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Impulse Oscillometry Metrics Differentiate Adults with Asthma from Non-Asthmatic Controls: A Meta-Analysis

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ABSTRACT

Background

Impulse Oscillometry (IOS), an effort-independent technique, assesses both central and peripheral airway function. The latter are major sites of inflammation in asthma, suggesting that IOS may help diagnose asthma. However, previous IOS studies, limited by sample size, report mixed results. Our objective was to establish whether IOS-based airway metrics can differentiate adults with asthma from non-asthmatic subjects.

Methods

A meta-analysis of 11 published oscillometric studies was performed including adult (18-70 years) patients with well-controlled asthma and non-asthmatic controls. IOS measurements included airway resistance metrics, at 5 Hz (R5), and R5 minus resistance at 20 Hz (R5-R20), and reactance at 5 Hz (X5) and Area of Reactance (AX). Standardized Mean Differences (SMD), and 95% confidence intervals were compared between populations to evaluate statistical significance. Sensitivity analysis was applied to assess the degree of heterogeneity. In addition, Minimal Clinical Important Difference (MCID) was determined.

Results

There were no significant differences in general demographics between study populations, consisting of 410 asthma patients and 211 controls. Significant differences between study populations were observed for FEV1 % predicted and all IOS metrics, with highly significant SMD differences for R5-0.88 ($p<0.0001$), R5-R20-0.85 ($p<0.0001$), X5 -0.78 ($p<0.0001$), and AX -1.15 ($p=0.0300$). The MCID for R5 was 0.046 kPa/L/s, R5-R20 0.013 kPa/L/s, X5 -0.022 kPa/L/s, and AX 0.088 kPa/L.

Conclusion

IOS-determined airway resistance (R5, R5-R20) and reactance (X5 and AX) can differentiate individuals with (controlled) asthma from non-asthmatic controls. Further research is needed to establish universal standardized reference values for IOS metrics to facilitate asthma diagnosis and management.

Keywords: Asthma; Adults; Impulse oscillometry; Airway resistance; Small airways

INTRODUCTION

Asthma is a highly prevalent chronic respiratory disease, characterized by recurring symptoms, airway inflammation, variable-often fully reversible-airflow obstruction and airway hyperresponsiveness to (non)specific stimuli. Asthma was reported affecting at least 300 million people worldwide [1]. Given this significant socio-economic burden, timely identification and adequate treatment is crucial to prevent damage inflicted by the sequelae of progressive disease. In the absence of a diagnostic gold standard, asthma is often mis-diagnosed [2]. Current guidelines recommend using a detailed history, physical exam, assessment of type 2 inflammation, spirometric-based identification of airflow obstruction and confirmation of reversibility or airway hyperresponsiveness [3,4]. Pulmonary function has been traditionally evaluated by spirometry, a worldwide standardized and validated technique that measures volume of air during forced inhalation and exhalation [1,5].

Although spirometry is the most common tool for pulmonary function testing,5 some limitations exist. First, several studies have shown that despite its high specificity, spirometry has relatively low sensitivity for guideline-based diagnosis of asthma, ranging from 23-29%. This is especially true for asthma patients with normal lung function [6-8].

Mechanistically different techniques have been designed to assess and interpret pulmonary function.However, all these tests depend on the ability of the patient to exhale and or inhale maximally [9]. Hence, in the past decades, non-invasive pulmonary function tests have come into use and became more popular. Impulse Oscillometry (IOS), is an effort-independent, non-invasive and relatively simple technique allowing the evaluation of both the central and the peripheral airways; the latter often referred to as “the silent zone” since difficult to measure and therefore often neglected during standard screening procedures. The peripheral or small airways, those with an internal diameter<2 mm, are considered major sites of airway inflammation and obstruction (“air trapping”) in asthma [10,11]. IOS measures airway impedance, which consists of airway resistance (R), detecting central and peripheral airway obstruction, and reactance (X), which reflects elasticity of the peripheral airways [12,13]. To this end, small pressure waves are transmitted to the airways with frequencies of 5-50 Hz superimposed on tidal breathing of the patient which provide data for detailed analysis of the lungs [14,15]. Commonly used IOS metrics to interpret airway mechanics include resistance at 5 Hz (R5), reactance at 5 Hz (X5), resistance at 5 Hz minus the resistance at 20 Hz (R5-R20), and the area of reactance (AX) [15]. Small Airway Dysfunction (SAD) assessed by IOS metrics R5-R20, X5 and AX, has been shown to correlate with asthma control, severity, bronchial wall thickening and exacerbations [16-18].

