



Reference equations for oscillometry and their differences among populations: a systematic scoping review

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Our scoping review on adult oscillometric reference equations describes divergence in model construction and variations between the same population-based equations, thus warranting careful selection of oscillometric reference values in clinical practice. <https://bit.ly/38a0xwn>

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Abstract

Respiratory oscillometry is gaining global attention over traditional pulmonary function tests for its sensitivity in detecting small airway obstructions. However, its use in clinical settings as a diagnostic tool is limited because oscillometry lacks globally accepted reference values. In this scoping review, we systematically assessed the differences between selected oscillometric reference equations with the hypothesis that significant heterogeneity existed between them. We searched bibliographic databases, registries and references for studies that developed equations for healthy adult populations according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A widely used Caucasian model was used as the standard reference and compared against other models using Bland–Altman and Lin’s concordance correlational analyses. We screened 1202 titles and abstracts, and after a full-text review of 67 studies, we included 10 in our analyses. Of these, three models had a low-to-moderate agreement with the reference model, particularly those developed from non-Caucasian populations. Although the other six models had a moderate-to-high agreement with the standard model, there were still significant sex-specific variations. This is the first systematic analysis of the heterogeneity between oscillometric reference models and warrants the validation of appropriate equations in clinical applications of oscillometry to avoid diagnostic errors.

Introduction

Pulmonary function tests (PFTs) are the most common method used to assess, diagnose and grade the severity of respiratory diseases [1–3]. These tests require forced breathing manoeuvres and substantial patient cooperation, thus limiting their use in paediatric, elderly and frail populations [4]. Moreover, spirometric manoeuvres must be repeated to achieve accurate and reproducible results [5], making it an exhaustive test to perform, particularly in patients with advanced lung conditions and limited abilities [4]. Since DuBois *et al.* [6] established the first forced oscillation technique (FOT), respiratory oscillometry has become an alternative diagnostic tool for respiratory disease. Respiratory oscillometry, formerly known as FOT, delivers external small amplitude oscillations (sinusoidal, random, impulse train or pseudorandom signals based on the device) in either pressure (P) or flow (V') superimposed on spontaneous tidal breathing to stimulate the respiratory system without imparting any physical stress to patients [7, 8]. It can be administered to all patients, does not require any special breathing manoeuvres or patient cooperation and has a higher sensitivity and capacity to detect small airway obstruction even before any such changes are detected by spirometry [9, 10].



The accuracy of PFTs in assessing respiratory health is based on validated reference values [1, 2, 11]. However, unlike globally accepted reference equations for spirometry [12], reference equations for oscillometric indices are diverse and were developed from country-specific populations [13–15]. At present, the oscillometric reference equations developed by OOSTVEEN *et al.* [16] are most commonly used as the standard model for adults. Nevertheless, these models have several limitations. First, these equations were developed only in Caucasian populations, while they are used indiscriminately by most oscillometry manufacturers and clinicians across the world. Validation of those reference equations in other populations or ethnic groups is rarely performed. Thus, the reference range of indices is not standardised for each population of interest, which may lead to an erroneous calculation of relative (percentage of predicted) values. Second, those models were constructed from measurements using five different instruments that could have possible instrument-wise variations in signal processing, optimisation and signal-to-noise ratio (interference). And third, participants in that study were recruited from four different countries; despite having the same ethnicity, possible anthropometric heterogeneity between populations could have a significant influence on oscillometric measurements, and this has not been properly addressed. Moreover, despite the availability of some population-specific reference equations [15–24], most of these equations are either based on a relatively small sample size [15, 16, 18, 19, 21, 22, 24], include an inappropriate sample selection (*e.g.* current or former smokers) [22, 24] or are mathematically complex [23].

Existing reviews on oscillometric techniques [25–30] have not systematically studied the heterogeneity between existing oscillometric reference models. In this scoping review, we aim to systematically assess the variability between existing adult reference equations for oscillometry by evaluating their agreement and biases with the most widely used standard model.

Methods

Scoping review approach and design

The main purpose of a scoping review is to synthesise an interpretable yet broad overview of available evidence without aiming to answer a single research question. Owing to our primary outcome, we decided to follow a scoping review study design for greater methodological flexibility while still incorporating components of a systematic review. We conducted this review based on previously described methodology [31] and according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping reviews [32]. The protocol was submitted to the Open Science Framework [33].

Eligibility criteria and outcomes of interest

Studies were included in our analyses if they developed oscillometric reference equations for respiratory resistance (R_{rs}) and respiratory reactance (X_{rs}) in healthy adults (≥ 18 years old). Healthy individuals were defined as participants who did not report any chronic respiratory diseases such as asthma or chronic obstructive pulmonary disease (COPD), tuberculosis, recent respiratory infections, cardiovascular disease, obesity or current pregnancy. Studies were excluded if they 1) were not written in English, 2) were not published in a peer-reviewed journal, 3) had not mentioned the inclusion/exclusion criteria properly, 4) did not have clearly defined variables or included smokers and 5) were not available as full texts.

Because there are several oscillometric indices, it is difficult to consider all of them in a single review. Therefore, we selected three principal indices of airway impedance: total airway resistance (R_5), central airway resistance (R_{20}) and total airway reactance (X_5). These indices were chosen because they are used most often in clinical diagnosis and clinical trials [34]. In studies in which resistance and reactance values at 5 Hz and 20 Hz were not available, we accepted values from the closest frequencies (*i.e.* 6 Hz and 19 Hz). Additionally, we also considered area under the reactance curve (AX) if it was included in studies. We also considered demographic data including height, weight, age and ethnicity or country of origin of the study. Where height and weight were not reported, we considered body mass index to allow us to compare these reference equations. Variables were extracted only from studies included in the final analysis.

Search strategy and study selection

We searched the bibliographic databases MEDLINE (1946 to present *via* Ovid), Embase, PubMed, Scopus, Web of Science Core Collection and Cochrane Database of Systematic Reviews (Cochrane Library) and registries such as Cochrane Registries (Cochrane Library) and the International Prospective Register of Systematic Reviews (PROSPERO) up to November 15, 2021. The first 100 results of a Google Scholar search, hand searches, contact with study authors and bibliographies from included studies, known reviews or texts were also considered. Full search strategies are included in the supplementary material.

