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Small-Airway Dysfunction Across Type 2 Inflammatory Phenotypes in Treatment-Naïve Asthma

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Research Article

Keywords: Type 2 inflammation, blood eosinophils, fractional exhaled nitric oxide, asthma, oscillometry, spirometry

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Original Article

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Author contributions

SD: Conceptualization, data analysis, and writing. KN: Data collection. All authors reviewed the manuscript and decided to submit it for publication.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

The study was approved by the Institutional Ethics Committee of All India Institute of Medical Sciences, Raipur, India (approval no. 4939/IEC-AIIMSRPR/2025, dated 31/01/2025) and complies with the Declaration of Helsinki.

Consent to participate

Informed consent to participate in the study was obtained from all participants.

Consent to publication

Not applicable.

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Abstract

Background: The relationship between type 2 (T2) inflammatory phenotypes and small airway dysfunction (SAD) in treatment-naïve asthma remains poorly characterized. This study aimed to characterize the distribution of T2 phenotypes and compare lung function parameters, including SAD, across these phenotypes in treatment-naïve adults with stable asthma.

Methods: In this cross-sectional study, we assessed consecutive asthma using pre- and post-bronchodilator oscillometry and spirometry, as well as fractional exhaled nitric oxide ($FeNO_{50}$). We defined T2-low asthma as blood eosinophil count (BEC) ≤150 cells·μL^{-1} and $FeNO_{50}$ <25 ppb, T2-high as BEC >300 cells·μL^{-1} and $FeNO_{50}$ ≥35 ppb, and T2-intermediate as neither criterion was met. Lung function and SAD (R5–19 z-score >1.64 and/or X5 z-score <−1.64) were compared across phenotypes**.**

Results: We included 206 patients (mean age 40.5 ± 13.9 years; 60.2% male). The median BEC and $FeNO_{50}$ were 292 cells·μL^{-1} and 28.5 ppb, respectively. T2-high, intermediate, and low phenotypes accounted for 27.2%, 55.8%, and 17.0%, respectively. Patients with T2-high asthma were younger, while other demographic characteristics and spirometric indices were comparable. Oscillometric parameters and the prevalence of their abnormalities did not differ significantly across the phenotypes. After adjustment, neither T2-intermediate (adjusted OR 1.02, 95% CI 0.47–2.19) nor T2-low asthma (adjusted OR 1.91, 95% CI 0.66–5.53) was significantly associated with SAD. Estimated marginal means of oscillometric parameters did not differ significantly across phenotypes.

Conclusion: In treatment-naïve adults with stable asthma, BEC- and $FeNO_{50}$-defined T2 phenotypes were not independently associated with the severity of lung function impairment or SAD.

Keywords: Type 2 inflammation; blood eosinophils; fractional exhaled nitric oxide; asthma; oscillometry; spirometry

Running title: T2 Phenotypes and Oscillometry in Asthma

Introduction

Type 2 (T2) inflammation is mediated by T helper 2 lymphocytes and type 2 innate lymphoid cells, which produce cytokines, including interleukin (IL)-4, IL-5, and IL-13. These cytokines promote eosinophilic airway inflammation, increase peripheral blood eosinophil counts (BEC), and upregulate inducible nitric oxide synthase expression in airway epithelial cells, thereby increasing fractional exhaled nitric oxide (FeNO) levels. BEC serves as a surrogate marker of eosinophilic inflammation, whereas FeNO predominantly reflects IL-4/IL-13-mediated airway inflammation. Together, these biomarkers provide complementary information on T2 inflammatory activity. Asthma is a heterogeneous disease characterized by distinct inflammatory phenotypes, including T2-high, T2-intermediate, and T2-low, which differ in their underlying inflammatory mechanisms and clinical characteristics [1,2].

Understanding the distribution of T2 inflammatory phenotypes in treatment-naïve adults with asthma provides insight into the underlying inflammatory profile before pharmacological treatment modifies it. Characterizing these phenotypes may also improve understanding of disease heterogeneity and its relationship with lung function impairment. Small-airway dysfunction (SAD) is an important feature of asthma that may remain undetected by spirometry. Respiratory

oscillometry measures respiratory resistance and reactance during tidal breathing and provides a complementary, minimally effort-dependent assessment of respiratory mechanics that helps to detect SAD [3]. However, it remains unclear whether BEC- and $FeNO_{50}$-defined inflammatory phenotypes differ in oscillometric abnormalities, spirometric indices, or SAD prevalence. Furthermore, evidence regarding the distribution of T2 inflammatory phenotypes and their relationship with lung function in Indian adults with asthma remains limited.