Several studies have shown that IOS may help to distinguish patients with asthma from control subjects [19-25]. Studies investigating the diagnostic accuracy concluded that IOS had a sensitivity of 72 to 77% and a specificity of 76 to 90%, i.e., a substantially higher sensitivity with comparable specificity to spirometry, thus, suggesting IOS may effectively complement spirometry as a diagnostic tool [6,26,27]. Furthermore, recent work has suggested that the use of oscillometry in tandem with spirometry has a high potential to detect clinically relevant small airway disease [28].

Although increasing evidence suggests that IOS may be a promising tool in asthma diagnosis and management, current literature shows mixed data with IOS parameters in some studies not significantly different between asthma patients and healthy controls, while other studies report statistical difference [29-31]. However, most of these studies

have relatively small sample size, ranging from 24-92 participants, and report on different combinations of the existing IOS parameters [25,32–38]. The aim of our study was to offset the mixed evidence based on single small sample sized studies with differing outcomes by performing a meta-analysis investigating the effectiveness of IOS metrics to differentiate asthma patients from subjects without asthma.

MATERIALS AND METHODS

Search strategy and eligibility of studies

Given the nature of this study, no IRB approval was required. Only published studies written in English language were considered for analysis. PubMed was utilized to review the literature. A protocol for this meta-analysis was not prospectively registered as review and data search began before registration could be planned. We followed the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA 2020) reporting guidance and report our eligibility criteria, search strategy, and planned analyses in full below. Studies were screened and retrieved by one reviewer. Data was reviewed by two authors independently. There was no inherent selection bias; selection was based strictly on inclusion and exclusion criteria. Search criteria to identify studies were "impulse oscillometry," "asthma" and "adult." Displays the search process for study identification (Figure 1). From the initial 174 studies, only 11 met all entry criteria. Studies were included if they met age eligibility (≥18 years), included participants with controlled asthma, i.e., without current or recent exacerbations, and reported on the oscillometry metric R5. The variable R5 was used to estimate the sample size required, with peripheral airway metrics resistance R5-R20, and reactance AX and X5 also reported where available as kPa/L/s (or kPa/L for AX) or cmH2O/L/s utilizing IOS. All studies employed a Jaeger IOS device (Jaeger, Wurzburg, Germany) except for one study in which the specific IOS device was not reported. Studies were excluded if the IOS metrics were only presented in percent predicted or if presented in a review format (i.e., no original research). All reported studies were conducted in an asthma specialist setting.

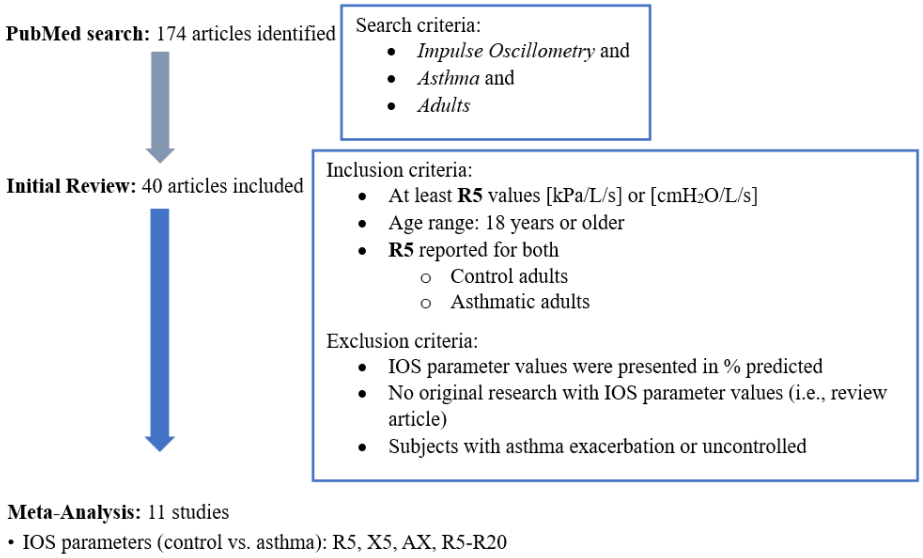


Figure 1: Criteria for selection of studies.