All identified studies were uploaded to systematic review management software (Covidence, Melbourne, Australia). After duplicates were removed, one author (AD) reviewed all titles and abstracts. Two authors (AD and SM) then independently reviewed full texts of all potentially eligible studies and identified additional documents through citations or hand searches. A third author (PL) adjudicated any disagreements, and some eligible studies were further excluded from analyses if they 1) did not develop oscillometric reference equations, 2) were only abstracts or preprints, 3) were duplicate studies, 4) had ineligible oscillometric parameters for this current analysis or 5) had an ineligible population.

Statistical analysis

We performed a set of analyses to compare different reference equations identified in our search. Using an imaginary dataset of age, height and weight for 50 men and 50 women, we created R_{rs} and X_{rs} values for each reference equation. We also created AX values for studies where available. Because one of the included studies [23] used quantile regression, we only used prediction equations of 50th quantile to create imaginary R_{rs} , X_{rs} and AX values for the specific study. We used Spearman's rank-order correlation to find associations between different equations for oscillometric indices separately for men and women. Because height was the common demographic variable in all reference equations included in our review, we also assessed sex-stratified correlations between height and the oscillometric indices. Considering that

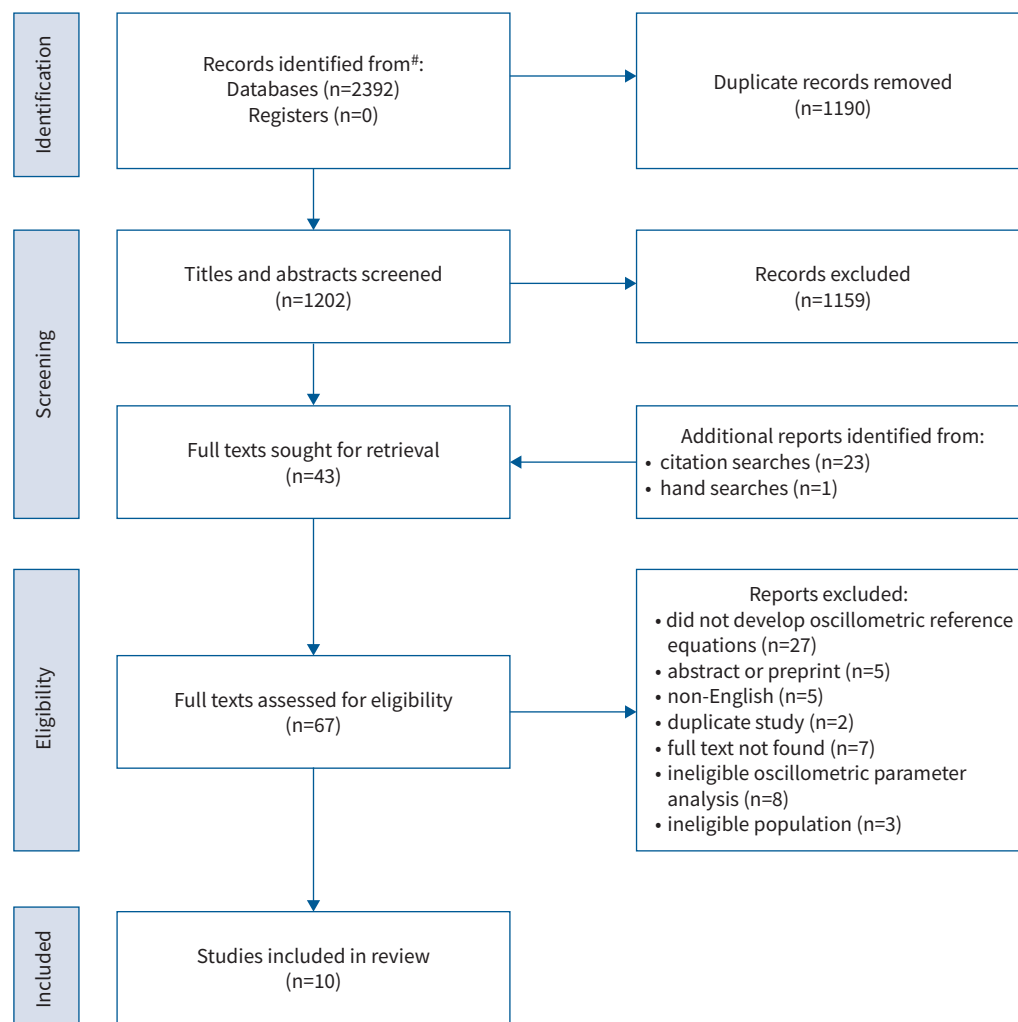


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the identification and selection process of studies that developed reference equations for oscillometric parameters of interest. #: MEDLINE: 348 results; Embase: 832 results; PubMed: 348 results; Scopus: 623 results; Web of Science Core Collection: 122 results; Cochrane Database of Systematic Reviews: 19 results; Google Scholar: first 100 results used; Cochrane Protocols: no results; PROSPERO: no results.

the reference equations developed by OOSTVEEN *et al.* [16] are the most widely used prediction models, we investigated the agreement between said equations and all other equations for resistance and reactance indices (R_5/R_6 , R_{20}/R_{19} , X_5/X_6 and AX) separately for men and women using Bland–Altman analysis of agreement [35] and Lin’s concordance correlation coefficient [36].

Results

Search results

Our search strategy identified 1202 unique studies related to oscillometry. After primary exclusion and scrutiny of titles and abstracts, we considered 67 studies for a full-text review (figure 1). Figure 2 represents the relative number of oscillometric reference equation studies (published in peer-reviewed journals only) identified in our search that were developed for three major ethnic groups in the past 20 years.

Study characteristics

We included 10 studies in the analyses, with the majority being Caucasian-derived ($n=6$). All eligible studies were cross-sectional in design, with some having comparative groups (*e.g.* patients with respiratory diseases). Studies included instruments generating either impulse or non-impulse signals or both types of instruments, and all developed reference equations for R_5 , R_{20} and X_5 (or the respective R_6 , R_{19} or X_6). Five studies developed reference equations for AX. Additionally, some studies considered R_{5-20} , otherwise known as the frequency dependence of resistance and resonant frequency. Studies that used non-impulse signals also provided equations for resistance values for a wide range of frequencies other than 5 Hz and 20 Hz. Some studies ($n=5$) included current and/or former smokers. Details of included studies are outlined in table 1 and table 2.

