






How Does Mild Asthma Differ Phenotypically from Difficult-to-Treat Asthma?

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Background: Despite most of the asthma population having mild disease, the mild asthma phenotype is poorly understood. Here, we aim to address this gap in knowledge by extensively characterising the mild asthma phenotype and comparing this with difficult-to-treat asthma.

Methods: We assessed two real-world adult cohorts from the South of England using an identical methodology: the Wessex AsThma CoHort of difficult asthma (WATCH) (n=498) and a mild asthma cohort from the comparator arm of the Epigenetics Of Severe Asthma (EOSA) study (n=67). Data acquisition included detailed clinical, health and disease-related questionnaires, anthropometry, allergy and lung function testing, plus biological samples (blood and sputum) in a subset.

Results: Mild asthma is predominantly early-onset and is associated with type-2 (T2) inflammation (atopy, raised fractional exhaled nitric oxide (FeNO), blood/sputum eosinophilia) plus preserved lung function. A high prevalence of comorbidities and multimorbidity was observed in mild asthma, particularly depression (58.2%) and anxiety (56.7%). In comparison to difficult asthma, mild disease showed similar female predominance (>60%), T2-high inflammation and atopy prevalence, but lower peripheral blood/airway neutrophil counts and preserved lung function. Mild asthma was also associated with a greater prevalence of current smokers (20.9%). A multi-component T2-high inflammatory measure was comparable between the cohorts; T2-high status 88.1% in mild asthma and 93.5% in difficult asthma.

Conclusion: Phenotypic characterisation of mild asthma identified early-onset disease with high prevalence of current smokers, T2-high inflammation and significant multimorbidity burden. Early comprehensive assessment of mild asthma patients could help prevent potential later progression to more complex severe disease.

Keywords: mild asthma, difficult asthma, multimorbidity, type 2 inflammation

Introduction

Asthma is a common heterogeneous inflammatory airway condition that places significant burden at individual, societal and health economic levels.¹

Difficult asthma is defined as asthma that remains poorly controlled despite maximal inhaled therapies.² This is often due to the complex interplay of comorbidities, poor inhaler technique and medication adherence.^{3,4} Approximately 17% of individuals with asthma have difficult asthma with only 3.7% having severe asthma, where disease control remains

poor despite optimising other contributory factors.² Though affecting a minority, difficult/severe asthma has attracted significantly more research focus than milder disease.

Much effort has been placed on characterising difficult asthma and identifying distinct clinical, physiological and pathological traits.^{5–9} This improved understanding of difficult/severe asthma has been pivotal in driving more personalised medicine approaches.¹⁰ Recent work has indicated that most difficult asthma is associated with type 2 (T2)-predominant inflammation that may be amenable to higher level T2-targeting biologics.^{11,12} Such treatments are becoming commonplace for difficult/severe asthma with good efficacy in most patients.¹² In parallel, there is growing recognition that difficult asthma is associated with numerous comorbidities within a complex multimorbidity model of ill-health.¹³

Conversely, mild asthma remains poorly defined but is typically described as asthma that is well controlled after several months of treatment with low to medium dose inhaled corticosteroid (ICS)/long-acting beta-agonist (LABA) or ICS alone.² Serra-Batlles et al found that the mean annual drugs cost per patient with mild asthma in Northern Spain was US\$253, amounting to a significant economic burden given that 50–75% of the asthma population have mild disease.^{2,14} Similarly, the United Kingdom (UK) National Review of Asthma Deaths (NRAD) found 58% of asthma deaths were in those with mild or moderate disease.¹⁵ Such findings emphasise the importance of better understanding mild asthma.

Key questions that merit further attention are as follows: when compared to difficult/severe asthma, does mild asthma a) show phenotypic differences, b) have similar degrees of T2-high inflammation, and c) exhibit different prevalence of comorbidities and multimorbidity? We sought to answer these questions by assessing two real-world adult cohorts from the same geographical population in the South of England, UK; the Wessex AsThma CoHort of difficult asthma (WATCH) and a mild asthma cohort from the comparator arm of the Epigenetics of Severe Asthma (EOSA) study.¹⁶

Methods

Data collection methodology is identical for the difficult and mild asthma cohorts as briefly outlined below and published elsewhere.¹⁶ Data acquisition included detailed clinical, health and disease-related questionnaires, anthropometry, allergy and lung function testing, plus a collection of biological samples (blood and sputum in a subset). A modified version of the 2021 Global Initiative for Asthma (GINA) T2-high classification algorithm was used to define T2-high status as follows: 1) fractional exhaled nitric oxide (FeNO) ≥ 20 parts per billion (ppb) and/or 2) blood eosinophil count (BEC) $\geq 0.15 \times 10^9/L$ (to 1 decimal place as reported by University Hospital Southampton NHS Foundation Trust (UHSFT) pathology system), and/or 3) maintenance oral corticosteroid (mOCS) use, and/or 4) clinically allergen-driven disease (ie ≥ 1 positive aeroallergen on skin prick testing (SPT) and reported allergen trigger).² Of note, the sputum parameter (sputum eosinophilia $\geq 2\%$) from the GINA guideline was excluded from the T2-high definition due to limited sputum sample size for each cohort. Comorbidities are defined by conventional clinical diagnostic criteria ([Table S1](#)). Multimorbidity counts were calculated for participants with complete comorbidity data (difficult asthma, $n=378$; mild asthma, $n=65$). Participants were awarded 1-point for each comorbidity out of a total of 14 with equal weighting.

