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Sex differences in asthma control, lung function and exacerbations: the ATLANTIS study

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ABSTRACT

Background Asthma is a heterogeneous disease with a prevalence and severity that differs between male and female patients.

Question What are differences between male and female patients with asthma with regard to asthma control, lung function, inflammation and exacerbations?

Methods We performed a post hoc analysis in the ATLANTIS (Assessment of Small Airways Involvement in Asthma) study, an observational cohort study including patients with asthma from nine countries with a follow-up of 1 year during which patients were characterised with measures of large and small airway function, questionnaires, inflammation and imaging. We compared differences in baseline characteristics and longitudinal outcomes between male and female patients with asthma.

Results 773 patients were enrolled; 450 (58%) of these were female. At baseline, female patients with asthma were in higher Global Initiative for Asthma (GINA) steps (p=0.042), had higher Asthma Control Questionnaire 6 (F: 0.83; M: 0.66, p<0.001) and higher airway resistance as reflected by uncorrected impulse oscillometry outcomes (ie, R_5-R_{20}: F: 0.06; M: 0.04 kPa/L/s, p=0.002). Male patients with asthma had more severe airway obstruction (forced expiratory volume in 1 s/forced vital capacity % predicted: F: 91.95; M: 88.33%, p<0.01) and more frequently had persistent airflow limitation (F: 27%; M: 39%, p<0.001). Blood neutrophils were significantly higher in female patients (p=0.014). With Cox regression analysis, female sex was an independent predictor for exacerbations.

Interpretation We demonstrate that female patients are in higher GINA steps, exhibit worse disease control, experience more exacerbations and demonstrate higher airway resistance compared with male patients. The higher exacerbation risk was independent of GINA step and blood eosinophil level. Male patients, in turn, have a higher prevalence of persistent airflow limitation and more severe airflow obstruction. These findings show sex can affect clinical phenotyping and outcomes in asthma.

Trial registration number NCT02123667.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ It is well recognised that the clinical presentation of asthma may differ across the sexes; however, how exactly sex affects severity of symptoms, large and small function, inflammation and exacerbation has not been systematically investigated in large clinical studies.

WHAT THIS STUDY ADDS

⇒ We use available data of the large and well-characterised ATLANTIS (Assessment of Small Airways Involvement in Asthma) study.
⇒ We show sex to have a significant impact on the clinical expression of asthma.
⇒ Female sex is associated with more severe symptoms, large and small airway function and bronchial hyperresponsiveness.
⇒ In addition, it is a risk factor for exacerbations independent of blood eosinophil levels.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Sex influences the clinical expression of asthma; therefore, it may be important for physicians and researchers to take into account this factor in daily clinical practice and in future studies, including those focusing on pharmacological treatment of asthma.

INTRODUCTION

In 2019, it was estimated that 262 million people worldwide were affected by asthma.[1] Asthma is a heterogeneous disease with distinctive phenotypes and endotypes.[2] Childhood-onset asthma is often atopic, whereas adult-onset asthma is frequently non-atopic and more severe.[3] The prevalence and severity of asthma also differ between male and female patients, and this ratio changes during the lifetime. Asthma is more common and severe in boys during childhood, but this changes around puberty after which asthma becomes more prevalent and severe in female patients.[4 5] Consequently, female patients with asthma have an increased risk of

exacerbations and asthma-related mortality in adulthood compared with male patients.[4 6]

It is already known that the sex disparity in asthma is multifactorial. Endogenous sex hormones are one of the widely studied factors; their fluctuations throughout life, such as in puberty, the menstrual cycle and menopause, play an important role in the increased prevalence and severity of asthma in female adults.[6–9] Additionally, male and female patients with asthma may also experience and report symptoms differently and throughout life may be exposed to different social and environmental factors.[6–9] Thus, sex disparity in asthma is highly complex and may have an impact on asthma severity as well as control and management. Therefore, it is important to gain more insight in the clinical differences between male and female patients with asthma, as this might ultimately lead to optimisation of precision asthma treatment.

Previous studies on sex differences in asthma lack extensive clinical characterisation or a broad spectrum of asthma severities and often did not take the presence and extent of small airways dysfunction (SAD) into account. The aim of this post hoc study was to investigate sex differences related to asthma control, lung function and exacerbations in extensively clinically characterised patients, including parameters of both large and small airway function.[10]

METHODS

ATLANTIS study design

The ATLANTIS study is an observational cohort including patients with asthma across all severities. Recruitment started 30 June 2014 and lasted until 3 March 2017 and took place in 9 countries across 29 centres.[10] A complete overview of the study design, including a list of all inclusion and exclusion criteria, can be found in online supplemental files 1 and 2. In short, the inclusion criteria were an age between 18 and 65 years and a confirmed asthma diagnosis according to Global Initiative for Asthma (GINA) 2012 guidelines,[11] without any recent (8 weeks) changes to their maintenance asthma medication. Participants were either non-smokers, current smokers or past smokers who had quit at least 12 months before inclusion. The main exclusion criteria were a smoking history of >10 packyears, an asthma exacerbation <8 weeks before inclusion, pregnancy or a confirmed diagnosis of chronic obstructive pulmonary disease (COPD). The study is registered on clinicaltrials.gov (NCT02123667). The names of the review boards are included in the online supplemental file.

Participants were characterised at the baseline visit including multiple questionnaires, such as the Asthma Control Questionnaire 6 (ACQ-6),[12] Mini Asthma Quality of Life Questionnaire (Mini AQLQ)[13] and asthma control test (ACT),[14] and lung function tests, such as fractional exhaled nitric oxide (FeNO), body plethysmography, impulse oscillometry (IOS), multiple breath nitrogen washout (MBNW) and prebronchodilator and postbronchodilator spirometry according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines.[15] Airway hyperresponsiveness (AHR) was tested using a methacholine challenge test in a subset of patients. Blood sample collection was done at baseline and during follow-up. Thoracic CT scans and sputum inductions were performed at baseline at selected sites. After the baseline visit, patients had follow-up phone calls at 3 and 9 months and physical visits at 6 and 12 months. Exacerbations were recorded throughout the study and defined as a deterioration of asthma requiring a systemic course of corticosteroids (≥3 days) and/or hospitalisation and/or emergency room attendance. During inclusion, participants received routine medical care provided by their own healthcare provider. Changes in medication were recorded.

Patient and public involvement

Initiation of the original ATLANTIS study was driven by unmet needs identified by patients. However, for these post hoc analyses, patients were not involved in the study design, recruitment or conduct of the study. Participants were not informed of the results of the post hoc analyses.