Structure of the reference equations

The construction of reference equations was different between included studies (table 3). In seven of the 10 studies [15–18, 21, 22, 24], either oscillometric indices or demographic variables were mathematically transformed (logarithmic, inverse or exponential function). While almost all studies referred to linear regression models for oscillometric indices, SCHULZ *et al.* [23] referred to a quantile regression method and BROWN *et al.* [18] suggested a polynomial (quadratic) regression model for reactance (X_6). Although all studies created reference equations separately for men and women, equations developed by SHIOTA *et al.* [22] were established for both sexes. One study [20] considered the variable weight in resistance (R_5 and R_{20}) equations for men but not women, while another study reported weight only in equations for women.

While all included equations showed a negative trend in total airway resistance (R_5) with increasing height, MOITRA *et al.* [15] demonstrated a positive trend for both sexes (*i.e.* R_5 increases with height) (figure 3). This trend was similar for central airway resistance (R_{20}) as well. For total airway reactance (X_5), all equations showed a positive trend of X_5 (*i.e.* X_5 becomes less negative) with increasing height in women; however, in men the previous equation [15] showed the opposite association (*i.e.* X_5 becomes more negative with increasing height). We found prediction equations for AX in five studies, which showed a negative association with height in all studies, except one in women [15], where it showed a positive association with increasing height (*i.e.* AX increases with increasing height). Therefore, it was evident that

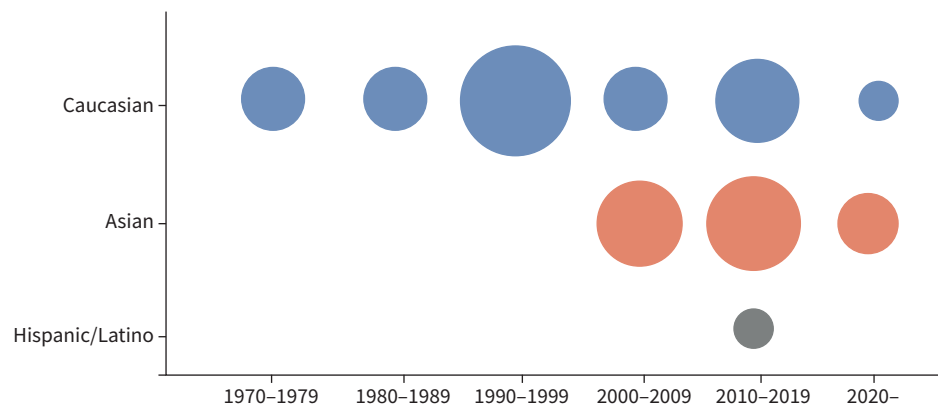


FIGURE 2 Bubble plot of the relative number of studies identified that developed oscillometric reference equations for three major ethnic groups in the past 20 years. Bubble size indicates the number of publications.

TABLE 1 Characteristics of included studies that developed reference equations for oscillometric parameters of interest

Study	Study country	Study population	Oscillometry device(s)	Signal type	Frequencies considered (Hz)	Reference parameters	Smoker inclusion
SHIOTA <i>et al.</i> [22]	Japan	Non-Caucasian	MasterScreen IOS	Recurrent impulses	5, 20	R ₅ , R ₂₀ , X ₅	Never-smokers, active smokers, ex-smokers
NEWBURY <i>et al.</i> [20]	Australia	Caucasian	MasterScreen IOS	Recurrent impulses	5, 10, 15, 20, 25, 35	Z ₅ , R _{rs} , X _{rs}	Never-smokers, ex-smokers
BROWN <i>et al.</i> [18]	Australia	Caucasian	Custom-made	Pseudorandom	6, 11, 19	R _{rs} , X _{rs}	Never-smokers, ex-smokers
AARLI <i>et al.</i> [24]	Norway	Caucasian	MasterScreen IOS	Recurrent impulses	5, 20	R ₅ , R ₂₀ , X ₅ , Fres, AX	Never-smokers, ex-smokers
SCHULZ <i>et al.</i> [23]	Germany	Caucasian	MasterScreen IOS	Recurrent impulses	5, 20	Z ₅ , R ₅ , R ₂₀ , R ₅₋₂₀ , X ₅ , Fres, AX	Never-smokers only
OOSTVEEN <i>et al.</i> [16]	Belgium, the Netherlands, Hungary, Australia	Caucasian	Custom-made (C1, C3), ROS Oscilink (C2), Quark i2m (C4), MasterScreen IOS (C5)	Pseudorandom (C1–C4), recurrent impulses (C5)	4, 5, 6, 8, 10, 12, 14, 15, 16, 18, 20, 22, 24, 26	R _{rs} , R _m , X _{rs} , Fres, AX	Never-smokers, ex-smokers
RIBEIRO <i>et al.</i> [21]	Brazil	Caucasian, Non-Caucasian	Custom-made	Pseudorandom	4, 6, 8, 10, 12, 14, 16, 18, 20, 22	Z _{rs} , R _{rs} , R _m , R ₀ , X _{rs} , Fres, X _m	Never-smokers only
DE <i>et al.</i> [19]	India	Non-Caucasian	Resmon Pro	Pseudorandom, relative primes	5, 19	R ₅ , R ₁₉ , R ₅₋₁₉ , X ₅	Never-smokers only
MOITRA <i>et al.</i> [15]	India	Non-Caucasian	MasterScreen IOS	Recurrent impulses	5, 20	Z ₅ , R ₅ , R ₂₀ , R ₅₋₂₀ , X ₅ , Fres, AX	Never-smokers only
BERGER <i>et al.</i> [17]	USA	Caucasian	MasterScreen IOS	Recurrent impulses	5, 10, 15, 20	R ₅ , R ₁₀ , R ₁₅ , R ₂₀ , R ₅₋₁₅ , R ₅₋₂₀ , X ₅ , X ₁₀ , Fres, AX	Never-smokers only

IOS: impulse oscillometry; R₅: resistance at 5 Hz; R₂₀: resistance at 20 Hz; X₅: reactance at 5 Hz; Z₅: impedance at 5 Hz; R_{rs}: respiratory resistance; X_{rs}: respiratory reactance; Fres: resonant frequency; AX: reactance area; R_m: mean respiratory resistance; R₀: resistance at 0 Hz; R₁₉: resistance at 19 Hz.

while reference equations for R₂₀ showed some degree of homogeneity regarding their association with height, equations for R₅ and X₅ demonstrated greater variability in terms of their association with height.