Sputum induction was performed in a subset of difficult asthma participants ($n=139$) at the UHSFT NIHR Clinical Research Facility, and mild asthma participants ($n=7$) at David Hide Asthma & Allergy Centre (DHAAC). Detailed sputum induction methodology is published elsewhere.¹⁶ Differential cell counts were obtained from sputum samples.

Difficult Asthma Cohort

The WATCH study is an ongoing “real-world” prospective observational study of patients under the UHSFT Difficult Asthma clinical service.¹⁶ Patients attending the Adult or Transitional Regional Asthma Clinic at UHSFT or satellite outreach clinics on the Isle of Wight and were managed with ‘high-dose therapies’ and/or ‘continuous or frequent use of oral steroids’, according to the British Thoracic Society (BTS) Adult Asthma Management guidelines 2016 (consistent with GINA asthma management steps 4 or 5), were eligible for inclusion in the WATCH study.^{2,16,17} Patients were only excluded if they were unable to provide informed consent or were not receiving treatment in keeping with these pre-determined thresholds.¹⁶ Data is recorded at enrolment as previously described with prospective longitudinal data captured in parallel to clinical follow-up appointments. Details of the study protocol are published elsewhere.¹⁶ Given their asthma severity, post-bronchodilator lung function tests were performed to prevent participants withholding regular inhaled therapy. Ethical approval was obtained from

the West Midlands – Solihull Research Ethics Committee (REC reference: 14/WM/1226). Here, we present data from the first 498 WATCH participants.

Mild Asthma Cohort

The EOSA study used identical data collection and assessments to the WATCH study. It is a cross-sectional observational study comparing clinical and endotypic features of participants with mild asthma to a subset with difficult/severe asthma from WATCH. The comparator mild asthma cohort from EOSA was established from the Isle of Wight Whole Population Birth Cohort (IOWBC, $n=22$),¹⁸ and from DHAAC clinics or the Isle of Wight (IOW) community ($n=45$), ensuring participants were broadly from the same geographical area as WATCH.¹⁸ All children born on IOW between January 1989 and February 1990 were eligible for inclusion in the IOWBC.¹⁸ Participants were eligible for inclusion in the EOSA study if on GINA asthma management step 1 or 2 and were excluded if unable to provide informed consent.² Sixty-seven participants with mild asthma were enrolled. Pre-bronchodilator lung function tests were performed in this cohort. The EOSA study received ethical approval from the South-Central Hampshire B – Southampton Research Ethics Committee (REC reference: 18/SC/0105).

Statistical Analysis

Statistical analysis was performed using SPSS 26 (NY, USA) and figures were generated in GraphPad Prism 9.1.4 (La Jolla, California, USA). For categorical variables, statistical significance was assessed using Chi-square test and Fisher's exact test for categorical variables where low cell counts were expected. Categorical variables are presented as frequencies and percentages. For continuous variables, the Shapiro–Wilk test of normality was used to determine if data sets are normally distributed. Mann Whitney *U*-tests were applied for non-parametric (skewed) continuous data with results displayed as median and interquartile ranges and unpaired *t*-test for parametric (normally distributed) continuous data with results displayed as mean and standard deviations. *P*-value of <0.05 was regarded as statistically significant.

Results

Demographic Characteristics

There was no significant difference in ethnicity between the mild and difficult asthma cohorts, with the majority of participants being Caucasian (98.6% vs 92.6%, $P = 0.0711$, [Table 1](#)). Both showed female predominance of $>60\%$ (62.7% vs 65.3%, $P>0.9999$). Mean age at study enrolment was significantly lower (by 12.5-years) in the mild asthma cohort compared to the difficult asthma cohort (38.3-years vs 50.8-years, $P<0.0001$). One-third of the mild asthma cohort were recruited from the IOWBC and were of similar age (median 28.8-years). Therefore, the mild asthma cohort was stratified by recruitment pool (ie IOWBC vs IOW clinic/community; [Table S2](#)) to determine if this affected the nature of mild asthma. Compared to mild asthma participants from the IOW clinic/community, the IOWBC participants were significantly younger (28.8-years vs 43.0-years, $P<0.001$) and had earlier asthma-onset (6.8-years vs 23.5-years, $P<0.001$), but did not differ in asthma duration. Additionally, IOWBC participants had significantly lower blood neutrophil counts ($3.4 \times 10^9/L$ vs $4.1 \times 10^9/L$, $P = 0.047$) and pre-bronchodilator (BD) forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) ratio (98.2% vs 100.7%, $P = 0.021$) and lower prevalence of gastro-oesophageal reflux disease (GORD) (36.4% vs 64.4%, $P = 0.038$) than IOW clinic/community participants ([Table S2](#)).

Body mass index (BMI) was significantly lower in mild asthma participants, within the overweight category, whilst difficult asthma participants were obese (27.8 kg/m² vs 30.9 kg/m², $P = 0.0002$, [Table 1](#)).