Definitions

Persistent airflow limitation (PAL) was defined as the postbronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) below the lower limit of normal. Early onset asthma was defined as an age of onset <18 years of age. IOS was used to measure resistance and reactance in the airways. It involves three separate measurements of breathing at tidal volume through a mouthpiece with an integrated speaker. The equipment measures the returning sound waves and calculates the resistance and reactance at different anatomical locations in the lung: R_5 reflects the total airway resistance, R_{20} reflects the large airway resistance and $R_{5\text{-}20}$ is thereby the calculated small airway resistance. At the time of writing, no reference equations endorsed by the ERS or ATS were available. We have applied the reference equations proposed by Oostveen *et al*.[16]

Statistical analysis

Statistical analyses were done using R (V.4.1.1)[17] and RStudio (V.1.3.959).[18] Baseline characteristics were stratified by sex using the R package TableOne (V.0.13.2).[19] Normality of distribution of data was assessed using histograms and QQ plots. Differences in baseline clinical characteristics, lung function or inflammatory parameters between sexes were tested using a Mann-Whitney U test, t-test or χ^2 test as appropriate.

Analysis and visualisation of time to first exacerbation were done using survival (V.3.3-1),[20] survminer (V.0.4.9)[21] and ggplot2 (V.3.3.6).[22] Subjects were censored after their first exacerbation or after their last visit. Cox proportional hazard analysis was performed in a model with

age, sex, GINA step 4–5 (yes/no), blood eosinophils and FEV_1 % predicted. First, baseline characteristics, blood cell count and pulmonary function variables with p value <0.05 in a univariate Cox regression analysis with exacerbations were selected. Thereafter, we decided on the final Cox model with backward selection, taking collinearity into account. Furthermore, a Poisson regression model was used to analyse the effect of the interaction term between sex and GINA step for the exacerbation rate during follow-up.

Lastly, the sex differences we found made us question whether male and female patients received similar medical treatment at the same asthma severity in terms of lung function, symptoms, exacerbations and AHR. Therefore, we performed a logistic regression for medication (ie, inhaled corticosteroid (ICS), long-acting beta-2 agonist, etc) prescriptions as a dependent variable. The independent variables were sex, different measures for severity of disease and an interaction term of this measure of severity and sex. We chose more subjective (ie, ACQ-6 score and number of exacerbations prior to and during inclusion) and objective (ie, FEV_1 % predicted and AHR) parameters of asthma severity.

RESULTS

Patients

In total, 773 patients were included at baseline, of which 450 were female and 323 were male. Baseline characteristics are presented in table 1. Male patients were younger at diagnosis and more likely to have early onset asthma (age of onset <18 years), with a prevalence of 44% in male patients and 35% in female patients (p=0.017). Male patients had a significantly higher number of packyears than female patients (M: 6 vs F: 3 packyears; p<0.001). While mean body mass index (BMI) was not significantly different between male and female patients, female patients were more often in either the normal or obese BMI category and male patients were more often in the overweight category.

At baseline, female patients reported significantly worse asthma control as reflected by higher ACQ scores than their male counterparts (F: 0.83 vs M: 0.66 points; p<0.001) (table 1). This was also the case for the ACT score, which was lower in female patients (p<0.001). Quality of life, as measured by the Mini AQLQ, was significantly lower in female patients with asthma (p<0.001).

Lung function

Postbronchodilator FEV_1 % predicted and reversibility in FEV_1 were not significantly different between sexes (table 2). Male patients had a lower prebronchodilator and postbronchodilator FEV_1/FVC ratio (postbronchodilator: F: 0.76 (91.95 % predicted) vs M: 0.71 (88.33 % predicted); p<0.001) and more frequently had PAL. The results for Z-scores and % predicted for spirometry yielded similar outcomes, with Z-scores included in the online supplemental table S1. The total lung capacity (TLC), residual volume (RV) and RV/TLC ratio % predicted were not significantly different between male and female patients. This was also the case for the forced expiratory flow at 50% and 25%–75% of FVC % predicted. Female patients more often had moderate and severe rather than mild AHR (p=0.017). FeNO levels were higher in male patients, trending towards significance (F: 23 vs M: 26 parts per billion; p=0.069). Male and female patients with asthma were similar in their MBNW outcomes; both S_{cond} and S_{acin} did not differ. In contrast, all unadjusted IOS parameters were significantly different between male and female patients with asthma at baseline. Resistance at 5 Hz (R_5), 20 Hz (R_{20}) and between 5 and 20 Hz (R_5-R_{20}), as well as the area under the curve of reactance between 5 Hz and resonant frequency (AX) were significantly higher in female patients, indicating higher resistance in both the small and large airways. The reactance at 5 Hz (X_5) was significantly more negative in female patients (p<0.001). We included reference equations by Oostveen *et al*,[16] which found similar R_5, AX, X_5 % predicted but a higher % predicted of R_{20} in male patients with asthma.

Exacerbations

755 patients were included in the analysis of the time to first exacerbation. A total of 136 first exacerbations were included in the analysis, with a median follow-up duration (to end of follow-up or censoring) of 365 days (range 0–564). Proportionally, fewer male patients experienced exacerbations during the 1-year follow-up period, as illustrated in figure 1. In a multivariable Cox regression model for exacerbations, as depicted in table 3, male sex was still associated with a lower exacerbation risk (HR 0.61 (95% CI 0.42 to 0.88, p=0.008)) adjusted for age, blood eosinophils at baseline, GINA steps 4 and 5 and FEV_1 % predicted. For reference, we have added the exacerbation rate (0, 1, 2+ per year during follow-up) per GINA step by sex to the supplement (online supplemental table S2).

CT scan parameters

304 patients had a CT scan at baseline (table 4). The wall area divided by the total area (WA%) was not significantly different between sexes (F: 63.2% vs M: 62.7%; p=0.226). The voxel index at −950 Hounsfield units (VI 950) was significantly higher in male patients (F: 2.73% vs M: 5.38%; p<0.001).

Inflammatory cells in blood and sputum

Blood eosinophil counts did not differ between male and female patients (F: 0.22×10^9/L vs M: 0.24×10^9/L; p=0.088) (table 5). Sputum eosinophil percentages were similar in male and female patients (F: 0.5% vs M: 0.4%; p=0.433). Blood neutrophils were significantly higher in female patients (p=0.014), but this was not the case for sputum neutrophils. Lastly, blood monocytes were significantly higher in male patients (p<0.001).

