forces, this pressure wave goes back to the airway opening. At low frequencies (*e.g.* 5 Hz), each pressure wave has enough time to complete this in and out movement, so its effect has completely disappeared before the arrival of the next wave. Thus, R5 mainly reflects the total airway resistance. However, at higher frequencies (*e.g.* 20 Hz), both entering and exiting waves interfere with each other, so incoming waves only reach the central airways, explaining why R20 mainly reflects large airway resistance [27]. Therefore, the difference between these two measurements (R5−R20) has been proposed as an indicator of resistance of more peripheral airways [37–39], and fixed cut-off points (>0.07 kPa/(L·s^{-1}) in adults and >0.15 kPa/(L·s^{-1}) in children) have been proposed for the identification of small airway dysfunction [40, 41]. In this context, our results clearly showed that R5−R20, like other IOS variables, also gradually changes according to age and suggest that a fixed cut-off value is inappropriate and that reference equations should also be used for its proper interpretation, similar to any other IOS variable. The R5−R20 difference can also be expressed as a percentage of the total airway resistance, *i.e.* 100×(R5−R20)/R5. Although the result of (R5−R20)/R5 is reported by the software of some IOS equipment, this is a rarely used index. It is known that the contribution of small airways to the total airway resistance below the larynx is <10% [42], so an arbitrary cut-off value of >30% has been proposed. Nevertheless, our study showed that normal values of (R5−R20)/R5 also varied according to age, so the same arguments posed for R5−R20 apply to (R5−R20)/R5, *i.e.* a fixed cut-off value is inappropriate, and the results must be interpreted according to reference equations.