Mild asthma participants had significantly lower proportions of never smokers (47.8% vs 52.3%) and ex-smokers (31.3% vs 42.1%) but notably higher current smokers compared to the difficult asthma cohort (20.9% vs 5.6%, $P = 0.0001$; [Table 1](#)). There was no significant difference in the number of ever (ex-combined with current smokers) and never smokers.

Table 1 Comparison of Clinical Characteristics Between Difficult and Mild Asthma Cohorts

Clinical Characteristics	Difficult Asthma Cohort	Mild Asthma Cohort	P-value
Demographics			
Number of subjects, (N)	498	67	
Sex, % (n)			
Female	65.3 (325)	62.7 (44)	>0.9999
Male	34.7 (173)	37.3 (23)	
Ethnicity, % (n/N)			
Caucasian	92.6 (460/497)	98.6 (66)	0.0711
Non-Caucasian	7.4 (37/497)	1.4 (1)	
Age at enrolment, years	50.8 (15.7)	38.3 (11.9)	<0.0001
Body mass index, kg/m ²	30.9 (7.3)	27.8 (5.9)	0.0002
Smoking Status, % (n)			
Never	52.3 (260)	47.8 (32)	<0.5165 [#]
Ever	47.7 (237)	52.2 (35)	
Asthma History			
Age of asthma onset, years	23.7 (20.4)	17.7 (16.0)	0.1587
Asthma duration, years	26.4 (17.4)	20.7 (12.3)	0.0288

Notes: Categorical variables are represented as percentages (%) and frequencies (n/N); continuous variables as mean (SD). Fisher's exact test and [#]Chi-squared test were applied for categorical variables, Mann Whitney U-test for non-parametric data. P-values <0.05 are statistically significant (in bold).

Table 2 Comparison of Asthma Morbidity Between Difficult and Mild Asthma Cohorts

Clinical Characteristics	Difficult Asthma Cohort N=498	Mild Asthma Cohort N=67	P-value
Healthcare Utilisation			
Hospitalisations in past 12-months	0.7 (1.7)	0 (0)	<0.0001
OCS courses in past 12-months	3.5 (3.5)	0.1 (0.4)	<0.0001
Asthma-related ICU visits ever	0.8 (1.9)	0 (0.3)	<0.0001
Days lost from work in past 12-months	23.4 (48.9)	0.56 (2.5)	<0.0001

Notes: Categorical variables are represented as percentages (%) and frequencies (n/N); continuous variables as mean (SD). Fisher's exact test was applied for categorical variables, Mann Whitney U-test for non-parametric data. P-values <0.05 are statistically significant (in bold).

Abbreviations: OCS, oral corticosteroids; ICU, intensive care unit.

Asthma Morbidity, Medication and Physiological Characteristics

Compared to difficult asthma, mild asthma participants had significantly lower asthma morbidity at study enrolment including health-care utilisation, acute oral corticosteroid (OCS) courses (0.1 vs 3.5, $P<0.0001$) and lost work-days (0.56 days vs 23.4 days, $P<0.0001$) in the past 12-months (Table 2). Consistent with the treatment-based definition for their mild status, mean ICS dose was significantly lower (447.4 μ g BDP equiv. vs 2588.6 μ g BDP equiv., $P<0.0001$) and they had no need for mOCS or T2-targeted biologics compared to the difficult asthma cohort where 30.0% were on mOCS and

17.1% were on an asthma biologic at enrolment (Table S3). Furthermore, lung function was preserved in the mild asthma group (Figure 1 and Table S4). Conversely, difficult asthma participants had significantly lower post-BD FEV₁% predicted (%pred., 91.6% vs 91.5%, $P = 0.974$), FVC %pred. (98.2% vs 100.7%, $P = 0.457$), FEV₁/FVC ratio % (78.4% vs 73.5%, $P = 0.021$) and forced expiratory flow between 25% and 75% exhalation (FEF_{25-75%}) %pred. (79.8% vs 77.3%, $P = 0.436$), consistent with moderate airflow limitation (Figure 1 and Table S4).

A subgroup analysis of the difficult asthma cohort stratified by lung function was performed (Table S5) since, as indicated in Figure 1, a proportion of difficult asthma patients had relatively preserved lung function. Of 338 difficult asthma participants with available spirometry, 56.8% had a post-BD FEV₁ <80%pred. and showed higher male frequency (45.3% vs 22.6% $P < 0.0001$), older age at enrolment (54.8 years vs 47.8 years, $P < 0.0001$), longer asthma duration (30.4 years vs 22.3 years, $P = 0.0003$), fewer days lost from work (20.5 days vs 30.1 days, $P = 0.0061$), greater mOCS use (36.4% vs 21.8%, $P = 0.0065$), higher blood and sputum neutrophils ($6.4 \times 10^9/L$ vs $6.0 \times 10^9/L$, $P = 0.0149$ and 44.0% vs 34.1%, $P = 0.0427$, respectively) and *A. fumigatus* prevalence of structural disease (non-CF bronchiectasis 19.4% vs 6.3%, $P = 0.0006$ and COPD 17.8% vs 4.2%, $P = 0.0001$).