Table 1 Baseline characteristics

	Female patients with asthma	Male patients with asthma	P value
N	450	323	
Age, years (mean (SD))	44.86 (13.02)	43.62 (12.94)	0.192
Age at diagnosis, years (median (IQR))	26.04 (10.29, 41.97)	22.00 (7.12, 39.55)	0.028
Age at diagnosis <18 years, n (%)	158 (35.3)	142 (44.1)	0.017
Duration of disease, years (median (IQR))	15.66 (4.99, 29.15)	18.56 (6.54, 29.39)	0.079
BMI, kg/m^2 (mean (SD))	27.25 (6.46)	27.20 (4.97)	0.902
BMI groups, n (%)			<0.001
≤18 kg/m^2	8 (1.8)	0 (0.0)	
>18, ≤25 kg/m^2	197 (43.8)	110 (34.1)	
>25, ≤30 kg/m^2	117 (26.0)	151 (46.7)	
>30, ≤40 kg/m^2	107 (23.8)	52 (16.1)	
>40 kg/m^2	21 (4.7)	10 (3.1)	
Smoking status, n (%)			0.184
Current smoker	15 (3.3)	12 (3.7)	
Past smoker	81 (18.0)	75 (23.2)	
Never smoker	354 (78.7)	236 (73.1)	
Ever smoker, n (%)			0.085
Current or past smoker	96 (21.3)	87 (26.9)	
Never smoker	354 (78.7)	236 (73.1)	
Packyears past and current smokers (median (IQR))	3.00 (1.15, 5.12)	6.00 (3.50, 8.85)	<0.001
Positive IgE screening for inhaled allergens, n (%)	265 (78.6)	189 (83.3)	0.211
ACQ-6 score (median (IQR))	0.83 (0.33, 1.67)	0.66 (0.16, 1.20)	<0.001
Mini AQLQ score (median (IQR))	5.40 (4.47, 6.20)	5.93 (5.07, 6.50)	<0.001
ACT score (median (IQR))	20.00 (17.00, 23.00)	22.00 (20.00, 24.00)	<0.001
MMAS score (median (IQR))	6.00 (4.50, 7.00)	5.75 (4.00, 7.00)	0.044
GINA treatment step, n (%)			0.042
1	72 (16.0)	63 (19.5)	
2	41 (9.1)	44 (13.6)	
3	117 (26.0)	90 (27.9)	
4	188 (41.8)	112 (34.7)	
5	32 (7.1)	14 (4.3)	
Current use of			
ICS, n (%)	368 (81.8)	262 (81.1)	0.888
LABA, n (%)	311 (69.1)	212 (65.6)	0.347
LAMA, n (%)	20 (4.4)	9 (2.8)	0.315
Montelukast, n (%)	97 (21.6)	47 (14.6)	0.018
Biologic, n (%)	20 (4.4)	12 (3.7)	0.75
Systemic corticosteriods, n (%)	16 (3.6)	6 (1.9)	0.238
Daily ICS dose in subjects on ICS (beclometasone equivalent), µg (mean (SD))	831.67 (547.31)	842.60 (705.17)	0.832
Daily ICS dose including patients not on (daily) ICS (median (IQR))	500.00 (362.50, 1000.00)	500.00 (200.00, 1000.00)	0.187

Univariable analyses of baseline characteristics of subjects with asthma in the ATLANTIS study, stratified by sex.
ACQ-6, Asthma Control Questionnaire 6; ACT, asthma control test; AQLQ, Asthma Quality of Life Questionnaire; BMI, body mass index; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonists; MMAS, Morisky Medication Adherence Scale.

Table 2 Lung function

	Female patients with asthma	Male patients with asthma	P value
N	450	323	
Spirometry			
Prebronchodilator FEV_1 % predicted (mean (SD))	82.09 (17.63)	79.90 (17.67)	0.092
FEV_1 reversibility, % change from baseline (median (IQR))	8.47 (4.58, 16.24)	9.84 (4.73, 17.31)	0.178
Postbronchodilator FEV_1 % predicted (mean (SD))	89.88 (15.76)	88.64 (16.24)	0.295
Postbronchodilator FVC % predicted (mean (SD))	98.01 (15.00)	100.90 (14.37)	0.008
Prebronchodilator FEV_1/FVC (mean (SD))	0.71 (0.11)	0.67 (0.11)	<0.001
Prebronchodilator FEV_1/FVC % predicted (mean (SD))	86.31 (12.10)	82.71 (12.57)	<0.001
Postbronchodilator FEV_1/FVC (mean (SD))	0.76 (0.10)	0.71 (0.11)	<0.001
Postbronchodilator FEV_1/FVC % predicted (mean (SD))	91.95 (11.38)	88.33 (12.42)	<0.001
Postbronchodilator FEF_{25-75} % predicted (mean (SD))	67.21 (32.17)	64.97 (29.06)	0.338
Postbronchodilator FEF_{50} % predicted (mean (SD))	82.54 (32.62)	79.81 (30.88)	0.268
PAL (%)	122 (27.11)	126 (39.00)	<0.001
Body plethysmography			
TLC, % of predicted (mean (SD))	105.41 (15.47)	103.40 (11.90)	0.065
RV, % predicted (mean (SD))	110.96 (28.78)	110.78 (27.77)	0.938
RV/TLC, (mean (SD))	0.35 (0.09)	0.31 (0.08)	<0.001
RV/TLC, % predicted (mean (SD))	101.43 (23.69)	98.79 (24.23)	0.153
Airway hyperresponsiveness			
Airway hyperresponsiveness category (%)			0.017
Very mild (*PC20 ≥4 and <16 mg/mL, PD20 ≥0.5 and <2 mg*)	70 (21.3)	76 (33.2)	
Mild (*PC20 ≥1 and <4 mg/mL, PD20 ≥0.13 and <0.5 mg*)	105 (31.9)	62 (27.1)	
Moderate (*PC20 ≥0.25 and <1 mg/mL, PD20 ≥0.03 and <0.13 mg*)	83 (25.2)	52 (22.7)	
Severe (*PC20 <0.25 mg/mL, PD20 <0.03 mg*)	71 (21.6)	39 (17.0)	
Impulse oscillometry			
X_5, kPa/L/s (median (IQR))	−0.12 (−0.17,−0.09)	−0.08 (−0.12,−0.06)	<0.001
X_5 % predicted* (mean (SD))	103.55 (42.16)	103.62 (52.10)	0.984
AX, Hz*kPa/L/s (median (IQR))	0.41 (0.22, 0.86)	0.23 (0.12, 0.54)	<0.001
AX % predicted* (mean (SD))	178.24 (173.01)	214.27 (291.26)	0.077
$R_{5,}$ kPa/L/s (mean (SD))	0.42 (0.14)	0.35 (0.14)	<0.001
R_5 % predicted* (mean (SD))	125.16 (38.24)	131.51 (48.08)	0.065
R_{20}, kPa/L/s (mean (SD))	0.35 (0.09)	0.30 (0.08)	<0.001
R_{20} % predicted* (mean (SD))	103.02 (24.98)	231.60 (65.75)	<0.001
R_{5-20} kPa/L/s (median (IQR))	0.06 (0.02, 0.11)	0.04 (0.02, 0.08)	0.002
Multiple breath nitrogen washout and FeNO			
S_{cond}, 1/L (median (IQR))	0.03 (0.02, 0.05)	0.03 (0.02, 0.04)	0.138
S_{cond}, % predicted (median (IQR))	86.73 (44.93, 136.10)	75.64 (45.42, 114.21)	0.183
S_{acin}, 1/L (median (IQR))	0.10 (0.06, 0.15)	0.10 (0.06, 0.15)	0.33
S_{acin}, % predicted (median (IQR))	121.44 (73.11, 172.51)	106.63 (66.84, 143.50)	0.16
FeNO, ppb (median (IQR))	23.00 (15.00, 36.50)	26.00 (16.75, 40.00)	0.069

Univariable analyses of lung function results at baseline of subjects with asthma in the ATLANTIS study, stratified by sex.
PAL was defined as postbronchodilator FEV_1/FVC lower than the lower limit of normal.
*Calculated using the IOS reference values proposed by Oostveen *et al.*[16]
AX, area of reactance; FEF_{50}, forced expiratory flow at 50% of FVC; FEF_{25-75}, forced expiratory flow at 25%–75% of FVC; FeNO, ractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IOS, impulse oscillometry; PAL, persistent airflow limitation; R_5, resistance at 5 Hz; R_{20}, resistance at 20 Hz; R_{5-20}, resistance at 5 Hz–resistance at 20 Hz; RV, residual volume; S_{acin}, ventilation homogeneity of the acinar zone of the lungs corrected for tidal volume; S_{cond}, ventilation heterogeneity in the conductive zone of the lungs corrected for tidal volume; TLC, total lung capacity; X_5, reactance at Hz.