Statistical methods

Meta-analysis was performed by the Biostatistics Department of the University of California, Irvine, California, USA, coordinated by Hye-Won Shin, PhD, to compare IOS parameters between asthma and control groups. For each included study, the Standardized Mean Difference (SMD) (difference in means between the asthma and control groups divided by the pooled standard deviation), a unitless value, and 95% Confidence Interval (CI) were calculated. When studies reported medians with interquartile ranges or ranges, data were transformed to approximate means and standard deviations using established formulas. The summary SMD was reported for each model. A sensitivity analysis was

conducted to investigate the robustness of the meta-analysis results in the presence of significant heterogeneity, as indicated by a significant chi-square test (Q statistic). The I2 statistic, providing the percentage of variation across studies due to heterogeneity rather than chance, is provided in each model. For example, an insignificant heterogeneity index implies homogeneity of the data set and conformity of the test. A random-effects meta-analysis model was used to pool SMDs across studies, accounting for between-study heterogeneity, although results for fixed effects models were similar (not reported). Analysis was implemented in the statistical software R package "metafor." In addition, absolute values for IOS metrics R5, R5-R20, AX, and X5 were compared between the cohorts. To facilitate clinical interpretation of the SMDs derived from our meta-analysis, we estimated the Minimal Clinically Important Difference (MCID) for each metric using a distributions-based approach [39].

RESULTS

Description of the studies identified

Based on our search criteria, we identified 11 studies involving both adult asthma patients and non-asthmatic controls for R5 and X5, 7 for R5-R20, and 4 studies for AX, with a number of participants ranging from 24 to 92 per study. Overall, 410 asthma patients and 211 non-asthmatic controls (age ranges 18-70 years) were included in our analysis, whose demographic and spirometric characteristics are shown in (Table 1). There were no statistically significant differences in age, sex, Body Mass Index (BMI), and smoking history between the two study populations, while despite being in the normal range, differences in the Forced Expiratory Volume in one second (FEV1) percent predicted were statistically significant (Table 2A). The absolute IOS values for R5, X5, R5-R20 and AX are shown in Supplemental Table 1. There were significantly higher values for R5, R5-R20, and AX and lower values for X5 in the asthma population compared to controls as shown in (Table 2B).

Table 1: Demographic and FEV1 % predicted characteristics of asthma patients and control subjects.

Ref	Author	Study Site	Group	# of Subjects	Age	Sex (% male)	BMI	FEV1 (% predicted)	Smoking History
25	Paredi	UK	Control	18	37 (2)	44%	NA	97 (3)	100% never
			Asthma	34	49 (3)	44%	NA	69 (4)	24% former, 76% never
29	Gonem	UK / Sweden / USA	Control	18	48.3 (3.9)	50	26.8 (1.2)	113.3 (4.8)	Current or 10 pack-year hx excluded
			Asthma	74	55.8 (2.2)	51	28.2 (1.1)	89.1 (4)	Current or 10 pack-year hx excluded
30	Aronsson	Sweden	Control	13	44 (19-56)[$]	NA	NA	107.3 (79-115.5)[$]	100% never
			Asthma	27	25 (18-58)[$]	NA	NA	95.5 (62.2-134.6)[$]	100% never
31	Houghton (2005)	UK	Control	12	43 (24-73)[Y]	34%	NA	107 (85-122)[Y]	8% current, 8% former
			Asthma	12	41 (22-65)[Y]	8%	NA	94 (82-111)[Y]	100% never
32	Guan	China	Control	21	18-65	NA	NA	107.3 (11.54)	NA
			Asthma	62	18-65	NA	NA	94.6 (15.2)	NA
33	Boudewijn	Netherlands	Control	15	26 (23; 32)[*]	33.30%	21.6 (20.6; 25.5)[*]	106 (10)	33% current, 67% never
			Asthma	15	45 (36; 52)[*]	13.30%	30.9 (28.4; 37.7)[*]	101 (15)	13% current, 60% never
34	Sugiyama	Japan	Control	29	47.6 (2.5)	66%	23.3 (0.4)	103.2 (2.1)	35% former, 65% never