Homogeneity between equations

The agreement between included reference equations with the standard model [16] is presented in table 4. Using reference equations for imaginary individuals, we found that one Caucasian study [18] yielded consistently higher resistance and reactance values than all other equations included in the study. For example, mean R₅ values in men and women according to the equation of BROWN *et al.* [18] were 0.92 kPa·L⁻¹·s⁻¹ and 1.15 kPa·L⁻¹·s⁻¹, respectively, which were significantly higher than others (range 0.08–0.39 and 0.08–0.60 kPa·L⁻¹·s⁻¹ in men and women, respectively). In the agreement analysis, the equations of BROWN *et al.* [18] were remarkably different from those developed by OOSTVEEN *et al.* [16]. While reference equations for R₅ and R₂₀ of other Caucasian studies [17, 20] showed homogeneity with the standard model [16] for men, there was some degree of heterogeneity for women. Intriguingly, reference equations developed in the Latin American population [21] showed significant homogeneity with the standard reference [16]. In the case of X₅, while there was significant homogeneity between the equations of the reference study [16] and equations of other studies [17, 19–24], equations developed by MOITRA *et al.* [15] and BROWN *et al.* [18] were markedly different from the standard reference [16]. The equations developed for AX were significantly different from the standard reference, except for one study [24] that showed low-to-moderate agreement with the reference study.

Discussion

Summary of findings

We identified 23 adult oscillometric reference equations published in the past 20 years. The majority of equations were developed for Caucasian populations while limited or no studies were found from Asian, Latin American, African, African American or Indigenous populations; this inequity of addressing race/

TABLE 2 Subject demographics from included studies that developed reference equations for oscillometric parameters of interest

Study	Subjects (n)	Males (n)	Height (cm)	Weight (kg)	Age (years)	Smoking history (pack-years)
SHIOTA <i>et al.</i> [22]	166	69	162.7±8.3	58.9±11.2	38.6±17.2 (20–81)	22.2±22.1
NEWBURY <i>et al.</i> [20]	125	59	175.89±8.77	87.3±11.49	49.54 (25–74)	<5
			164.58±6.56	73.3±12.41	48.76 (25–74)	
BROWN <i>et al.</i> [18]	904	341	176.7±6.7	84.2±13.1	55.6±17.5	<5
			163.5±6.5	69.3±13.5	54.7±17.7	
AARLI <i>et al.</i> [24]	75	40	173±6	76.4±12.7	79.4±6.9	20/4
			159±6	65.5±10.8	78.8±6.3	
SCHULZ <i>et al.</i> [23] [#]	397	154	173.30 (163.00–188.41)	80.89 (67.02–106.76)	64.89 (46.00–84.75)	0
			160.07 (149.00–172.24)	68.37 (53.40–91.05)	67.26 (46.00–85.00)	
OOSTVEEN <i>et al.</i> [16]	368	180	171.44 [#]	54–128	49.55 [#] (18–84)	4.4
			43–111			
RIBEIRO <i>et al.</i> [21]	288	144	173±1 (153–189)	78.78±2.07 (49–128)	49.04±2.88 (20–81)	
			160±1 (145–181)	65.02±1.79 (47–96)	49.0±2.88 (20–86)	
DE <i>et al.</i> [19]	323	122	168.1±8.2	65.5±13.3	42.7±13.7	<1
			154.8±6.5		40.9±13.7	
MOITRA <i>et al.</i> [15]	190	92			45±18	
					41±17	
BERGER <i>et al.</i> [17]	439	223	177±7 (157–203)	83.1±17.1 (51.3–170.0)	46.7±11.2 (21–85)	<5
			164±7 (146–183)	63.9±12.7 (43.1–147.4)	44.0±11.9 (21–76)	

Data are presented as pooled totals (n) or according to sex (male/female) in mean±SD or mean (range), unless otherwise indicated. #: calculated from means of subgroups within study.

ethnicity has also been persistent in the construction of spirometric reference equations [11]. However, most studies had considerable limitations in terms of poorly defined inclusion/exclusion criteria and having equations for only selected oscillometric indices. Our included studies (n=10) consisted of Caucasian, Asian and Latin American populations and had all the clinically relevant oscillometric indices for comparison. Our comparative analyses of heterogeneity between a standard reference model and all other models provide a clinically important overview of similarities and dissimilarities between equations.

Critical evaluation of the reference equations

While the majority of included studies used some forms of mathematical transformation of either the oscillometric indices or physiological variables to fit them into a linear relationship, no such transformation was performed in two studies [19, 20]. It is important to note that those studies did not mention anything about the nature of distribution of oscillometric indices or physiological variables. Several studies [23, 28, 37] have reported typical non-normal distributions of oscillometric indices because of the influence of heterogeneous airway branching, even in healthy individuals. Therefore, the assumption of a “by default” linear relationship between oscillometric indices and physiological variables could be erroneous. While SCHULZ *et al.* [23] used a more realistic model (quantile regression) assuming a non-normal distribution of the oscillometric indices, there is substantial skewness in the oscillometric variables between the median (50th quantile) and lower and upper (5th and 95th) quantiles; in such cases, applying the most appropriate equation (quantile value) is a challenge. Therefore, it is recommended that, first, a thorough examination (nature of distribution, missingness, input errors, *etc.*) of dependent (oscillometric indices) and independent (demographics) variables should be undertaken. Second, different regression models should be applied to control for the non-normality, followed by appropriate model-fitting criteria. Third, a collinearity check between independent variables should be performed because a strong intercorrelation between independent variables may result in over-fitting of models [30]. And last, it is important to remember that reference models must not be extremely complex and should be executable in clinical practice.