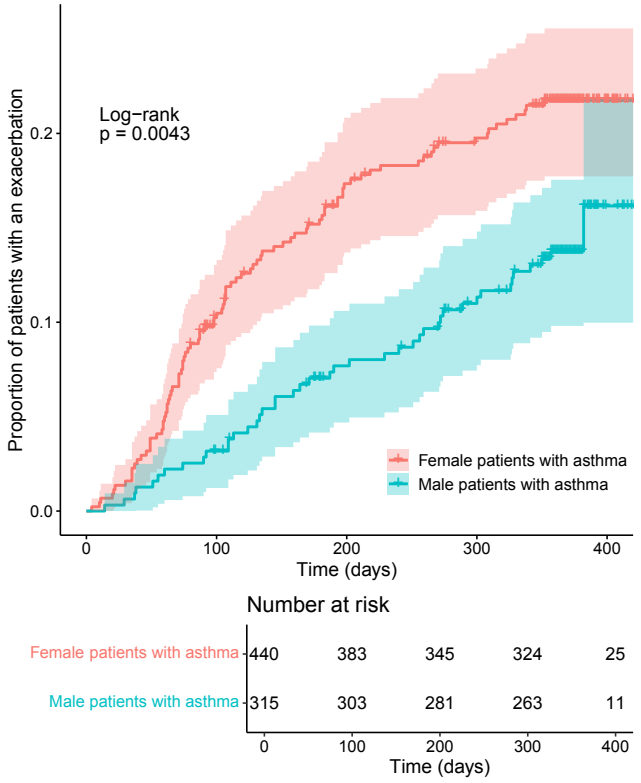

Figure 1 Exacerbations during follow-up, stratified by sex.

Prescribed medication

When stratifying for sex, we found the distribution of GINA steps to be skewed towards higher GINA steps in female patients (p=0.042). The prescription and dose of daily ICS were similar between male and female patients. Female patients were more likely to have been prescribed montelukast (F: 21.6% vs M: 14.6%; p=0.018). Female patients scored higher on Morisky Medication Adherence Scale score, reflecting a higher medication adherence.

Furthermore, we assessed whether differences in asthma characteristics between male and female patients, as detailed above, were attributable to variations in their treatment regimens. We also investigated whether male and female patients were treated similarly despite having similar disease severity. This was done by assessing the prescribed medication by sex, an indicator of asthma severity and the interaction between sex and the indicator of asthma severity (online supplemental tables S3-S7). FEV_1 % predicted, ACQ6 score, AHR and exacerbations were used as indicators for severity of disease. The only significant finding was that female patients were more likely to use montelukast than male patients when they had milder disease with regard to FEV_1 % predicted. In general, male and female patients were treated similarly at baseline when adjusting for severity of disease during inclusion, and differences in asthma characteristics between the sexes could not be explained by difference in prescribed medication.

Table 3 Cox regression analysis for exacerbations

	HR (95% CI)	P value
Male sex	0.61 (0.42 to 0.88)	0.008
Age, years	1.01 (1.00 to 1.03)	0.044
GINA steps 4–5	2.26 (1.52 to 3.37)	<0.001
Blood eosinophil counts	3.29 (1.95 to 5.54)	<0.001
FEV_1 % predicted (post-BD)	0.98 (0.97 to 0.99)	0.001

BD, bronchodilator; FEV_1, forced expiratory volume in 1 s; GINA, Global Initiative for Asthma.

DISCUSSION

We show that female patients with asthma exhibit poorer disease control, a higher risk of exacerbations and greater airway resistance, as evidenced by worse impulse oscillometry results. In contrast, male patients with asthma suffer from more severe airflow obstruction and more frequently experience PAL. The latter finding was previously described in a separate publication.[23]

IOS has previously been suggested to be more suitable for detecting SAD than spirometry.[10 24] We found that female patients had worse results for all uncorrected IOS parameters, while FEV_1 % predicted was similar. These findings of a higher resistance in the central and peripheral airways may reflect more large airways dysfunction and SAD and IOS might be more sensitive than FEV_1. However, it should be noted that proper reference values are currently lacking.[25] Alternatively, it could be speculated that our results are merely based on an anatomical difference, that is, dysanapsis. Dysanapsis is a mismatch between the size of the airway lumen in relation to the lung parenchyma. This could explain the differences between male and female patients with asthma rather than a clinically significantly higher level of SAD. This would be in accordance with literature on dysanapsis, which suggests that adult female patients have higher small airways resistance than male patients.[26] We have applied reference equations by Oostveen *et al*,[16] which, in contrast to unadjusted IOS values, suggest a higher peripheral airway resistance in male patients (R_{20}) while other IOS parameters did not differ (R_5, AX and X_5). These results need to be interpreted with caution as these reference equations have not been widely accepted. In 2020, the ERS task force on technical recommendations for oscillometry acknowledged that large studies are necessary to determine normal values.[25] Clearly, sex is one of the factors that should be taken into account.

Apart from a significantly higher use of leukotriene modifiers in female patients, we found no differences in asthma medication prescription between male and female patients. Nevertheless, female patients reported more symptoms and were classified in higher GINA treatment steps and male patients more frequently had PAL and had worse airflow obstruction (FEV_1/FVC). Therefore, we questioned whether male and female patients

Table 4 CT scan parameters

	Female patients with asthma	Male patients with asthma	P value
N	184	120	
CT scan-derived parameters			
Median lumen area, mm^2 (mean (SD))	18.15 (4.27)	22.11 (5.53)	<0.001
Median wall area, mm^2 (mean (SD))	31.11 (5.08)	36.91 (6.46)	<0.001
Median total area, mm^2 (mean (SD))	49.59 (8.61)	59.37 (11.14)	<0.001
WA% (wall area/total area), % (mean (SD))	63.22 (3.36)	62.73 (3.63)	0.226
Pi10, mm (mean (SD))	7.14 (0.90)	7.29 (1.06)	0.195
VI 856, % (median (IQR))	7.83 (2.49, 18.18)	8.40 (2.58, 20.64)	0.897
VI 950, % (median (IQR))	2.73 (1.11, 6.06)	5.38 (2.27, 10.19)	<0.001

CT scan parameters at baseline of subjects with asthma in the ATLANTIS study, stratified by sex.
Pi10, 10 mm internal luminal perimeter; VI 856, voxel index at −856 Hounsfield units; VI 950, voxel index at −950 Hounsfield units.

in the same class of asthma severity received similar medical treatment or whether either one of the sexes was undertreated. To determine whether this was the case, we performed a subgroup analysis to assess whether male and female patients with asthma classified by quartiles of disease severity (ie, FEV_1, AHR) and subjective outcomes (ie, ACQ-6, annual exacerbation rate prior to inclusion/during follow-up) received similar medical treatment. Overall, these analyses did not show major differences in pattern of medication prescriptions by asthma severity between male and female patients with asthma.