			Asthma	54	52.1 (2.6)	24%	23.0 (0.6)	86.1 (2.8)	100% never
35	Qi	China	Control	20	46.2 (40.5, 51.8)[CI]	70%	21.0 (19.9, 22.1)[CI]	101.87 (98.19, 105.55)[CI]	100% never
			Asthma	20	54.8 (50.1, 59.4)[CI]	45%	23.9 (22.3, 25.6)[CI]	87.61 (83.0, 92.21)[CI]	NA
36	Williamson	UK	Control	24	26 (2)	13%	NA	103.8 (2.5)	NA
			Asthma	36	47 (4)	61%	NA	78.4 (4)	100% never
37	Kanda	Japan	Control	29	69.8 (1.3)	41%	23.3 (0.6)	104.9 (3.5)	100% never
			Asthma	52	69.8 (0.8)	46%	23.5 (0.5)	79.5 (2.9)	100% never
38	Houghton (2004)	UK	Control	12	40.5 (27-66)	42%	NA	105 (92-115)	17% current, 25% former
			Asthma	24	43.8 (21-69)	25%	NA	79.5 (49-117)	0% current 5% former

Note: [*]median (interquartile range); [Y]mean (range); [$]mean (range); [CI]mean (95% confidence intervals); NA: Not Available

Table 2A: Comparison of demographic and FEV1% predicted characteristics between asthma patients and control subjects.

Variable	Number of Studies	Difference of Means (MD) or Odds Ratio (OR) and 95% CI	p-value
Age	9	MD=-5.37 (-13.09; 2.35)	0.1727
Sex (% Male)	9	OR=1.45 (0.63; 3.33)	0.3813
BMI	5	MD=-2.39 (-5.47; 0.68)	0.1275
FEV1	11	MD=19.15 (14.87; 23.42)	<0.0001
Smoking status	5	OR=0.39 (0.01; 13.55)	0.6092

Table 2B: Comparison of oscillometry metrics between asthma patients and control subjects.

Parameter	N studies	Mean Difference	95% CI	p-value
R5	11	0.14 [kPa/L/s]	0.12; 0.18	<0.0001
X5	11	-0.07 [kPa/L/s]	-0.11; -0.05	<0.0001
R5–20	7	0.08 [kPa/L/s]	0.05; 0.12	<0.0001
AX	4	0.37 [kPa/L]	0.15; 0.58	0.0009

Ios parameter: R5

Analysis was based on summary data of R5 (sample size, measures of central tendency and dispersion) for both study populations in the 11 qualifying studies. There was a significantly higher mean R5 in asthma patients compared to non-asthmatic controls (Table 2B). The SMD in R5 between asthma *vs.* controls (reported as controls minus asthma) was: -0.88 (95% CI: [-1.10, -0.66], p<0.0001), where the SMD refers to the model-based pooled effect size across the studies (Table 3) and (Figure 2A). Heterogeneity was found not statistically significant (I2=26.04%, Q=13.52; 10; p=0.196) (Table 4).

Table 3: Standard mean difference (95% confidence interval) based on random effect model for IOS parameters.