Another aspect is the omission of body weight from equations in some studies [20, 22, 24]. Although these reports did not describe model-fitting criteria in detail, it can be assumed that weight was an insignificant variable in equations and was omitted to achieve a more stable model. However, several studies have shown that body weight significantly influences the physiology of the airways [38–41] and correlates with increased airway resistance [42, 43]. The same was observed for age because this was either deleted from equations [17, 24] or was discriminately used for resistance or reactance [18, 22] or a selective sex [19]. Although one previous study described that the airway resistive property remains

TABLE 3 Reference equations developed from included studies for oscillometric parameters of interest

Study	Indices	Male	Female
SHIOTA <i>et al.</i> [22]	R ₅	R ₅ =8.67158–3.841167·log(h)	R ₅ =8.67158–3.841167·log(h)
	R ₂₀	R ₂₀ =5.841867–2.546561·log(h)	R ₂₀ =5.841867–2.546561·log(h)
	X ₅	X ₅ =–2.343672–0.000097a+1.018597·log(h)	X ₅ =–2.343672–0.000097a+1.018597·log(h)
	AX	Not available	Not available
NEWBURY <i>et al.</i> [20]	R ₅	R ₅ =1.1672–0.0017a–0.007h+0.0043w	R ₅ =0.768–0.00064a–0.00276h
	R ₂₀	R ₂₀ =0.9216–0.0013a–0.0049h+0.0027w	R ₂₀ =0.4821+0.00034a–0.00125h
	X ₅	X ₅ =–0.3593+0.00013a+0.0016h	X ₅ =–0.4689–0.00092a+0.00245h
	AX	Not available	Not available
BROWN <i>et al.</i> [18] [#]	R ₆	log(R ₆)=3.18955–0.01617h+0.00882w	log(R ₆)=3.88965–0.01944h+0.00812w
	R ₁₉	log(R ₁₉)=2.89318–0.01445h+0.00789w	log(R ₁₉)=3.25796–0.01519h+0.00605w
	X ₆	exp(X ₆)=–1.23047+0.01286a–0.00013712a ² +0.01098h–0.00323w	exp(X ₆)=–1.36295+0.00845a–0.0001035a ² +0.01282h–0.00449w
	AX	Not available	Not available
AARLI <i>et al.</i> [24]	R ₅	ln(R ₅)=3.02–0.023h	ln(R ₅)=2.68–0.026h+0.012w
	R ₂₀	ln(R ₂₀)=1.52–0.016h	ln(R ₂₀)=1.26–0.017h+0.009w
	X ₅	ln(–X ₅)=3.57–0.033h	ln(–X ₅)=3.85–0.041h+0.014w
	AX	ln(AX)=12.0–0.074h	ln(AX)=10.8–0.074h
SCHULZ <i>et al.</i> [23]	R ₅	5th quantile: R ₅ =1.0685571–0.0022403a–0.004312h	R ₅ =0.5012224+0.0002940a–0.0037866h+0.0045199w
		50th quantile: R ₅ =0.9861137–0.0001223a–0.0055278h+0.0029891w	R ₅ =0.7887960+0.0015118a–0.0046594h+0.0029768w
	R ₂₀	95th quantile: R ₅ =0.6683472+0.0029051a–0.0026280h	R ₅ =0.1926787+0.0004133a+0.0016756h
		5th quantile: R ₂₀ =0.6342369–0.0019656a–0.0021069h	R ₂₀ =0.5970057–0.0006897a–0.0030934h+0.0016623h
		50th quantile: R ₂₀ =0.7722257–0.0006446a–0.0037120h+0.0013924w	R ₂₀ =0.4505645+0.0001251a–0.0020488h+0.0017939w
	X ₅	95th quantile: R ₂₀ =1.1824320–0.0003590a–0.0048639h	R ₂₀ =0.8177947–0.0003549a–0.0025771h
		5th quantile: X ₅ =–0.5568254–0.0004762a+0.0025397h	X ₅ =–0.5446960–0.0018068a+0.0029323h
		50th quantile: X ₅ =–0.4670275–0.0003344a+0.0027755h–0.0010424w	X ₅ =–0.3313017–0.0007541a+0.0022090h–0.001413w
	AX	95th quantile: X ₅ =–0.2058333+0.0006944a+0.0006944h	X ₅ =–0.1831886+0.0003607a+0.0005743h
		5th quantile: AX=0.0430162+0.0012195a–0.0002327h	AX=1.0968758–0.0001349a–0.0077805h+0.0048793w
50th quantile: AX=1.7584772+0.0027451a–0.0132469h+0.0077552w		AX=1.7909627+0.0110077a–0.0168559h+0.0104360w	
	95th quantile: AX=2.2955939+0.0161916a–0.0139157h	AX=2.7124098+0.0173679a–0.0227368h+0.0152978w	
OOSTVEEN <i>et al.</i> [16] ^{†,‡}	R ₅	ln(R ₅)=5.327–0.00381a–3.032h+0.01390w	ln(R ₅)=2.591+0.00279a–1.461h+0.0121w
	R ₂₀	ln(R ₂₀)=3.540–0.0033a–1.824h+0.00888w	ln(R ₂₀)=2.482+0.00135a–1.122h+0.00695w
	X ₅	ln(4–X ₅)=2.683+0a–0.703h+0.0019w	ln(4–X ₅)=2.373+0.0015a–0.607h+0.00312w
	AX ₅	ln(AX ₅)=9.730+0a–6.107h+0.02122w	ln(AX ₅)=5.490+0.00960a–4.122h+0.02836w
RIBEIRO <i>et al.</i> [21] ^{‡,§}	R ₆	ln(R ₆)=2.964–0.002a–1.545h+0.009w	R ₆ =8.164–0.006a–3.563h+0.014w
	R ₂₀	ln(R ₂₀)=2.196–0.002a–0.970h+0.005w	R ₂₀ =9.142–0.005a–3.811h+0.003w
	X ₆	exp(X ₆)=–1.082+0a+0.983h–0.003w	X ₆ =–5.293+0a+2.759h–0.007w
	AX	Not available	Not available
DE <i>et al.</i> [19] [#]	R ₅	R ₅ =10.035+0.008a–0.057h+0.036w	R ₅ =9.697–0.046h+0.033w
	R ₁₉	R ₁₉ =8.077–0.040h+0.02w	R ₁₉ =8.683–0.038h+0.019w
	X ₅	X ₅ =–3.334–0.004a+0.018h–0.009w	X ₅ =–4.40+0.02h
	AX	Not available	Not available
MOITRA <i>et al.</i> [15] [†]	R ₅	ln(R ₅)=–0.30+0.003a–0.83h+0.01w	ln(R ₅)=0.003+0.004a–0.66h+0.007w
	R ₂₀	ln(R ₂₀)=–0.14–0.001a–0.99h+0.01w	ln(R ₂₀)=0.164+0.0003a–0.92h+0.007w
	X ₅	X ₅ =–0.23–0.002a+0.15h–0.002w	X ₅ =–0.60–0.004a+0.37h–0.001w
	AX	ln(AX)=–0.20+1.24ln(a)–2.98h+0.01w	ln(AX)=–2.33+0.76ln(a)–0.004h+0.004w
BERGER <i>et al.</i> [17] ^{†,‡}	R ₅	ln(R ₅)=2.07069–1.05124h+0.03337·BMI	ln(R ₅)=2.22395–0.98351h+0.02903·BMI
	R ₂₀	ln(R ₂₀)=1.95570–0.81148h+0.02042·BMI	ln(R ₂₀)=2.01077–0.72768h+0.02009·BMI
	X ₅	ln(X ₅ +4)=0.10509+0.82626h–0.01775·BMI	ln(X ₅ +4)=0.29066+0.73387h–0.01984·BMI
	AX	ln(AX)=4.36142–3.47450h+0.08784·BMI	ln(AX)=4.67153–3.31633h+0.06719·BMI