We found significantly higher blood neutrophil counts in female patients with asthma. This was an expected result as neutrophilic inflammation is predominantly present in patients with late-onset and severe asthma, who are more frequently female.[27] Possibly, the higher blood neutrophil counts are explained by the higher prevalence of obesity in female patients. Previous studies show that blood neutrophilia is associated with increased exacerbation risk and lower quality of life.[28] In addition, a significantly higher number of female patients in our study were obese, which is also known to be associated with neutrophilic infiltration in the airways.[29]

Male patients with asthma tended to have higher blood eosinophil counts and FeNO levels, both indicators of type 2 inflammation which is often predominant in patients with early onset asthma.[7 30] Blood eosinophil counts were also higher in men in the general population, so this finding may not be specific for asthma.[31] We also found higher blood monocyte counts in male patients. The role of blood monocytes in asthma is less well elucidated. Although absolute monocyte counts are infrequently elevated in asthma, it has now been described that there are three subsets of blood monocytes (ie, classical

Table 5 Inflammatory cell counts in blood and proportions in sputum at baseline of subjects with asthma in the ATLANTIS study, stratified by sex

	Female patients with asthma	Male patients with asthma	P value
N	450	323	
Blood cell counts			
Blood cell counts available, n	450 (100%)	317 (98.1%)	
Eosinophils 10^9/L (median (IQR))	0.22 (0.12, 0.37)	0.24 (0.16, 0.38)	0.088
Neutrophils 10^9/L (median (IQR))	3.80 (3.04, 4.89)	3.56 (2.86, 4.41)	0.014
Monocytes 10^9/L (median (IQR))	0.44 (0.36, 0.54)	0.50 (0.40, 0.60)	<0.001
Sputum cell proportions			
Sputum cell proportions available, n (%)	116 (25.8%)	112 (34.7%)	
Bronchial cells % (median (IQR))	1.50 (0.68, 4.03)	1.85 (1.00, 3.95)	0.165
Lymphocytes, % (median (IQR))	0.70 (0.30, 1.52)	0.50 (0.30, 1.22)	0.230
Eosinophils, % (median (IQR))	0.50 (0.00, 1.93)	0.40 (0.10, 4.00)	0.433
Macrophages, % (median (IQR))	38.30 (19.02, 60.80)	33.85 (18.00, 57.12)	0.669
Neutrophils, % (median (IQR))	50.50 (26.17, 71.50)	52.40 (31.18, 70.43)	0.968

C14++CD16−, non-classical CD14+CD16+, intermediate CD14++CD16+) of which higher proportions of intermediate monocytes have been found in severe patients with asthma.[32–34] In the current study, we did not perform detailed flow cytometry to identify monocyte subsets and therefore we cannot make a definite conclusion about the monocyte subsets in our study. Interestingly, all aforementioned differences in blood leucocyte counts could not be replicated in sputum.

Analysis of CT scans showed that male and female patients with asthma have similar thickness of the airway walls as reflected by WA% and Pi10 (ie, the average wall thickness for a hypothetical airway of 10 mm lumen perimeter). Both the airway lumens as well as the airway walls, as reflected by median wall and lumen area, were significantly smaller in female patients with asthma, but this is logically explained by the fact that women overall have smaller lungs and therefore smaller airways. Quantitative CT scanning has made a lot of progress in the past decades, but bronchial wall parameters might need reference values, that also take sex into account, something that has recently been explored in a systematic review and meta-analysis by Dudurych *et al*.[35] Lastly, VI 950 was significantly higher in male patients with asthma, indicating more emphysema-like lung on CT. This may be a physiological phenomenon, as the percentage of emphysema-like lung was relatively low and Hoffman *et al* previously showed that respiratory-healthy male never-smokers have a higher percentage of emphysema-like lung than female never-smokers.[36] However, male current-smokers and past-smokers in ATLANTIS had a significantly higher number of packyears, which was also associated with a higher VI 950. Thus, some degree of overlap with COPD in these subjects cannot be excluded even though all subjects had a confirmed diagnosis if asthma and a smoking history of >10 packyears was an exclusion criterium in the ATLANTIS study.

Our findings of a significantly higher risk of exacerbations and more severe AHR in female patients with asthma are in accordance with literature.[6 37 38] Sex hormones might play a role in both the increased exacerbation risk as well as the more severe AHR in female patients.[7] It has, for example, been shown that AHR is increased during the luteal phase of the menstrual cycle and that the risk of exacerbations increases during pregnancy.[39 40] In contrast, androgens, such as testosterone, may actually reduce asthma incidence and symptoms.[7] However, a lot is still unknown about the exact mechanisms by which sex hormones influence asthma pathogenesis and more research is needed in this area. Lastly, contrary to previous findings, current smoking was not a significant predictor of exacerbations in our study, likely due to the small number of current smokers in this cohort.[41]

We found multiple differences between female and male patients in key features of asthma, some of which can be integrated. The clearest interplay between our findings are mechanical in nature; a smaller airway lumen size in female patients can increase both airway resistance as well as induce more severe AHR. Furthermore, there is a known interplay between sex hormones, differences in body composition, airway inflammation and exacerbations. The exact mechanisms of the latter interplay are beyond the scope of this study. Lastly and most hypothetically, an interplay can be observed between the development of asthma earlier in life in male patients, a more dominant type 2 inflammation, lower therapy adherence and impaired lung function with ageing with a higher prevalence of PAL.

A strength of this study is the fact that it covers a large cohort of patients with asthma, from a varied range of countries, with extensive clinical characterisation including small and large airway function and across all asthma severities. A limitation of our study was the fact that this cohort was not specifically designed to unravel sex differences in asthma and therefore the post hoc analyses performed were exploratory.

Interpretation

We find that in asthma, female patients experience worse disease control, have a higher risk of exacerbations and potentially have more small airways and less large airways dysfunction compared with male patients with asthma, who have more severe airflow obstruction and a higher prevalence of PAL. These findings are significant because they highlight the potential importance of precision treatment of patients with asthma, possibly taking sex into account. We hope these results increase awareness among clinicians.