Comparison	Variable	R5	X5	R5–R20	AX
Control *vs* Asthma	Number of studies	11	11	7	4
	Number of subjects (control/asthma)	211/410	211/410	148/278	80/175
	Random-effects model (95% CI)	-0.88 (-1.10, -0.66) P<0.0001	0.78 (0.60, 0.97) P<0.0001	-0.85 (-1.16, -0.53) P<0.0001	-1.15 (-2.20, -0.11) p=0.0300

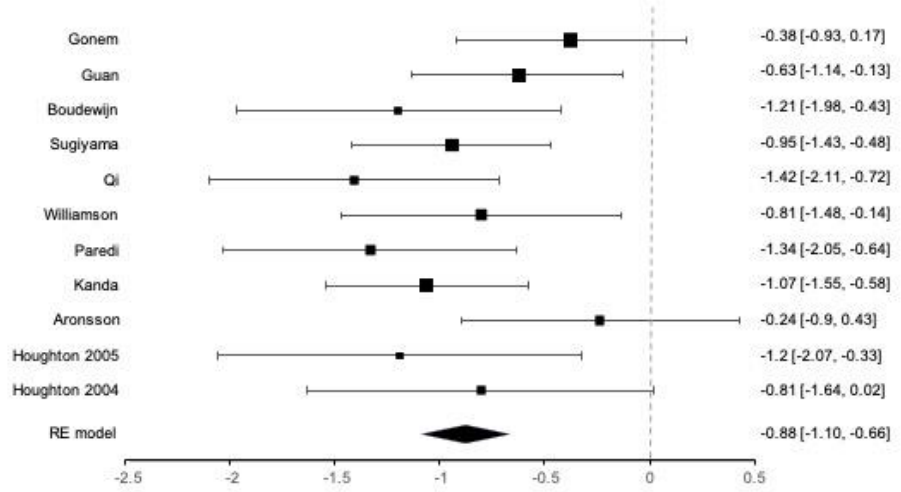


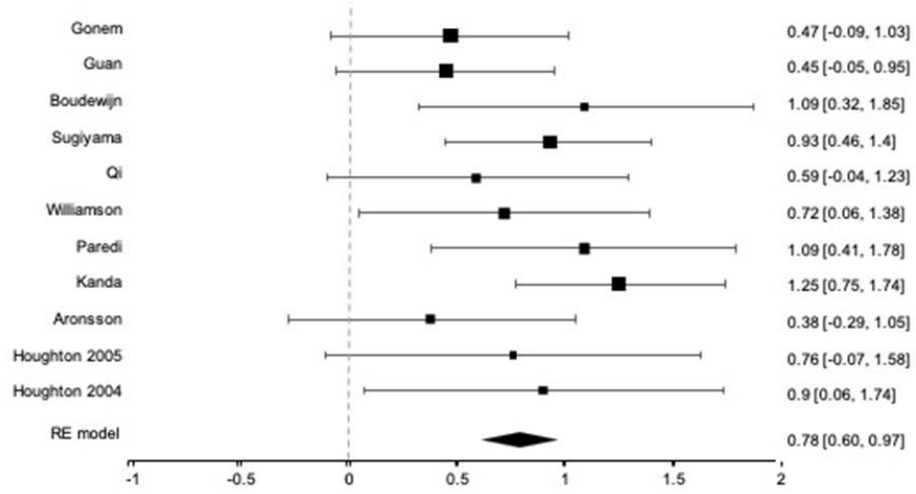
Figure 2: Forest plot based on random effect model for standardized mean difference of IOS parameters as available, including R5 (A), X5 (B), R5-R20 (C), and AX (D). The diamond indicates the final model-based summary standard mean difference with 95% confidence interval numerically. The size of the squares for each study is the weight of that study based on sample size and variance.

Table 4: Index of heterogeneity (I^2).

Parameter	R5 All available studies	X5 All available studies	R5–R20 All available studies	AX All available studies	AX Exclude 1 study
Number of studies	11	11	7	4	3
Number of subjects (control/asthma)	211/410	211/410	148/278	80/175	51/121
I^2	26.04% P=0.2	0.00% P=0.45	47.30% P=0.08	91.19% p<0.0001	0.00% P=0.45