Reference equations developed by included studies for R₆, R₁₉ and X₆ instead of R₅, R₁₉ and X₅, respectively were considered. Respiratory resistance (R_{rs}) and respiratory reactance (X_{rs}) measured in kPa·L⁻¹·s⁻¹ and AX measured in kPa·L⁻¹ unless otherwise indicated. Age (a), height (h), weight (w) and body mass index (BMI) measured in years, cm, kg and kg·m⁻², respectively, unless otherwise indicated. SHIOTA *et al.* [22] developed unisex reference equations. SCHULZ *et al.* [23] developed reference equations for the 5th, 50th and 95th quantiles. For OOSTVEEN *et al.* [16] the equations for AX₅ are included. R₅: resistance at 5 Hz; R₂₀: resistance at 20 Hz; X₅: reactance at 5 Hz; AX: reactance area; R₆: resistance at 6 Hz; R₁₉: resistance at 19 Hz; X₆: reactance at 6 Hz. [#]: R_{rs} and X_{rs} measured in cmH₂O·L⁻¹·s⁻¹ and AX measured in cmH₂O·L⁻¹; [†]: height measured in metres (m); [‡]: R_{rs} and X_{rs} measured in hPa·L⁻¹·s⁻¹ and AX measured in hPa·L⁻¹.