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Competing interests SM reports a travel grant from GSK outside of the submitted work. MK reports grants paid to her institution by National Institutes of Health, American Lung Association, Synairgen, Janssen, AstraZeneca and Sanofi; personal consulting fees from AstraZeneca, Sanofi, Chiesi, GSK, Kinaset, Genentech; presentation fees from Chiesi; support for attending the European Respiratory Society annual conference; one issued and two filed patents by RaeSedo; participation in data safety and monitoring board at ALung and past membership of the National Heart, Lung and Blood Advisory Council; current membership of Association of Professor of Medicine; equity ownership in RaeSedo and is a section editor for UptoDate. SS reports consulting fees from CSL Behring, AstraZeneca, GSK, Areteia Therapeutics, Novartis; speaker fees for presenting ATLANTIS data by Chiesi; support from ERS for attending ERS science council meetings and membership of the ALTANTIS scientific steering group. LMF reports being a consultant for Chiesi; consulting fees by Chiesi, GSK, AstraZeneca, Novartis, Alfasigma and participation in a board with Novartis and Chiesi. KFR reports presenter fees by AstraZeneca, Boehringer Ingelheim, Chiesi, Novartis, Sanofi, Regeneron, GSK, Berlin Chemie, Roche Pharma; participation in data safety and monitoring boards for AstraZeneca, Boehringer Ingelheim, Sanofi and Regeneron; leadership of German Center for Lung Research (DZL), German Chest Society (DGP) and American Thoracic Society. AP reports grants or contracts paid to institution by Chiesi, AstraZeneca, GSK, Sanofi, Agenzia Italiana del farmaco (AIFA); consulting fees from Chiesi, AstraZeneca, GSK, Novartis, Sanofi, Avillion, Elpen Pharmaceuticals; speaker fees from Chiesi, AstraZeneca, GSK, Menarini, Novartis, Zambon, Mundipharma, Sanofi, Edmond Pharma, Iqvia, Avillion, Elpen Pharmaceuticals, membership of advisory board for Chiesi, AstraZeneca, GSK, MSD, Novartis, Sanofi, Iqvia, Avillion, Elpen Pharmaceuticals. CEB reports grants paid to institution by GSK, AstraZeneca, Sanofi, Regeneron, Roche, Genentech, Boehringer Ingelheim, Chiesi, Novartis, Mologic, Areteia and consulting fees paid to institution by GSK, AstraZeneca, Sanofi, Regeneron, Roche, Genentech, Boehringer Ingelheim, Chiesi, Novartis, Mologic, Areteia. DS reports consulting fees from Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, EpiEndo, Genentech, GSK, Glenmark, Gossamer Bio, Kinaset Therapeutics, Menarini, Novartis, Orion, Pulmatrix, Sanofi, Synairgen, Teva, Theravance Biopharma, Verona Pharma. TvdM reports presenter fees paid to institution by Chiesi and GSK. MCN reports unrestricted research grants paid to institution: European Union's H2020 Research and Innovation Programme under grant agreement, the Ministry of Economic Affairs and Climate Policy (the Netherlands) through a PPP allowance from the Top Sector Life Sciences & Health, GSK, Stevenage (UK), Netherlands Lung Foundation, the Chan Zuckerberg Initiative, The Stichting Astmabestrijding; support of travel costs by the Belgian Respiratory Society and unpaid leadership of the Lung Bionetwork of the Human Cell Atlas consortium. HAMK reports that his institution has received fees per patient for recruitment in trials from GSK, Novartis and FLUIDDA, grants for investigator-initiated studies from GSK, Novartis and Boerhinger. Additionally, his institution has received consultancy fees from Novartis, AstraZeneca, Boehringer Ingelheim, Chiesi and GSK. MvdB reports grants paid to the University from GSK, Chiesi, Teva, AstraZeneca, Genentech, outside the submitted work.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval The following review boards or institutions approved the protocol: Comitato Etico dell'Azienda Ospedaliera V. Cervello di Palermo (Palermo 2), Comitato Etico della Provincia di Ferrara, Comitato Etico dell'Azienda Ospedaliero-Universitaria di Parma, Comitato Etico di Area Vasta Nord-Ovest per la sperimentazione clinica, Comitato Etico per la Sperimentazione Clinica delle Province di Verona e Rovigo, Comitato Etico dell'Azienda Ospedaliera dei Colli, Comitato Etico della Fondazione Salvatore Maugeri, Comitato Etico dell'A.O.U Ospedali Riuniti di Foggia, NHS Health Research Authority NRES Committee North West—Greater Manchester South (for all UK sites), UMCG Medical Ethical Review Committee, Forest Medical School, Jeroen Bosch Ziekenhuis, Martini Ziekenhuis, Comité Ético de Investigación Clínica, Ethikkommission bei der Ärztekammer Schleswig-Holstein, Ethik-Kommission der Medizinischen Hochschule Hannover, Ethik-Kommission bei der Sächsischen Landesärztekammer, Institutional review board for human investigation (Cleveland, Ohio), Western Institutional Review Board, Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals, University of Arizona Institutional Review Board, Biomedical Research Ethics Board of the McGill University Health Center, Comitê de Ética em Pesquisa com Seres Humanos da Universidade Federal de Santa Catarina, Comissão de Ética para Análise de Projetos de Pesquisa—CAPPesq do HCFMUSP, Coordinator EC—Comitê de Ética em Pesquisa da Fundação ABC—FMABC, Medical Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. Participants gave informed consent to participate in the study before taking part.

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Supplementary Appendix

Kole TM, *et al. BMJ Open Respir Res* 2024; 11:e002316. doi: 10.1136/bmjresp-2024-002316

Supplementary Appendix

Inhoud

1. Eligibility Criteria

1.1 Inclusion Criteria

- Male or female patients aged ≥ 18 and ≤ 65 years, who have signed an Informed Consent form prior to initiation of any study-related procedure.
- Clinical diagnosis of asthma for at least 6 months confirmed by a chest physician according to international guidelines (GINA 2012) supported by objective evidence of any of the following at the baseline visit or in the previous 5 years:
    - Positive response to methacholine challenge test [PC20 < 8 mg/mL or PD20 < 0.7 mg for those subjects not using inhaled corticosteroids (ICS), and PC20 < 16 mg/mL or PD20 < 1.4 mg for subjects using ICS];
    - Positive response to a reversibility test, defined as ΔFEV_1 ≥ 12% and ≥ 200 mL over baseline FEV_1, within 30 minutes after administration of 400 µg of salbutamol pMDI administered with or without Spacer;
    - Peak Flow variability (i.e. highest - lowest PEF over the day/mean value of the two, × 100) > 20%, measured over a follow-up period of 7 days;
    - Documented response (defined as ΔFEV_1 ≥ 12% and ≥ 200 mL) after a cycle (e.g., 4 weeks) of regular maintenance anti-asthma treatment.
- Patients with stable asthma, on any previous regular asthma treatment ("rescue" β2-agonists alone included) at a stable dose, for at least 8 weeks prior to baseline visit.
- Current smoker, ex-smoker (since the past 12 months) or lifelong non-smoker (total lifetime smoking history < 10 packyears defined as [(number of cigarettes smoked per day)x(number of years of smoking)] / 20).