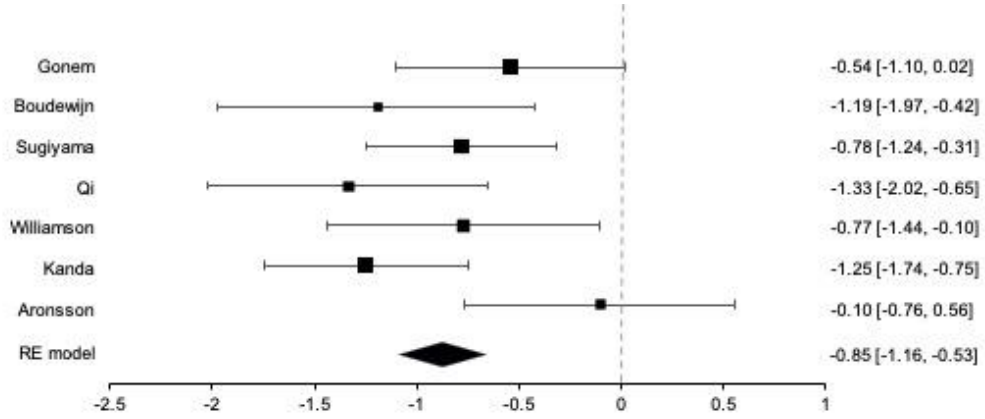
IOS parameter: X5

Based on the 11 studies analyzed, significantly lower mean X5 values were observed in the asthma patients compared to controls (Table 2B). The SMD in X5 (reported as controls minus asthma) was 0.78 (95% CI: [0.60, 0.97, p<0.0001) Table 3 and (Figure 2B). The result of heterogeneity test was not statistically significant (I2=0.0%, Q=9.89; p=0.450; Table 4).



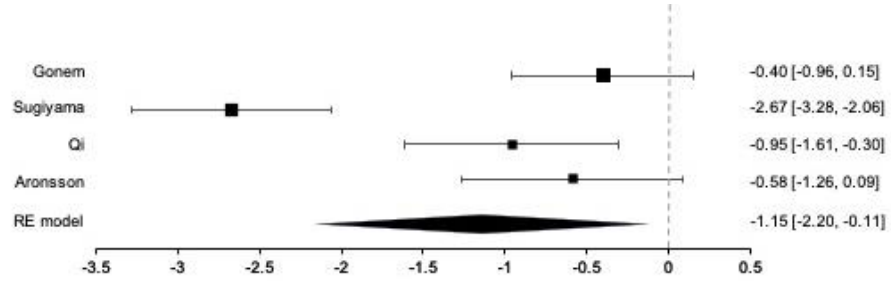
IOS parameter: R5-R20

Seven of the studies analyzed, including 278 asthma patients and 148 control subjects, also reported on the difference in R5-R20. A meta-analysis of these studies showed that the mean R5-R20 was significantly higher in asthma compared to the control group (Table 2B). The SMD in R5-R20 between asthma *vs*. controls (reported as controls minus asthma) was -0.85 (95% CI: [-1.16, -0.53], p<0.0001) Table 3 and (Figure 2C). The heterogeneity test was not statistically significant (I2=47.3%, Q=11.39; p=0.077; Table 4).



IOS parameter: AX

Summary data of AX for both the asthma and control groups were available in 4 of 11 eligible studies, including 175 asthma patients and 80 control subjects. AX values were significantly higher in the asthma patients (Table 2B). The SMD in AX between asthma patients *vs*. controls (reported as controls minus asthma patients) was -1.15 (95% CI: [-2.20, -0.11], p=0.0300) Table 3 and (Figure 2D). The heterogeneity test of AX was statistically significant (I2=91.2%, Q=34.04; p<0.0001; Table 4). For the sensitivity analysis, one outlier study was removed [34]. The result of the meta-analysis after excluding that study remained statistically significant. The standard mean difference became -0.62 (95% CI: [-0.98, -0.26 p=0.001). Heterogeneity index I2 dropped from 91.19% to 0.00%, becoming statistically insignificant (Q=1.59; p=0.451; Table 4).



Minimal Clinically Important Difference (MCID)

The MCID for resistance metrics R5 and R5-R20 were 0.046 kPa/L/s and 0.013 kPa/L/s, respectively, and for reactance metrics AX and X5 were 0.088 kPa/L and -0.022 kPa/L/s, respectively.