Therefore, this study aimed to determine the distribution of T2-high, T2-intermediate, and T2-low phenotypes in treatment-naïve adults with clinically stable asthma and investigate their associations with oscillometric and spirometric parameters, including SAD.

Methods

Study Design

This observational cross-sectional study was conducted between February 2025 and July 2026. The study protocol was approved by the Institutional Ethics Committee (approval no. 4939/IEC-AIIMSRPR/2025, dated 31/01/2025) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants before their enrolment.

Study population

Consecutive adults (≥18 years) with newly diagnosed bronchial asthma who attended the outpatient department were screened for eligibility criteria. Treatment-naïve status was defined as not being on inhaled/systemic corticosteroids.

Bronchial asthma was diagnosed according to the Global Initiative for Asthma (GINA) guidelines, based on characteristic respiratory symptoms, including wheezing, shortness of breath, chest tightness, and cough [4]. Exclusion criteria included coexisting respiratory diseases (such as bronchiectasis or post-tuberculosis lung disease), inability to perform acceptable pulmonary function tests, and refusal to participate.

Assessment

Demographic and clinical characteristics, including age, sex, body mass index, smoking status, respiratory symptoms, disease duration, and comorbidities, were recorded using a structured case record form. BEC was determined using an automated analyzer. All participants underwent chest radiography, oscillometry, FeNO estimation at multiple expiratory flow rates, and spirometry with bronchodilator responsiveness.

Oscillometry was performed using a Resmon Pro Full FOT device (Restech Srl, Milan, Italy) at 5, 11, and 19 Hz. Oscillometry was performed in the seated position according to the guidelines [5]. The mean of three acceptable recordings was used, with a coefficient of variation for R5 <10% for analysis. The evaluated parameters included respiratory system resistance at 5 Hz (R5), reactance at 5 Hz (X5), frequency dependence of resistance (R5–R19), resonant frequency (Fres), and reactance area (AX). Oscillometry parameters were expressed as z-scores using reference values derived from the local population [6]. Z-scores of pre-bronchodilator R5 and R5–R19 > +1.64 and X5 < -1.64 were considered abnormal. Because no local reference limits existed for Fres and AX, values of AX >15 $cmH_2O \cdot s$ and Fres >12 Hz were considered abnormal [6]. SAD was defined as the presence of abnormal X5 or R5–R19.

FeNO: FeNO was measured using the Hyp'Air FeNO analyser (MediSoft, Belgium). Measurements were performed according to the American Thoracic Society recommendations [7]. Participants exhaled at controlled flow rates of 50, 100, 150, and 350 $mL \cdot s^{-1}$, and the mean of three acceptable measurements at each flow rate was recorded. NO obtained at multiple expiratory flow rates was subsequently used to estimate airway nitric oxide flux and alveolar nitric oxide concentration according to the lung model suggested by Tsoukias et al [8].

Spirometry: Spirometry was performed using a GANSHORN spirometer (GANSHORN Medizin Electronic GmbH, Germany) in accordance with the 2019 ATS/ERS standards [9]. The highest values of forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and maximal mid-expiratory flow (MMEF) obtained from three acceptable and reproducible spirometry maneuvers were recorded. The severity of airflow limitation was expressed as FEV_1 % predicted according to the 2012 Global Lung Function Initiative (GLI) reference equations and classified as mild (≥80%), moderate (50–79%), severe (35–49%), and very severe (<35%) of predicted values [10].

Post-bronchodilator oscillometry and spirometry were performed 15–20 min after the administration of 400 µg inhaled salbutamol. Bronchodilator response (BDR) in oscillometry was defined according to the ERS technical standard as a ≥40% decrease in R5, ≥50% in X5, and ≥80% in AX [5]. BDR in spirometry was defined as an increase of ≥12% and ≥200 mL in FEV_1 and/or FVC from baseline.