1.2 Exclusion Criteria

- Cigarette smoking > 10 packyears defined as [(number of cigarettes smoked per day) x (number of years of smoking)] / 20.
- Diagnosis of COPD confirmed by a chest physician.
- Asthma exacerbation in the 8 weeks prior to baseline visit (defined as a significant deterioration of asthma and signalled by any or more of the following: need for a systemic corticosteroid course (≥ 3 days); hospitalisation for asthma; emergency room attendance for asthma).
- Clinical or functional uncontrolled respiratory, haematological, immunologic, renal, neurologic, hepatic, endocrinal or other disease, or any condition that might, in the judgment of the investigator, compromise the results or interpretation of the study.
- Pregnant or lactating women (a urine pregnancy test will be performed).
- Participation in an interventional clinical trial with intake of the last dose of any investigational drug <12 weeks preceding baseline visit (last dose < 5 half-lives prior to baseline visit for biologics).
- Inability to comply with study procedures.
- Alcohol or drug abuse.

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1.3 IRB or institutions that approved the protocol

The following review boards or institutions approved the protocol; Comitato Etico dell'Azienda Ospedaliera V. Cervello di Palermo (Palermo 2), Comitato Etico della Provincia di Ferrara, Comitato Etico dell'Azienda Ospedaliero-Universitaria di Parma, Comitato Etico di Area Vasta Nord-Ovest per la sperimentazione clinica, Comitato Etico per la Sperimentazione Clinica delle Province di Verona e Rovigo, Comitato Etico dell'Azienda Ospedaliera dei Colli, Comitato Etico della Fondazione Salvatore Maugeri, Comitato Etico dell'A.O.U Ospedali Riuniti di Foggia, NHS Health Research Authority NRES Committee North West - Greater Manchester South (for all UK sites), UMCG Medical Ethical Review Committee, Foreest Medical School, Jeroen Bosch Ziekenhuis, Martini Ziekenhuis, Comité Ético de Investigación Clínica, Ethikkommission bei der Ärztekammer Schleswig-Holstein, Ethik-Kommission der Medizinischen Hochschule Hannover, Ethik-Kommission bei der Sächsischen Landesärztekammer, Institutional review board for human investigation (Cleveland, OH), Western Institutional Review Board, Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals, University of Arizona Institutional Review Board, Biomedical Research Ethics Board of the McGill University Health Center, Comitê de Ética em Pesquisa com Seres Humanos da Universidade Federal de Santa Catarina, Comissão de Ética para Análise de Projetos de Pesquisa – CAPPesq do HCFMUSP, Coordinator EC - Comitê de Ética em Pesquisa da Fundação ABC – FMABC, Medical Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University.

2. Study Design

2.1 Measurements at each visit

	Visit 1 T=0 months		**TC 1 T=3 months**	**Visit 2 T=6 months**	**TC 2 T=9 months**	**Visit 3 T=12 months**
	1a	1b				
Written informed consent	X					
Review in-/exclusion criteria	X	X				
Medical history	X					
Concomitant medication	X		X	X	X	X
Exacerbations	X		X	X	X	X
Physical examination	X			X		X
Urine pregnancy test	X					
Blood sample	X			X		X
Phadiatop test	X					
Asthma Control Test	X		X	X	X	X
Impulse Oscillometry		X		X		X
Fraction of exhaled NO	X			X		X
Multiple Breath Nitrogen Washout		X		X		X
Body plethysmography		X		X		X
Spirometry		X		X		X
Sputum induction*		X				
Nasal brushing	X			X		
Methacholine challenge test	X					
Asthma Control Questionnaire	X		X	X	X	X
Asthma Quality of Life Questionnaire	X		X	X	X	X
Computed tomography scan*		X				

Table 2.1: Measurements at each visit. Abbreviations: NO: Nitric oxide. * Sputum induction and computed tomography were performed in a subset of patients depending on the availability of equipment in participating centers.

Table S1. Z-scores for spirometry

	Female asthma patients	Male asthma patients	P-value
N	450	323	
Prebronchodilator FEV_1 Z-score (mean (SD))	-1.36 (1.31)	-1.52 (1.37)	0.084
Postbronchodilator FEV_1 Z-score (mean (SD))	-0.73 (1.22)	-0.84 (1.28)	0.214
Postbronchodilator FVC Z-score (mean (SD))	-0.23 (1.15)	0.01 (1.13)	0.004
Prebronchodilator FEV_1/FVC Z-score (mean (SD))	-1.51 (1.25)	-1.92 (1.29)	<0.001
Postbronchodilator FEV_1/FVC Z-score (mean (SD))	-0.89 (1.27)	-1.30 (1.33)	<0.001

Table S1: Univariable analyses of spirometry Z-scores at baseline of asthma subjects in ATLANTIS, stratified for sex. FEV_1: Forced expiratory volume in 1 second, FVC: Forced vital capacity.

Table S2. Exacerbations during 1 year follow-up per GINA step by sex

	Female patients			Male patients		
Exacerbations/year	**0**	**1**	**2+**	**0**	**1**	**2+**
GINA step 1 (%)	92,8	7,2	0,0	93,5	4,8	1,6
GINA step 2 (%)	87,2	10,3	2,6	97,6	2,4	0,0
GINA step 3 (%)	87,0	9,6	3,5	83,9	11,5	4,6
GINA step 4 (%)	69,9	19,1	10,9	80,9	10,0	9,1
GINA step 5 (%)	43,8	21,9	34,4	61,5	0,0	38,5

Table S3. Medication use related to FEV_1 stratified for sex

	Quartile 1		**Quartile 2**		**Quartile 3**		**Quartile 4**		**p-value for logistic regression**
	Female	Male	Female	Male	Female	Male	Female	Male	
n	109	82	113	78	104	87	117	73	-
FEV_1 % predicted (median [IQR])	70.83 [66.07, 75.02]	70.21 [59.59, 74.18]	85.14 [82.58, 88.29]	85.22 [81.74, 88.06]	96.39 [93.72, 98.04]	95.94 [93.53, 99.14]	107.12 [104.58, 112.98]	107.68 [104.90, 111.71]	-
ICS use, n (%)	100 (91.7)	75 (91.5)	93 (82.3)	61 (78.2)	86 (82.7)	69 (79.3)	85 (72.6)	54 (74.0)	0.369
LABA use, n (%)	90 (82.6)	68 (82.9)	79 (69.9)	51 (65.4)	67 (64.4)	57 (65.5)	72 (61.5)	34 (46.6)	0.360
LAMA use, n (%)	10 (9.2)	8 (9.8)	4 (3.5)	1 (1.3)	1 (1.0)	0 (0.0)	4 (3.4)	0 (0.0)	0.087
Montelukast use, n (%)	30 (27.5)	21 (25.6)	20 (17.7)	9 (11.5)	16 (15.4)	12 (13.8)	30 (25.6)	5 (6.8)	0.007
Biological use, n (%)	8 (7.3)	7 (8.5)	5 (4.4)	3 (3.8)	2 (1.9)	1 (1.1)	5 (4.3)	0 (0.0)	0.117
Systemic corticosteroid use, n (%)	8 (7.3)	4 (4.9)	3 (2.7)	1 (1.3)	3 (2.9)	1 (1.1)	2 (1.7)	0 (0.0)	0.805