DISCUSSION

Our meta-analysis data, generated predominately with the same equipment (Jaeger IOS device) demonstrates that all of the analyzed IOS parameters (R5, R5-R20, X5 and AX) can distinguish adults with asthma with controlled disease from control subjects using the SMD test, which is a standardized measure of change or difference between populations and provides an indication of the effect size. Effect size can range from <0.20 which is negligible, to >/=.80, which is very large effect size. In our study, almost all IOS metrics yielded SMD values of approximately 0.8, suggesting a clear difference in lung function, including the peripheral airways, between populations. In addition, the MCID, which provides the smallest absolute values that can differentiate clinically different outcomes, showed that very small IOS metric differences could differentiate even well-controlled asthma patient from normal controls subjects. To our knowledge, this is the first meta-analysis, determining the effect size and MCID to provide IOS cut-points in differentiating asthmatic adults from control subjects. Additionally, the 11 studies we used for the meta-analysis include adults from 6 different countries (the United Kingdom, Sweden, China, Japan, the Netherlands, and the United States) and 3 different continents (Europe, Asia, and North America) making our findings more generalizable.

This meta-analysis proves that the changes in R5 and R5-R20, although the latter based on slightly less (7 versus 11) studies, appear very similar when comparing asthma patients with healthy controls. Additionally, it implies that the change in R5, i.e., the total airway resistance, including the upper, central and peripheral airway resistance, is in this case similar or equal to the peripheral airway resistance.

In a similar study, implementing systematic review, evaluating the ability of techniques designed to assess the small airways such as IOS, Almeshari et al, observed that R5 was consistently higher in asthma patients than in control groups. In our meta-analysis, R5 was significantly higher in patients with asthma compared to controls. Almeshari et al, highlight study heterogeneity as a key limitation to their design [40]. Our study directly addresses this issue by evaluating the heterogeneity index across the pooled studies, which revealed considerable variability within the AX parameter. When the outlier study was removed by sensitivity analysis, the pooled effect estimate for AX remained statistically significant, indicating that the observed effect was not driven solely by the outlier. Furthermore, in addition to R5, this meta-analysis evaluated other IOS parameters, including X5, AX, and R5-R20, all of which consistently demonstrated differences between individuals with asthma and controls across the various study populations, thereby reinforcing the overall findings.

Individual studies used for our meta-analysis had relatively low sample size, ranging from 24 to 92 participants. When pooled together, our meta-analysis includes a total sample size of 621 subjects, consisting of 410 individuals with asthma and 211 control subjects without asthma, creating more robust data with a more adequate sample size to distinguish the asthma cohort [21, 25-32].

Our study has also several limitations. First, asthma duration and severity varied between and within the analyzed studies and was not accounted for in our analysis, which grouped all levels of severity together. However, inclusion criteria required patients to be well-controlled and not experiencing a current or recent exacerbation and the asthma and control cohorts were well matched for age, gender, BMI, and smoking history. Additionally, while our data are somewhat generalizable across multiple ethnicities, the lack of representation of participants from African and Latin American countries limits its

applicability to these regions, which will require further studies with a large sample size of subjects. Although we did find, in addition to significant IOS differences between the 2 populations, significant differences in the FEV1 % predicted, a meta-analytic approach does not allow for determining the independence of these two metrics, owing to the lack of sufficient data for a proper multivariate analysis.

CONCLUSION

Our meta-analysis establishes that IOS total resistance of the respiratory system (R5) and peripheral airway metrics (R5-R20) and reactance (AX and X5) provide a large effect size that can differentiate (controlled) asthma patients from non-asthmatic adults with small MCID cut points suggesting high sensitivity across a diverse population. Although this is a clinically useful first step, future work is necessary to create universal standardized reference values for IOS metrics, accounting for age, to facilitate the diagnosis and management of asthma.

DECLRATIONS

Conflict of interest

There are no conflicts of interest related to this meta-analysis.

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Author contributions

Each author contributed to all aspects of manuscript preparation.

Ethical approval

This article does not contain any studies with human participants or animals performed by the author. Ethical approval was not required for this study.

Competing interests

The authors declare no competing interests.

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Consent for publication

Not applicable.

Data availability

Not applicable.

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