Patients were classified into three inflammatory phenotypes based on BEC and $FeNO_{50}$ values according to criteria proposed by Celis-Preciado et al. [2]. T2-low inflammation was defined as BEC ≤150 cells/µL and $FeNO_{50}$ <25 ppb, and T2-high inflammation as BEC >300 cells/µL and $FeNO_{50}$ ≥35 ppb. Patients who did not meet the criteria for either T2-low or T2-high inflammation were classified as having T2-intermediate inflammation.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation, or median (interquartile range), as appropriate, while categorical variables were expressed as frequencies and percentages. The associations between continuous variables were examined using Spearman's correlation coefficient. Differences across the three T2 inflammatory phenotype groups were assessed using one-way analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables.

Multivariable binary logistic regression was performed to assess the independent association between the T2 inflammatory phenotype and SAD. SAD was the dependent variable, whereas T2 inflammatory phenotype, age, sex, FEV_1 (% predicted), and FVC (% predicted) were included as independent variables, with the T2-high phenotype as the reference category. Results were expressed as adjusted odds ratios (aORs) with 95% confidence intervals (CIs).

To evaluate the association between T2 inflammatory phenotypes and oscillometric parameters, separate general linear models were fitted, with each oscillometric parameter as the dependent variable. T2 inflammatory phenotype and sex were included as fixed factors, and age, height, FEV_1 (% predicted), and FVC (% predicted) as covariates. Adjusted estimated marginal means with 95% confidence intervals (CIs) were estimated for each phenotype. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

Sample Size

This was an exploratory observational study. Because data on the distribution of BEC–FeNO-based Type 2 inflammatory phenotypes among treatment-naïve patients with asthma in the

local population were lacking, we did not conduct a formal sample size calculation. Consecutive eligible patients attending the study center during the recruitment period were enrolled to provide preliminary estimates of phenotype prevalence and to explore differences in lung function characteristics across phenotypic groups

Results

A total of 364 consecutive adults with a clinical diagnosis of asthma were screened for their eligibility. Of these, 158 were excluded for the reasons shown in Figure 1, and the remaining 206 treatment-naïve adults with clinically stable asthma were enrolled.

Baseline Characteristics

The cohort had a mean age of 40.5±13.9 years, and 60.2% were male. Overall, 13.4% of participants had comorbidities, with hypertension (4.9%) being the most common, followed by diabetes mellitus (3.2%); concomitant allergic rhinitis was present in 7.3%. Current or former smokers accounted for 11.6% of the study cohort. The median BEC and $FeNO_{50}$ were 292 cells $\cdot \mu L^{-1}$ (IQR: 128-483) and 28.5 ppb (IQR: 15.8-56.3), respectively. BEC >300 cells$\cdot \mu L^{-1}$ was observed in 49% of participants, whereas BEC >150 cells$\cdot \mu L^{-1}$ was observed in 71.4%. Overall, 55.3% of patients had $FeNO_{50}$ levels >25 ppb, 63.6% had levels >20 ppb, and 26.7% had levels >50 ppb. Multiple-flow FeNO measurements were successfully obtained in 86.8% of participants. The median alveolar nitric oxide and airway nitric oxide flux were 4.74 ppb (IQR, 2.77–7.17) and 68.9 nL$\cdot min^{-1}$ (IQR, 26.9–150.5), respectively. BEC was weakly to moderately correlated with $FeNO_{50}$ ($\rho = 0.41$; $p < 0.001$), airway nitric oxide flux ($\rho = 0.36$; $p < 0.001$), and alveolar nitric oxide ($\rho = 0.28$; $p < 0.001$).

Mean FEV_1 and FVC were 60.2 ± 15.8% predicted and 74.5 ± 14.2% predicted, respectively. Mild, moderate, severe, and very severe airflow obstruction were observed in 8.7%, 70.4%, 13.6%, and 7.3% of patients, respectively. The mean coefficient of variation for R5 was 8.2%, indicating acceptable within-session repeatability of oscillometry measurements.Abnormal R5, X5, and R5–R19 values were observed in 60.2%, 43.7%, and 46.6% of patients, respectively. BDR was observed in 57.3% of patients for FEV_1, 33.5% for FVC, 42.7% for R5, 34.5% for X5, and 24.9% for AX.