Table S2. Medication use in quartiles for (post-bronchodilator) FEV_1 % predicted stratified for sex. The presented p-values are derived from a logistic regression analysis for medication use, i.e. ICS use, LABA use etc (dependent variable), with as covariates: sex, FEV_1% predicted , FEV_1% predicted sex (interaction term). The presented p-value is that for the interaction term. FEV_1: forced expiratory volume in 1 second, GINA: Global Initiative for Asthma, ICS: inhaled corticosteroids, LABA: long-acting beta2 agonist, LAMA: long-acting muscarinic antagonists*

Table S4. Medication use in quartiles for ACQ-6 stratified for sex

	Quartile 1		**Quartile 2**		**Quartile 3**		**Quartile 4**		**p-value for logistic regression**
	Female	Male	Female	Male	Female	Male	Female	Male	
n	92	101	112	81	111	82	135	58	-
ACQ-6, median [IQR]	0.00 [0.00, 0.16]	0.00 [0.00, 0.16]	0.50 [0.33, 0.66]	0.50 [0.33, 0.66]	1.16 [1.00, 1.33]	1.13 [1.00, 1.20]	2.16 [1.83, 2.83]	2.33 [2.00, 3.27]	-
ICS use, n (%)	70 (76.1)	79 (78.2)	90 (80.4)	64 (79.0)	95 (85.6)	66 (80.5)	113 (83.7)	52 (89.7)	0.852
LABA use, n (%)	54 (58.7)	65 (64.4)	74 (66.1)	48 (59.3)	78 (70.3)	58 (70.7)	105 (77.8)	41 (70.7)	0.205
LAMA use, n (%)	1 (1.1)	1 (1.0)	2 (1.8)	3 (3.7)	8 (7.2)	1 (1.2)	9 (6.7)	4 (6.9)	0.640
Montelukast use, n (%)	12 (13.0)	11 (10.9)	19 (17.0)	11 (13.6)	22 (19.8)	15 (18.3)	44 (32.6)	10 (17.2)	0.311
Biological use, n (%)	3 (3.3)	3 (3.0)	4 (3.6)	1 (1.2)	4 (3.6)	5 (6.1)	9 (6.7)	3 (5.2)	0.651
Systemic corticosteroid use, n (%)	3 (3.3)	0 (0.0)	4 (3.6)	0 (0.0)	1 (0.9)	4 (4.9)	8 (5.9)	2 (3.4)	0.634

*Table S3. Medication use in quartiles for ACQ-6 stratified for sex. ACQ-6: Asthma Control Questionnaire, GINA: Global Initiative for Asthma, ICS: inhaled corticosteroids, LABA: long-acting beta2 agonist, LAMA: long-acting muscarinic antagonists. The presented p-values are derived from a logistic regression analysis for medication use, i.e. ICS use, LABA use etc (dependent variable), with as covariates: sex, ACQ6 score, ACQ-6 score * sex (interaction term). The presented p-value is that for the interaction term.*

Table S5. Medication use in categories of airway hyperresponsiveness stratified for sex

	Very mild - mild		**Moderate – severe**		**p-value for logistic regression**
	Female	Male	Female	Male	-
n	175	138	154	91	-
ICS use, n (%)	143 (81.7)	109 (79.0)	129 (83.8)	72 (79.1)	0.759
LABA use, n (%)	122 (69.7)	83 (60.1)	102 (66.2)	54 (59.3)	0.728
LAMA use, n (%)	5 (2.9)	2 (1.4)	5 (3.2)	2 (2.2)	0.807
Montelukast use, n (%)	33 (18.9)	15 (10.9)	26 (16.9)	11 (12.1)	0.619
Biological use, n (%)	8 (4.6)	0 (0.0)	4 (2.6)	4 (4.4)	0.990
Systemic corticosteroid use, n (%)	6 (3.4)	1 (0.7)	5 (3.2)	3 (3.3)	0.225

*Table S4. Medication use in categories of airway hyperresponsiveness stratified for sex. The p-value in the right hand column is derived from a logistic regression with medication use (i.e. ICS use, LABA use, LAMA use, etc) as a dependent variable and sex, moderate or severe airway hyperresponsiveness and sex*moderate or severe airway hyperresponsiveness (interaction term). The presented p-value is that of the interaction term. ICS: inhaled corticosteroids, LABA: long-acting beta2 agonist, LAMA: long-acting muscarinic antagonists.*

Table S6. Medication use in categories of exacerbations prior to inclusion stratified for sex

Exacerbations prior to inclusion	**0**		**1 or more**		**p-value for logistic regression**
	Female	Male	Female	Male	-
n	373	291	77	32	-
ICS use, n (%)	294 (78.8)	232 (79.7)	74 (96.1)	30 (93.8)	0.564
LABA use, n (%)	240 (64.3)	184 (63.2)	71 (92.2)	28 (87.5)	0.497
LAMA use, n (%)	12 (3.2)	6 (2.1)	8 (10.4)	3 (9.4)	0.694
Montelukast use, n (%)	70 (18.8)	38 (13.1)	27 (35.1)	9 (28.1)	0.831
Biological use, n (%)	16 (4.3)	10 (3.4)	4 (5.2)	2 (6.2)	0.664
Systemic corticosteroid use, n (%)	4 (1.1)	1 (0.3)	12 (15.6)	5 (15.6)	0.363

Table S5. Medication use in category based on exacerbations prior to inclusion stratified for sex. The p-value in the right hand column is derived from a logistic regression with medication use (i.e. ICS use, LABA use, LAMA use, etc) as a dependent variable and sex, exacerbation count ≥ 1 prior to inclusion and sex exacerbation count ≥ 1 prior to inclusion (interaction term). The presented p-value is that of the interaction term.GINA: Global Initiative for Asthma, ICS: inhaled corticosteroids, LABA: long-acting beta2 agonist, LAMA: long-acting muscarinic antagonists.*

Table S7. Medication use in categories of exacerbations during follow-up stratified for sex

Exacerbations during follow-up	**0**		**1 or more**		**p-value for logistic regression**
	Female	Male	Female	Male	-
n	340	269	98	45	-
ICS use, n (%)	271 (79.7)	214 (79.6)	90 (91.8)	41 (91.1)	0.901
LABA use, n (%)	222 (65.3)	171 (63.6)	83 (84.7)	37 (82.2)	0.838
LAMA use, n (%)	8 (2.4)	5 (1.9)	11 (11.2)	4 (8.9)	0.983
Montelukast use, n (%)	65 (19.1)	32 (11.9)	31 (31.6)	14 (31.1)	0.237
Biological use, n (%)	7 (2.1)	8 (3.0)	13 (13.3)	4 (8.9)	0.301
Systemic corticosteroid use, n (%)	7 (2.1)	2 (0.7)	9 (9.2)	3 (6.7)	0.520

Table S6. Medication use in categories of exacerbations during follow-up stratified for sex. The p-value in the right hand column is derived from a logistic regression with medication use (i.e. ICS use, LABA use, LAMA use, etc) as a dependent variable and sex, exacerbation count ≥ 1 during follow-up and sex exacerbation count ≥ 1 prior to inclusion (interaction term). The presented p-value is that of the interaction term. GINA: Global Initiative for Asthma, ICS: inhaled corticosteroids, LABA: long-acting beta2 agonist, LAMA: long-acting muscarinic antagonist*