T2 Biomarkers and Inflammometry Characteristics

Blood neutrophil counts ($3.85 \times 10^9/L$ vs $6.27 \times 10^9/L$, $P < 0.0001$) and % sputum neutrophils (24.1% vs 43.1%, $P = 0.0450$) were significantly lower in mild asthma participants (Table 3). *Aspergillus fumigatus* (*A. fumigatus*)-specific immunoglobulin E (IgE) levels were also significantly lower in the mild asthma cohort (0.18 IU/L vs 1.46 IU/L, $P = 0.0041$) consistent with low *A. fumigatus* sensitisation. Furthermore, mild asthma participants had significantly higher FeNO levels (35.0 ppb vs 30.6 ppb, $P = 0.0053$). Other T2 biomarkers did not differ including BECs ($0.22 \times 10^9/L$ vs $0.26 \times 10^9/L$, $P = 0.5185$), total IgE levels (267.1 IU/L vs 298.2 IU/L, $P = 0.5475$) and % sputum eosinophils (6.0% vs 8.5%, $P =$

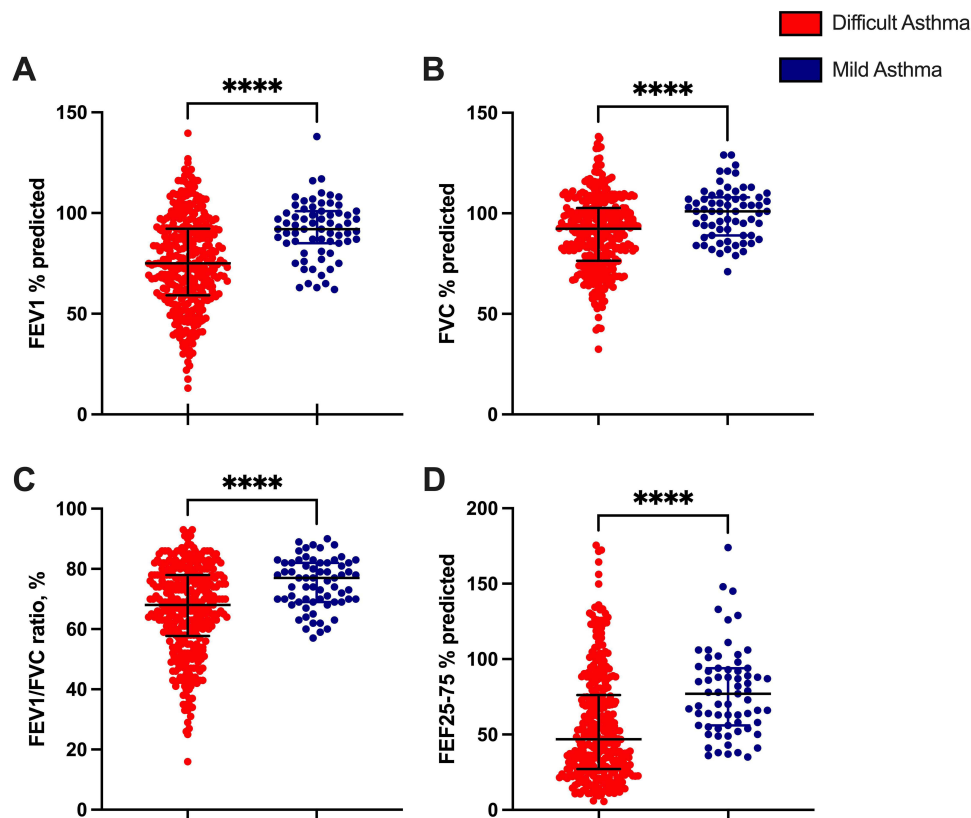


Figure 1 Lung function characteristics between the difficult and mild asthma cohorts. Post-BD spirometry values shown for difficult asthma and pre-BD spirometry values shown for mild asthma. (A) Clinic FEV₁ % predicted., (B) Clinic FVC % predicted, (C) Clinic FEV₁/FVC ratio %, (D) Clinic FEF_{25-75%} % predicted. Data presented as median ± interquartile range. **** $P < 0.0001$. A full breakdown of the results and statistics is available in Table S4.

Abbreviations: FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; FEF 25–75%, forced expiratory flow between 25% and 75% exhalation.

Table 3 Comparison of T2 Biomarkers and Inflammometry Between Difficult and Mild Asthma Cohorts

Clinical Characteristics	Difficult Asthma Cohort N=498	Mild Asthma Cohort N=67	P-value
Blood Inflammometry			
Blood eosinophil count, $\times 10^9/L$	0.26 (0.33)	0.22 (0.14)	0.5185
Blood neutrophil count, $\times 10^9/L$	6.27 (2.85)	3.85 (1.83)	<0.0001
Total IgE, IU/L	298.2 (595.4)	267.1 (448.9)	0.5475
A.fumigatus-specific IgE, IU/L	1.46 (7.40)	0.18 (0.58)	0.0041
Airway Inflammometry			
FeNO, ppb	30.6 (34.0)	35.0 (27.3)	0.0053
Sputum eosinophils, % N	8.5 (14.1) 140	6.0 (8.0) 7	0.7636
Sputum neutrophils, % N	43.1 (25.0) 140	24.1 (23.8) 7	0.0450
T2-high Inflammation			
GINA T2-high status, % (n/N)	93.5 (435/465)	88.1 (59)	0.1238
Atopy status			
Number of positive SPT	2.9 (3.0)	3.4 (2.9)	0.1352
Subjects with ≥ 1 positive SPT, % (n/N)	68.3 (265/388)	73.8 (48/65)	0.4684

Notes: Categorical variables are represented as percentages (%) and frequencies (n/N); continuous variables as mean (SD). Fisher's exact test was applied for categorical variables, and Mann Whitney U-test for non-parametric data. P-values <0.05 are statistically significant (in bold).