T2 Phenotypes

The T2 inflammatory phenotypes were distributed as follows: T2-high, 27.2% (95% CI: 20.9-33); T2-intermediate, 55.8% (95% CI: 49-62.6); and T2-low, 17.0% (95% CI: 12.1-22.3). Patients with T2-high asthma were younger, whereas other demographic characteristics and spirometric indices were comparable across phenotypes (Table 1). Oscillometry parameters and the proportion of abnormal oscillometry parameters did not differ significantly between phenotypes. The proportion of patients exhibiting BDR in FEV_1 was significantly higher in the T2-high phenotype, whereas the proportions of patients exhibiting oscillometric BDR did not differ significantly across phenotypes. Airway nitric oxide flux and alveolar nitric oxide concentrations differed significantly across T2 inflammatory phenotypes, with the highest values observed in the T2-high group, followed by the T2-intermediate and T2-low groups.

After adjusting for age, sex, and spirometric indices, neither the T2-intermediate (adjusted OR, 1.02; 95% CI, 0.47–2.19) nor the T2-low phenotype (adjusted OR, 1.91; 95% CI, 0.66–5.53) was significantly associated with abnormal SAD.

Association Between Phenotype and Oscillometry Parameters

After adjusting for age, sex, and baseline spirometric indices, the estimated marginal means of the oscillometric parameters did not differ significantly across the T2 inflammatory phenotypes (overall p = 0.13–0.42; Table 2). However, the estimated marginal means of R5, X5, R5–R19, and Fres increased from T2-high to T2-intermediate and T2-low, except for Fres.

Discussion

This single-center observational study evaluated the prevalence of BEC and $FeNO_{50}$-defined T2 inflammatory phenotypes among treatment-naïve patients with bronchial asthma and examined their associations with oscillometry and spirometry parameters. No significant differences were observed in spirometric or oscillometric parameters or SAD prevalence across T2 inflammatory phenotypes. Adjusted estimated marginal means of oscillometric parameters showed a trend toward higher values in T2-high than in T2-intermediate and T2-low phenotypes, except for Fres; however, none of these differences reached statistical significance.

BEC and $FeNO_{50}$ are widely used biomarkers for characterising T2 inflammatory phenotypes in asthma. However, thresholds for defining these phenotypes remain inconsistent and vary considerably across studies [1,11,12]. The distribution of T2 inflammatory phenotypes varied according to the biomarker cut-offs applied, highlighting the influence of threshold selection on phenotype classification. In our cohort, BEC was weakly correlated with $FeNO_{50}$, airway nitric oxide flux, and alveolar nitric oxide concentration. This suggests distinct inflammatory pathways and anatomical compartments represented by these biomarkers. The highest prevalence of T2 intermediate in our cohort reflects the heterogeneity of airway inflammation in asthma and the incomplete concordance between different T2 inflammatory biomarkers. Accordingly, the T2-intermediate category should not be regarded as a distinct biological endotype, but rather as a biomarker-defined group encompassing diverse inflammatory profiles.

Previous studies have predominantly investigated T2 phenotypes in patients with severe asthma [12-14]. In contrast, we characterised phenotypes in treatment-naïve adults with asthma, minimising the potential influence of treatment on biomarker levels. T2-intermediate was the predominant phenotype in our cohort, consistent with previous reports. In the population-based West Sweden Asthma Study, 14.3% of adults with asthma exhibited a T2-low inflammatory phenotype [11]. Two institution-based studies from India involving patients with severe or uncontrolled asthma reported T2-low prevalences of 15–16.3% [13-14]. A study conducted in China reported a T2-low phenotype prevalence of 19.5% among patients attending a specialist severe asthma center [15]. Notably, the prevalence of T2-low asthma in our cohort was similar to that reported in severe asthma cohorts, despite differences in biomarker thresholds used for phenotyping. The similar proportion of T2-low asthma in our treatment-naïve cohort suggests that its occurrence cannot be attributed solely to corticosteroid-mediated suppression of T2 biomarkers and asthma severity.

Patients with T2-high asthma were younger in our cohort, consistent with previous observations linking T2-high asthma in adults to childhood-onset disease [1]. Although spirometric parameters were comparable across T2 inflammatory phenotypes, the prevalence of BDR in FEV_1 was significantly higher in the T2-high phenotype, consistent with previous reports [1,2]. In contrast, the West Sweden Asthma Study reported better spirometric parameters among adults with T2-low asthma than those with T2-high asthma [11].