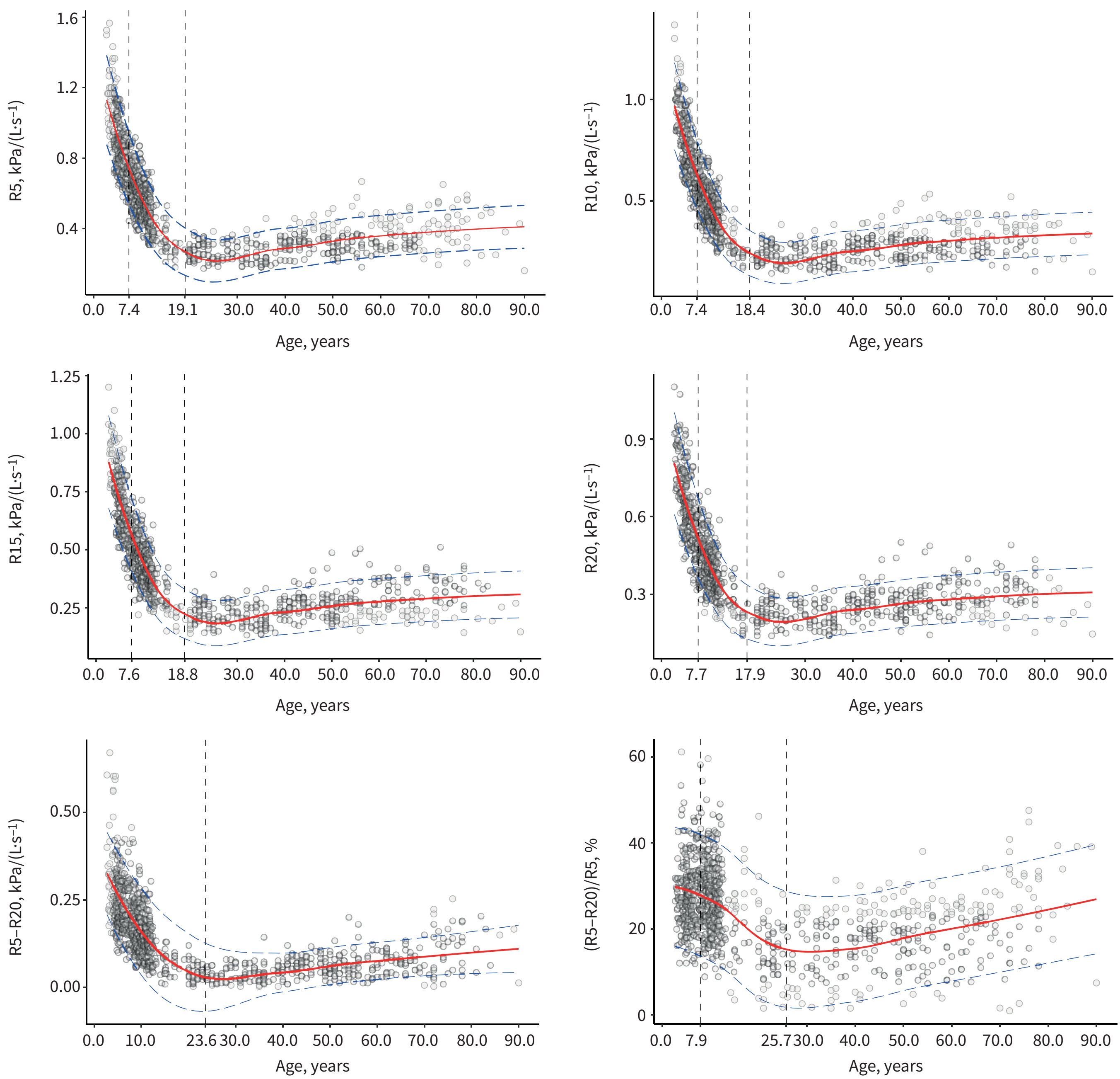

FIGURE 1 Illustration of how impulse oscillometry reference equations fit the study population according to age. Plotted values correspond to resistances (R) at 5, 10, 15 and 20 Hz, R5-R20, and (R5-R20)/R5. Open circles correspond to the study subjects (830 men and women). Curved lines indicate the predicted value (continuous line) and the 95% confidence intervals (dotted lines). Vertical dotted lines indicate the breakpoints identified by the *segmented* package of the R program and used by this package for constructing the reference equations.

Several reference equations for IOS variables have been published. These equations yield different predicted values (supplementary figure S4 and S5). Although differences among the studies, such as ethnicity, equipment, nutritional status, altitude and air pollution, might be a reasonable explanation of this variability, a more worrying possibility is that such variability is due to nonuniformity of technical standards among manufacturers of IOS equipment. This underscores that stringent and uniform international technical standards need to be implemented in the manufacture of IOS apparatuses. In the meantime, it is evident that resistances (at least R5 and R20) are less affected by differences among studies, so resistances should be preferred when comparisons are made among different populations.