Abbreviations: IgE, immunoglobulin E; A.fumigatus, Aspergillus fumigatus; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; T2, type 2; GINA, Global Initiative for Asthma; SPT, skin prick test.

0.7636). GINA T2-high status did not significantly differ between cohorts (88.1% vs 93.5%, $P = 0.1238$); both showed overwhelming T2-high status. Lastly, no significant differences were seen in atopic status (ie number of positive SPTs and subjects with ≥ 1 positive SPT, 73.8% vs 68.3%, $P = 0.4684$). When comparing atopy based on allergy skin prick tests, the mild asthma cohort showed greater Cladosporium herbarum (70.8% vs 12.3%, $P < 0.0001$) and Dermatophagoides farinae (37.0% vs 56.9%, $P = 0.0036$) sensitisation ([Table S6](#)). As expected, the difficult asthma cohort showed greater A. fumigatus sensitisation (4.6% vs 15.8%, $P = 0.0183$)

Comorbidity and Health and Disease-Related Questionnaire Characteristics

Several comorbidities were common to both cohorts (mild vs difficult asthma) including GORD (55.2 vs 65.1, $P = 0.0068$), dysfunctional breathing (31.3 vs 48.6, $P = 0.6024$), inducible laryngeal obstruction (6.0 vs 14.6, $P = 0.0554$), and sulphite sensitivity (7.5 vs 7.8, $P > 0.9999$, [Figure 2](#) and [Table S7](#)). Difficult asthma participants showed significantly greater prevalence of obesity (31.3 vs 48.6, $P = 0.0089$), nasal polyposis (9.1 vs 23.4, $P = 0.0064$) and salicylate sensitivity (7.5 vs 25.0, $P = 0.0009$). Structural lung diseases including allergic bronchopulmonary aspergillosis/severe asthma with fungal sensitisation (ABPA/SAFS), non-cystic fibrosis bronchiectasis and chronic obstructive pulmonary disease (COPD) were present in the difficult asthma cohort but absent in the mild asthma cohort ([Table S7](#)). In contrast, mild asthma participants had a significantly higher prevalence of rhinitis (83.6% vs 67.6%, $P = 0.0068$) and eczema (49.3% vs 25.8%, $P = 0.0001$). Over 50% of the mild asthma cohort had depression and anxiety, which was significantly

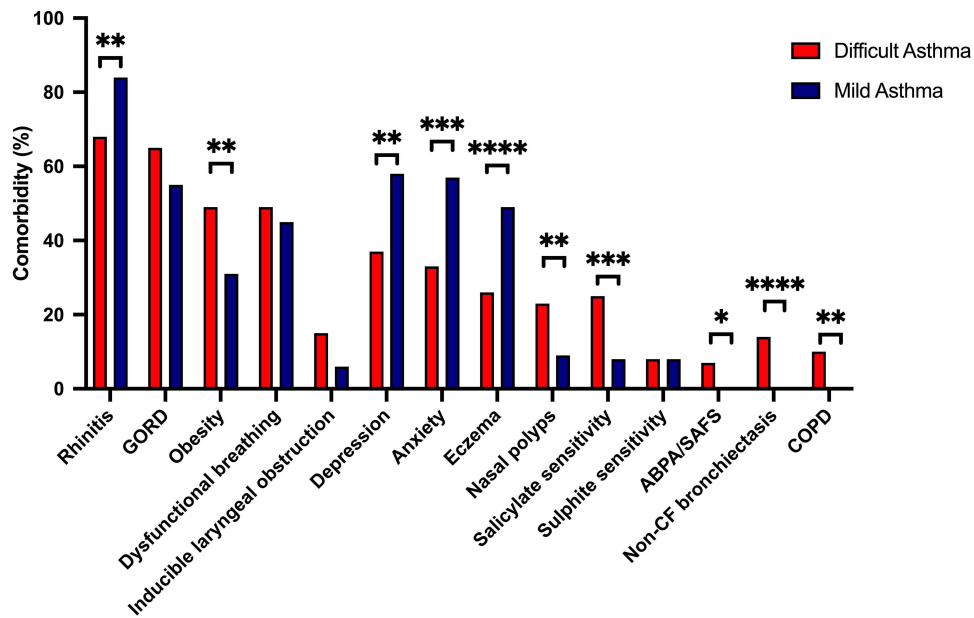


Figure 2 Comparison of physician and/or clinically diagnosed comorbidity characteristics between the difficult and mild asthma cohorts. Comorbidities are represented as percentages (%). Fisher’s exact test was applied for categorical variables. *P <0.05, **P <0.01, ***P <0.001, ****P <0.0001. A full breakdown of the results and statistics is available in [Table S7](#).