To our knowledge, oscillometric characteristics across T2 inflammatory phenotypes have not been investigated in treatment-naïve asthma. In our study, oscillometric parameters, except Fres, showed numerically higher values in the T2-low phenotype. However, these differences were not statistically significant after adjusting for demographic and spirometric indices. T2-low asthma

is a heterogeneous phenotype that involves neutrophilic and paucigranulocytic inflammation and pathways such as IL-17, TNF-α, and innate immune responses. The more negative X5 and numerically higher AX in the T2-low phenotype reflect increased respiratory elastance and heterogeneity of peripheral airway mechanics. However, the absence of statistically significant differences in the present study suggests that peripheral airway dysfunction may represent a physiological characteristic partly independent of T2 inflammatory status.

An important strength of this study is the inclusion of treatment-naïve adults with stable asthma, enabling the evaluation by oscillometry across T2 inflammatory phenotypes while minimizing the potential influence of corticosteroid exposure on inflammatory biomarkers and airway mechanics. However, the single-centre, cross-sectional design limits generalizability and precludes causal inference. Furthermore, single measurements of BEC and $FeNO_{50}$ may not capture biomarker variability over time.

In conclusion, in treatment-naïve adults with stable asthma, BEC- and $FeNO_{50}$-defined T2 inflammatory phenotypes were not significantly associated with SAD or differences in spirometric and oscillometric parameters. The findings suggest that the T2 phenotype alone may not adequately identify patients with SAD, highlighting the importance of directly assessing small airway function, regardless of inflammatory phenotype. Further longitudinal studies are warranted to clarify the relationship between T2 inflammation and SAD.

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Table 1**. Baseline demographic and lung function characteristics of bronchial asthma according to T2 inflammatory phenotype**

Parameters	**Total (N = 206)**	**T2-High (n = 56)**	**T2-intermediate (n = 115)**	**T2-low (n = 35)**	**p-value**
Age, year	40.5±13.9	36.8±12.1	40.3±14.8	46.7±11.4	0.004
Male, n (%)	124 (60.2)	39 (69.6)	65 (56.5)	20 (57.1)	0.238
BMI, Kg/m^2	24.6±4.7	23.6±3.9	25.1±4.9	24.6±5.1	0.153
Pre-BD %predicted FEV_1	60.2±15.8	59.8±14.3	60.2±15.6	60.4±18.9	0.982
Pre-BD %predicted FVC	74.5±14.2	75.9.1±12.5	74.7±14.2	71.5±16.5	0.347
Pre-BD %predicted MMEF,	38.5±16.3	36.3±13.5	38.5±16.1	42.1±20.1	0.257
Pre-BD R5, z-score	2.95±2.85	2.98±2.77	2.88±2.77	3.13±3.28	0.899
Pre-BD abnormal R5, n (%)	124 (60.2)	34 (60.7)	69 (60)	21 (60)	0.996
Pre-BD X5, Z-score	-2.75±3.89	-2.09±3.24	-2.84±3.91	-3.48±4.63	0.238
Pre-BD abnormal X5, n (%)	90 (43.7)	21 (37.5)	50 (43.5)	19 (54.3)	0.291
Pre-BD R5-19, z-score	2.45±3.29	2.35±3.26	2.37±3.23	2.85±3.61	0.73
Pre-BD abnormal R5-19, n (%)	96 (46.6)	25 (44.6)	52 (45.2)	19 (54.3)	0.605
Pre-BD abnormal AX, n (%)	94 (45.6)	21 (37.5)	54 (47)	19 (54.3)	0.268
Pre-BD abnormal Fres, n (%)	184 (89.3)	48 (85.7)	106 (92.2)	30 (85.7)	0.329
Bronchodilator response					
ΔFEV_1 (% baseline), n (%)	118 (57.3)	37 (66.1)	69 (60)	12 (34.3)	0.008
ΔFVC (% baseline), n (%)	69 (33.5)	21 (37.5)	36 (31.3)	12 (34.3)	0.719
ΔR5 (% baseline), n (%)	88 (42.7)	26 (46.4)	48 (41.7)	14 (40)	0.792
ΔX5 (% baseline), n (%)	71 (34.5)	16 (28.6)	43 (37.4)	12 (34.3)	0.523
ΔAX (% baseline) n (%)	51 (24.9)	15 (27.3)	29 (25.2)	7 (20)	0.733
Airway nitric oxide flux, nl/s	99±95	205±99	74±65	30±25	<0.001

Alveolar nitric oxide, ppb	6.07±5.47	8.19±6.69	5.95±5.22	3.44±2.33	0.001

Data are presented as mean ± standard deviation.