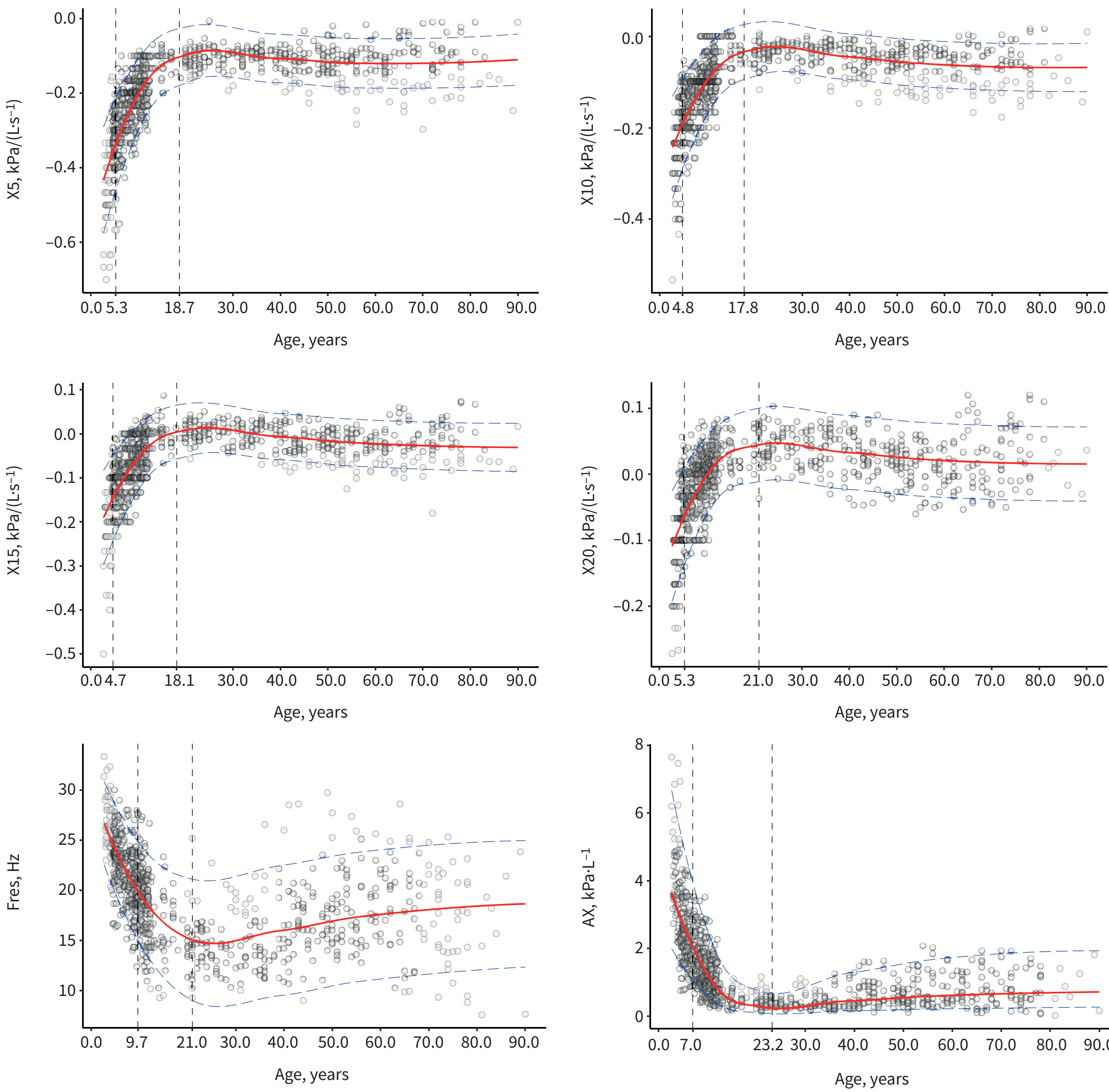

FIGURE 2 Illustration of how impulse oscillometry reference equations fit the study population according to age. Plotted values correspond to reactances (X) at 5, 10, 15 and 20 Hz, resonance frequency (Fres), and area of reactance (AX). Open circles correspond to the study subjects (830 men and women). Curved lines indicate the predicted value (continuous line) and the 95% confidence intervals (dotted lines). Vertical dotted lines indicate the breakpoints identified by the *segmented* package of the R program and used by this package for constructing the reference equations.

Our equations may be applicable to other Latin American populations, especially those with an ethnic background comparable to that of most Mexican people. Moreover, they might also be applicable to non-Latin American populations considering that our equations give results that approximate those obtained in other populations (supplementary figure S4 and S5) [9, 11, 17–26].

Although a potential limitation of our study is that some age ranges had a relatively low number of subjects, we consider that it was large enough to delineate a confident trend for predicted parameters. Likewise, because IOS results may vary among different commercial equipment [43, 44], our equations obtained with the MS-IOS Jaeger must be interpreted with caution when other equipment is used.

Conclusion

Herein, we propose IOS reference equations based on segmented (piecewise) linear regression modelling that encompass most of the lifespan and include major influential variables such as sex, height, age and BMI. These equations can easily be implemented in clinical settings and PFT laboratories.

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Acknowledgements: The population evaluated in the present study (n=830 subjects) included some participants already reported in previous publications [9–11].

Conflict of interest: L. Gochicoa-Rangel reports lecture honoraria from GSK, AstraZeneca, Chiesi, Thorasys and Vyaire; travel support from Chiesi for the Latin America Thoracic Association meeting in 2022; advisory board participation with GSK; and a leadership role as unpaid chief of the respiratory physiology section in the Mexican Pulmonology and Thorax Surgery Society, outside the submitted work. R. Del-Río-Hidalgo reports lecture honoraria from GSK and Chiesi, and travel support Chiesi for ALAT meeting 2022, outside the submitted work. All other authors have nothing to disclose.

Ethics statement: Research Committee and Ethics in Research Committee of the Instituto Nacional de Enfermedades Respiratorias: C43-17.

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