Abbreviations: GORD, gastro-oesophageal reflux disease; ABPA/SAFS, allergic bronchopulmonary aspergillosis/severe asthma with fungal sensitisation; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease.

greater than that observed in difficult asthma participants (36.5% and 32.7% respectively) ([Figure 2](#) and [Table S7](#)). Both cohorts had a median multimorbidity count of 4.0 ([Table S7](#)).

Table 4 Comparison of Asthma and Comorbidity-Related Questionnaire Characteristics Between Difficult and Mild Asthma Cohorts

	Difficult Asthma Cohort N=498	Mild Asthma Cohort N=67	P-value
Asthma Control & Health-related QoL			
ACQ-6 score	2.50 (1.35)	0.72 (0.70)	<0.0001
ACQ-6 score ≥ 1.50, % (n/N)	76.9 (357/464)	16.7 (11/66)	<0.0001
EQ5D-5L Health Today VAS, %	63.1 (20.3)	84.2 (14.7)	<0.0001
SGRQ total score	50.7 (21.0)	17.7 (13.2)	<0.0001
Comorbidity-related Questionnaires			
SNOT22 score	35.1 (21.4)	21.3 (17.9)	<0.0001
Hull Cough Hypersensitivity score	26.2 (15.6)	11.6 (10.2)	<0.0001
Nijmegen score	22.1 (12.4)	15.1 (10.0)	<0.0001
HADS-D score	5.4 (4.4)	2.7 (2.6)	<0.0001
HADS-A score	7.0 (4.7)	7.3 (4.2)	0.4392

Notes: Disease-related questionnaire scores are represented as mean (SD). Fisher’s exact test was applied for categorical variables and Mann Whitney U-test for non-parametric data. P-values <0.05 are statistically significant (in bold).

Abbreviations: QoL, quality of life; ACQ-6, asthma control questionnaire-6; EQ5D-5L, EuroQoL5D-5L; VAS, visual analogue scale; SGRQ, St George’s respiratory questionnaire; SNOT22, sino-nasal outcome test-22; HADS-D, hospital anxiety and depression scale-depression component; HADS-A, hospital anxiety and depression scale-anxiety component.

Several differences were observed in health and disease-related questionnaire scores (Table 4). Mean Asthma Control Questionnaire-6 (ACQ-6) score was significantly lower in mild asthma (0.72 vs 2.50, $P<0.0001$), whereas >76% of difficult asthma participants exhibited poor asthma control (defined by an ACQ-6 score ≥ 1.5 , 16.7% vs 76.9%, $P<0.0001$). Health-related quality of life (HRQoL) outcome measures (ie EuroQoL5D-5L visual analogue scale (EQ5D-5L VAS) and St George's Respiratory Questionnaire (SGRQ) total score) showed significantly better HRQoL (ie higher EQ5D-5L VAS, 84.2% vs 63.1%, $P<0.0001$ and lower SGRQ scores, 17.7 vs 50.7, $P<0.0001$) in mild asthma participants compared to the difficult asthma cohort. In addition, significantly lower scores for the Sino-Nasal Outcome Test-22 (SNOT22, >7 suggests prevalence of rhinosinusitis, 21.3 vs 35.1 $P<0.0001$), Hull Cough Hypersensitivity (>13 suggests GORD-related cough, 11.6 vs 26.3, $P<0.0001$) and Nijmegen questionnaires (>23 suggests dysfunctional breathing, 15.1 vs 22.1, $P<0.0001$), and Hospital Anxiety and Depression Scale Depression component (HADS-D, ≥ 11 suggests depression, 2.7 vs 5.4, $P<0.0001$) were observed in mild asthma participants compared to the difficult asthma cohort (Table 4). Of note, difficult asthma participants had clinically significant SNOT22, Hull Cough Hypersensitivity and Nijmegen questionnaires scores that were all above the pre-defined cut-off. No significant difference was observed in the HADS-Anxiety component (HADS-A) score (≥ 11 suggest anxiety), contrary to physician diagnosed anxiety, which was more prevalent in mild asthma (Figure 2 and Table S7).

Discussion

We undertook one of the most comprehensive assessments of the phenotypic nature of mild asthma and compared this with more difficult disease. The mild asthma phenotype was predominantly female, atopic, and associated with early-onset disease, T2-high inflammation, raised FeNO and preserved lung function. Most strikingly, some comorbidities, but not multimorbidity, were significantly higher in mild asthma, particularly depression and anxiety. When compared to difficult asthma, mild disease showed similar female predominance, atopy and T2-high status, but better lung function, higher FeNO level, lower peripheral blood/airway neutrophil counts and higher prevalence of current smoking (Figure 3).