Abbreviations: Pre-BD: pre-bronchodilator; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; MMEF: maximal mid-expiratory flow; R5: whole-breath respiratory system resistance at 5 Hz; R19: whole-breath respiratory system resistance at 19 Hz; R5-19: difference in whole-breath resistance at 5 and 19 Hz; X5: whole-breath respiratory system reactance at 5 Hz; AX: reactance area; Fres: resonant frequency.

Table 2. Adjusted estimated marginal means of oscillometric parameters according to inflammatory phenotype after adjustment for demographic and spirometric indices

Parameters	Adjusted mean (95% CI)			P value
	T2-high	T2-intermediate	T2-low	
R5	6.63 (5.94 to 7.32)	6.79 (6.35 to 7.22))	7.36 (6.55 to 8.18)	0.376
X5	−2.38 (−2.93 to −1.84)	−2.92 (−3.27 to −2.58)	−3.19 (−3.84 to −2.55)	0.134
R5–R19	1.56 (1.17 to 1.94)	1.62 (1.38 to 1.87)	1.92 (1.48 to 2.37)	0.39
Fres	20.28 (18.16 to 22.09)	21.21 (20.06 to 22.36)	2219 (20.04 to 24.3)	0.417
AX	21.29 (15.19 to 27.39)	25.69 (21.85 to 29.54)	29.77 (22.57 to 36.97)	0.213

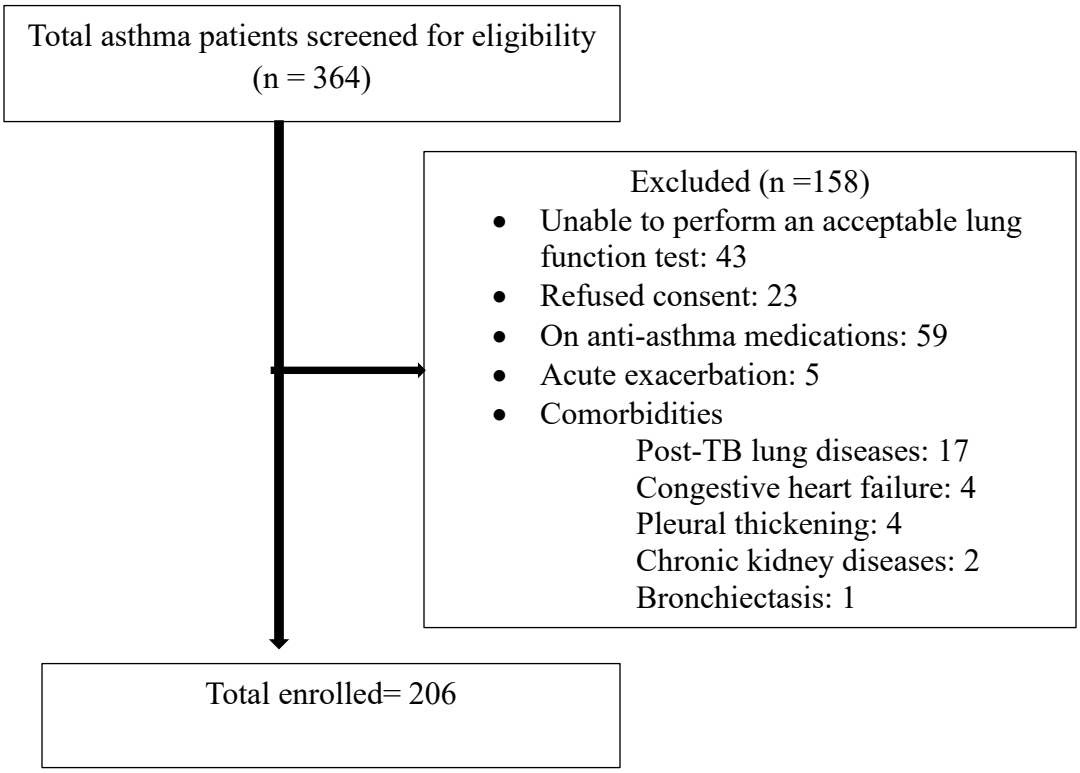


Figure 1. Study participant enrolment flowchart.