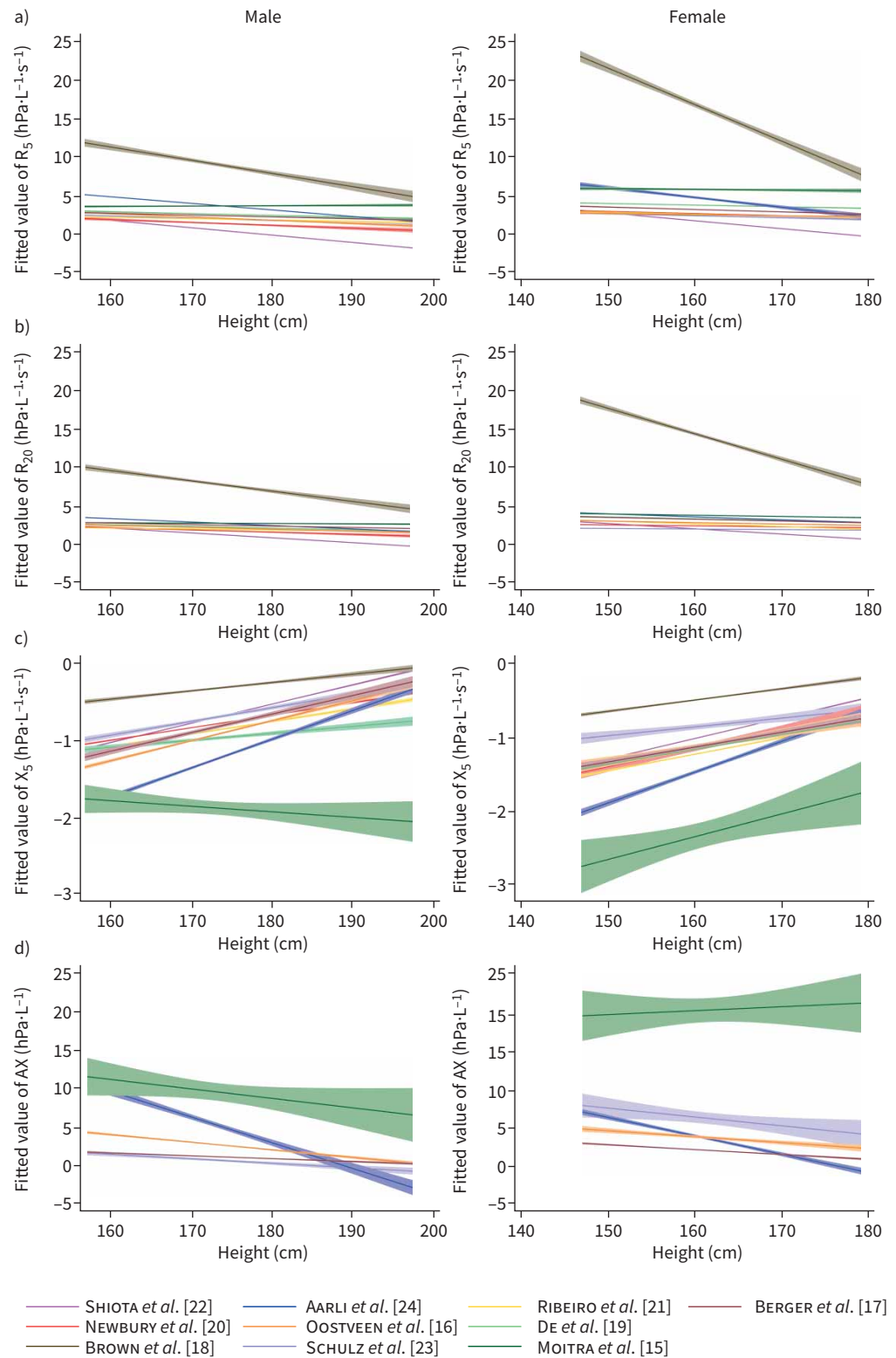


FIGURE 3 Differences in predicted values for oscillometric indices of interest from reference equations of included studies as functions of height for men and women. Predicted values for resistance and reactance at 6 Hz and 19 Hz are considered for some equations, please see the text and footnote of table 3 for details. R_5 : resistance at 5 Hz; R_{20} : resistance at 20 Hz; X_5 : reactance at 5 Hz; AX: reactance area.

TABLE 4 Assessments of agreement between predicted values for oscillometric parameters of interest from reference equations of included studies and a standard reference for men and women

OOSTVEEN <i>et al.</i> [16] versus	Sex		R ₅	R ₂₀	X ₅	AX
SHIOTA <i>et al.</i> [22]	Male	Bias (LoA)	0.15 (0.06, 0.25)	0.08 (0.01, 0.15)	-0.02 (-0.03, -0.01)	NA
		ρ _c	0.19	0.22	0.65	NA
	Female	Bias (LoA)	0.09 (-0.05, 0.23)	0.09 (0.006, 0.17)	-0.01 (-0.04, 0.01)	NA
		ρ _c	0.14	0.15	0.67	NA
NEWBURY <i>et al.</i> [20]	Male	Bias (LoA)	0.07 (0.04, 0.10)	0.03 (0.02, 0.05)	-0.01 (-0.03, 0.005)	NA
		ρ _c	0.41	0.57	0.68	NA
	Female	Bias (LoA)	-0.01 (-0.07, 0.04)	0.04 (0.01, 0.07)	0.001 (-0.02, 0.02)	NA
		ρ _c	0.27	0.11	0.93	NA
BROWN <i>et al.</i> [18] [#]	Male	Bias (LoA)	-0.69 (-0.94, -0.43)	-0.57 (-0.78, -0.36)	-0.06 (-0.08, -0.03)	NA
		ρ _c	0.03	0.02	0.10	NA
	Female	Bias (LoA)	-1.35 (-2.09, -0.61)	-1.09 (-1.59, -0.60)	-0.06 (-0.09, -0.04)	NA
		ρ _c	0.006	0.007	0.09	NA
AARLI <i>et al.</i> [24]	Male	Bias (LoA)	-0.16 (-0.24, -0.08)	-0.06 (-0.11, -0.02)	0.03 (0.01, 0.06)	-0.26 (-0.69, 0.18)
		ρ _c	0.16	0.28	0.55	0.31
	Female	Bias (LoA)	-0.21 (-0.41, -0.01)	-0.07 (-0.11, -0.04)	0.03 (-0.01, 0.07)	0.01 (-0.30, 0.32)
		ρ _c	0.05	0.17	0.44	0.49
SCHULZ <i>et al.</i> [23]	Male	Bias (LoA)	0.01 (-0.02, 0.04)	0.04 (0.006, 0.07)	-0.02 (-0.04, -0.006)	0.20 (0.09, 0.31)
		ρ _c	0.84	0.55	0.55	0.18
	Female	Bias (LoA)	0.01 (-0.01, 0.04)	0.06 (0.03, 0.08)	-0.03 (-0.04, -0.01)	-0.25 (-0.66, 0.15)
		ρ _c	0.79	0.10	0.46	0.28
RIBEIRO <i>et al.</i> [21] [#]	Male	Bias (LoA)	0.02 (-0.03, 0.06)	0.02 (-0.006, 0.04)	-0.006 (-0.02, 0.01)	NA
		ρ _c	0.66	0.55	0.86	NA
	Female	Bias (LoA)	-0.01 (-0.05, 0.04)	0.02 (-0.02, 0.06)	0.01 (-0.01, 0.03)	NA
		ρ _c	0.43	0.51	0.72	NA
DE <i>et al.</i> [19] [¶]	Male	Bias (LoA)	-0.05 (-0.11, 0.01)	-0.01 (-0.03, 0.01)	0.004 (-0.03, 0.04)	NA
		ρ _c	0.34	0.78	0.59	NA
	Female	Bias (LoA)	-0.12 (-0.15, -0.10)	-0.05 (-0.06, -0.03)	0.003 (-0.02, 0.03)	NA
		ρ _c	0.05	0.22	0.73	NA
MOITRA <i>et al.</i> [15]	Male	Bias (LoA)	-0.15 (-0.25, -0.06)	-0.06 (-0.10, -0.02)	0.09 (0.01, 0.17)	-0.68 (-1.46, 0.10)
		ρ _c	-0.01	0.11	-0.02	0.03
	Female	Bias (LoA)	-0.33 (-0.38, -0.28)	-0.09 (-0.11, -0.08)	0.12 (0.02, 0.21)	-1.68 (-2.68, -0.69)
		ρ _c	0.01	0.06	0.12	0.02
BERGER <i>et al.</i> [17]	Male	Bias (LoA)	-0.03 (-0.07, 0.01)	-0.04 (-0.06, -0.01)	-0.01 (-0.02, -0.0001)	0.16 (0.05, 0.26)
		ρ _c	0.59	0.37	0.89	0.18
	Female	Bias (LoA)	-0.07 (-0.10, -0.03)	-0.04 (-0.06, -0.03)	-0.0001 (-0.02, 0.02)	0.17 (0.06, 0.28)
		ρ _c	0.18	0.28	0.82	0.20

Data presented as bias (lower and upper LoA) and Lin’s concordance correlation coefficient (ρ_c). Reference values developed by OOSTVEEN *et al.* [16] were considered as the standard model and these were compared with other reference values for R₅, R₂₀ and X₅. Bias and LoA should be read as a percentage (e.g. a bias of 0.15 should be read as 15%). [#]: resistance and reactance values measured at 6 Hz (R₆, X₆) and 19 Hz (R₁₉) were considered in the comparison; [¶]: resistance value at 19 Hz (R₁₉) was considered in the comparison. R₅: resistance at 5 Hz; R₂₀: resistance at 20 Hz; X₅: reactance at 5 Hz; AX: reactance area; LoA: limit of agreement; NA: not applicable.

unchanged after 5 years of age [44], this concept has not been confirmed by follow-up reports. Interestingly, OOSTVEEN *et al.* [16] and RIBEIRO *et al.* [21] did not eliminate age from their equations despite achieving negligible coefficient values (which were very small). Although there could be a debate on which variables are to be considered in prediction equations, a more inclusive approach (considering all relevant anthropometric variables) followed by statistical criteria for model stability could be considered when constructing reference models for oscillometric indices.