NRAD found that 58% of those who died from asthma were being treated for either mild or moderate disease.¹⁵ In a large observational study, 8% of mild asthma participants developed severe asthma over a 10-year period.¹⁹ Thus,

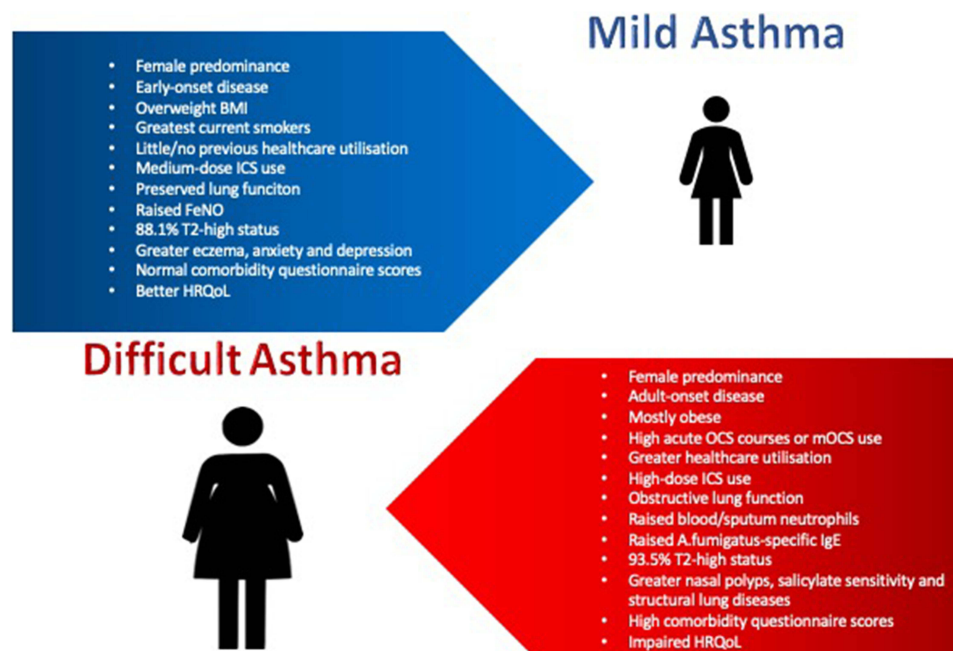


Figure 3 Summary of mild and difficult asthma phenotypes. Early-onset <18 years, Adult onset ≥ 18 years.

Abbreviations: BMI, Body mass index; ICS, inhaled corticosteroid; FeNO, fractional exhaled nitric oxide; T2, type 2; HRQoL, health-related quality of life; OCS, oral corticosteroid; mOCS, maintenance oral corticosteroids; A. fumigatus, Aspergillus fumigatus; IgE, Immunoglobulin E.

improving our understanding of the mild asthma phenotype is crucial to risk stratify the asthma population to prevent future disease progression.

Baseline demographics in our mild asthma cohort were consistent with existing knowledge showing female predominance, overweight BMI and an early age of disease-onset.⁵⁻⁹ Asthma has consistently been shown to be a female-predominant disease in adulthood but the literature varies for early-onset asthma. The Severe Asthma Research Program (SARP) III cohort found male predominance in childhood-onset asthma regardless of severity.⁶ Female asthma predominance with increasing age is thought to be down to differential effects of male and female sex hormones during reproductive years.²⁰ Additionally, the prevalence of obesity in asthma populations is known to increase with age and is associated with more severe disease.²¹

Our study found a significantly higher proportion of current smokers in the mild asthma cohort (20.9%) compared to the difficult asthma cohort (5.6%). Of note, percentages of ever-smokers were not significantly different between asthma cohorts. While we have no data on smoking duration, we might assume that both cohorts started smoking at a similar age, usually adolescence. Eisner et al found that in ever-smokers with asthma, the median time to smoking cessation was 17-years perhaps explaining the lower number of current smokers and higher number of former smokers in our difficult asthma cohort who had an older age at study enrolment.²² Alternatively, this may reflect increased motivation to stop smoking in the difficult asthma group given their greater asthma morbidity. Smoking in asthma has been associated with accelerated lung function decline and greater fixed airflow obstruction.²³⁻²⁵ One study reported a 10.1% decline in FEV₁ over 10-years in non-smokers with asthma versus a 17.8% decline in smokers with asthma, suggesting a synergistic effect.²⁴ Smoking in people with asthma has also been shown to increase neutrophil counts and lower sputum eosinophils, suggesting a shift in the inflammatory phenotype, which may have implications on clinical disease manifestations.²⁵ Smoking can also reduce efficacy of ICS in mild asthma, meaning higher doses are needed to achieve asthma control.²⁶ Chaudhuri et al showed significant improvements in FEV₁ and asthma control as early as 1-week post-smoking cessation.²⁷ This suggests a reversible component to the harmful effects of cigarette smoking and a potentially modifiable risk factor for disease progression. Focusing efforts on smoking cessation within primary care may therefore prevent future morbidity in mild asthma.