Similarly, the inclusion of participants with a smoking history is inappropriate in any lung function reference framework given the significant impact of smoking on airway physiology. Paradoxically, almost half of the studies included in this analysis recruited smokers (current or former). Although it was unclear from these studies [16, 18, 20, 22, 24] whether the presence of current or former smokers influenced measurements of oscillometric indices, it was evident that the forced expiratory volume in 1 s/forced vital capacity ratio of participants in one study [24] was lower than in other reports. It is well known that smokers tend to develop subtle yet significant changes in their small airways even before they can be

detected by spirometry [45]. A recent report has also described an accelerated decline of lung function in former smokers compared to never-smokers [46], suggesting that the decline of airway function is not restricted to current smokers. One study [24] included participants who were ≥ 70 years of age. Such an advanced age group would be expected to exhibit naturally reduced lung function and thus would generate potential bias in measurements.

Another key feature missing in the included studies is the description of the use of short-acting bronchodilator response and its effect on oscillometry [47]. Previous studies have shown that airway impedance can be significantly altered upon short-acting bronchodilator administration in healthy individuals [48–50]. However, only one study [16] included in our analyses explicitly described the use of short-acting bronchodilators while performing oscillometry. While there is inconsistency in the recommendation of whether pre- or post-bronchodilation values should be used for oscillometric reference equations, it is an important issue because it is essential to report the use of short-acting bronchodilators for the development of appropriate oscillometric reference equations.

While Caucasian models were expected to be similar or have less heterogeneity, we observed that one Caucasian study [18] generated very high impedance values and was significantly different from standard reference values. Therefore, it is important to understand potential sources of heterogeneity and to be vigilant while considering reference models. Last, it is very important to report sample size and power calculations so that the robustness of the constructed models can be determined; these were unfortunately lacking in several studies considered in this review. Therefore, the generalisability of those models cannot be confirmed.

Implications for clinical practice and future research

Considering the increasing popularity of oscillometry as a sensitive and user-friendly approach for the detection of small airway changes in a wide variety of lung diseases, eliminating the potential risk of over- and under-diagnosing respiratory abnormalities is a priority. Because oscillometry has relatively high within-subject variability compared with other conventional lung function tests, it is important to consider such variations while developing reference equations. This also applies when assessing patients in clinical settings, particularly if patients are at early stages of respiratory disease or if they are elderly. The importance of our study is that it will help inform clinicians on the use of proper reference equations appropriate to their patient populations.

Notably, there are some fundamental differences among different oscillometry devices in terms of their engineering and functionality, as previous reports have demonstrated [8, 51–53]. These differences may lead to measurement bias for certain indices, particularly X_{rs} values [53]. Therefore, it is important to consider the measurement technique and device when choosing a suitable reference equation [28, 52]. It is also important to remember that, apart from differences between devices, model developers should also consider posture, sequence of testing before or after spirometry, physical exertion, exposure to first- or second-hand smoke and consumption of caffeine or menthol products as potential influencers [54–56]. Therefore, it is important that desired models are validated in larger samples before their use in clinical settings, even though these models could have been developed from similar populations [28, 57]. Additionally, large sample sizes, inclusion of only non-smoking individuals, generalised random sampling and broad intra-population demographic ranges are encouraged for better model efficacy, translatability and specificity of testing [12, 28, 57]. Our study advocates for the importance of a globally accepted reference standard for oscillometry, particularly considering African, African American, Hispanic, North American, Asian, Indigenous and other populations. Meanwhile, ongoing standardisation of oscillometric testing, as has been implemented for spirometry, will be of great benefit in increasing testing quality and repeatability [5, 28, 52].

Strengths and limitations

To date, the most important question remains of which oscillometric reference equations should one adopt for a specific population, and this has been cited as a limiting factor in the widespread adoption of oscillometry in PFTs. This review provides the first quantitative evaluation of the heterogeneity of equations obtained from different populations, and a comprehensive overview of their features and shortcomings. Our study also demonstrates that there are population-specific and country-specific variations in reference equations, and that no equations should be adapted indiscriminately, even though populations are apparently the same.

There are, however, some limitations regarding our review. First, our inclusion of studies with patients' age ≥ 18 years might have excluded other studies on adults where the lower limit of age was 16 years. Second, we only considered studies that showed a linear relationship between oscillometric indices and

demographic variables. Therefore, we may have excluded studies with some robust yet statistically complex results. Third, although frequency dependence (R_{5-20}) is a sensitive parameter for small airway disease and is of particular interest in COPD, we could not include this index in our study because of the non-availability of its reference equations in some studies [16]. Moreover, because the included studies used two different types of devices (devices that produce impulse and non-impulse signals), the different wave function of these devices could have possible artefacts in reference equations even though both devices generate nearly the same frequency of sound waves. Additionally, we excluded some studies owing to the unavailability of full-text versions or for being reported in a language besides English, and these studies could have had important observations. Finally, the nature of this scoping review with selected outcomes did not allow us to assess any potential bias for study selection.

Conclusions

In this comprehensive review, we, for the first time, systematically evaluated different adult oscillometric reference equations. We found considerable heterogeneity between equations that warrants focused attention while using oscillometric reference values. We also propose that a large-scale, multinational study for developing a global reference model for oscillometry is urgently required because a population-adjusted oscillometric reference model could be beneficial in the diagnosis and clinical care of respiratory diseases.

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