Our study demonstrated significant comorbidity in mild asthma. Comparable multimorbidity burden was observed in the two cohorts. Some comorbidities were similarly prevalent in mild and difficult asthma; GORD, dysfunctional breathing and inducible laryngeal obstruction. However, rhinitis, eczema, depression and anxiety were more prevalent in mild asthma. Difficult asthma was associated with greater prevalence of obesity,^{5,6,21} COPD,^{7,21} nasal polyps (7.23), salicylate sensitivity (23.30) and ABPA/SAFS.²⁸ We previously demonstrated that *A. fumigatus* sensitisation is associated with more severe airways disease, greater morbidity, impaired lung function and structural airway damage.²⁸ Early screening for *A. fumigatus* sensitisation should also be incorporated into the assessment of mild asthma.

One striking feature was that >50% of our mild asthma cohort suffered from psychological comorbidities, namely depression and anxiety, which has not been widely reported before with most prior studies showing significant psychological burden in patients with difficult/severe asthma.²⁹⁻³¹ Rimington et al looked at the relationship between anxiety and depression and asthma morbidity in patients in a primary care setting.³² Just over 70% of their cohort were on BTS step 1 or 2 for their asthma management suggestive of milder disease.³² They demonstrated a weak correlation between lung function decline and asthma symptom burden but much stronger correlations with HADS-A and HADS-D scores suggesting the assessment of a patient's asthma control in primary care is complex and under-acknowledged psychological morbidity may lead to increased asthma symptom reporting.³²

Whilst the prevalence of depression was higher in the mild asthma cohort, depression severity (as measured by HADS-D scores) was significantly higher in the difficult asthma cohort. Fong et al suggested a severity-graded relationship between HADS-A and HADS-D and difficult asthma outcomes.³¹ They reported association of anxiety and/or depression in difficult asthma with poorer asthma control, more lost work-days, higher Nijmegen scores, and greater FeNO.³¹ Therefore, a worsening psychological state may either drive asthma severity or be a consequence of high disease burden feeding into the complexities of asthma multimorbidity. Earlier psychological interventions in primary care may minimise the multimorbidity burden in mild asthma and potentially interrupt pathways to more complex disease.

Comorbidity in difficult asthma is strongly associated with poorer asthma control, greater symptom burden, frequent exacerbations, mOCS dependency and non-adherence to asthma treatment.^{29-31,33,34} We found that severity of

comorbidities based on questionnaire scores was lower and HRQoL was better in mild asthma compared to difficult disease. To et al found 6% of hospitalisations were related to asthma and asthma comorbidity in their population-based cohort study of 12 million residents in Ontario, Canada.³³ Optimising comorbidity in asthma management is well acknowledged in severe asthma services. It has recently been proposed that we shift our focus to the concept of complex asthma as a multimorbidity “Difficult Breathing Syndrome” rather than a severe asthma-centric state, recognising the constellation of conditions with multiple “treatable traits” contributing to difficult asthma.³⁴ Whether such notions are relevant to mild asthma too is worth consideration.

The importance of distinguishing T2-high from T2-low asthma is well established with a growing focus on use of T2-targeting biologics in difficult/severe asthma. Definitions of T2-high status vary. For example, in the ALLIANCE cohort, T2-high inflammation was defined by BEC ≥ 360 cells/ μL and serum IgE ≥ 0.7 kU/L derived from blood counts above the 90th percentile in healthy participants.³⁵ Alternatively, in the UK severe asthma registry, biomarker cut-offs of FeNO >25 ppb BEC >150 cells/ μL were used, based on Phase 3 trials showing little efficacy of biologics below these thresholds.³⁶ They reported greater T2-high predominance in their severe asthma registry (mean BECs $0.3 \times 10^9/\text{L}$, FeNO 39ppb, and IgE 181 IU/mL).³⁶ Previous work from our group highlighted the importance of longitudinal BEC monitoring and unmasked a high proportion of T2-high severe asthma patients.³⁷

Atopy prevalence and coexisting allergic rhinitis and eczema observed in our mild asthma cohort has been described elsewhere.^{5–9} However, the T2-high inflammatory phenotype is less well described in mild asthma. Previous studies in mild asthma suggested a T2-high phenotype prevalence of 50%.³⁸ We found comparable T2-high biomarker signals between mild and difficult asthma cohorts in relation to BECs and total IgE levels, however FeNO levels were significantly higher in mild asthma participants. These results may be confounded by higher use of ICS and mOCS in the difficult asthma cohort (2588.6 μg BDP equiv. vs 447.4 μg BDP equiv. in mild asthma). Similarly, blood and sputum neutrophil counts were significantly higher in the difficult asthma cohort, likely reflecting the pathophysiological consequences of higher steroid use as previously described.⁷ In turn, associations of blood and sputum neutrophilia with difficult asthma were found to be relevant only for those with more severe disease as defined by impaired lung function. Aligned to an overwhelmingly T2-high status, this indicates that a proportion of such patients show a mixed inflammatory response. Nonetheless, 88.1% of the mild asthma cohort also had a GINA T2-high status, suggesting a greater degree of T2-inflammation in mild asthma than previously described.^{2,38} This emphasises the importance of early ICS prescribing in all asthma patients regardless of disease severity, as reflected in recent international guidelines.²

Our study had limitations including small sample size of the mild asthma cohort. The IOWBC recruitment pool meant a proportion of mild asthma participants were all of similar age, but this was the minority, and sub-analysis suggested no significant differences in phenotypic traits. Data collection was also limited with respect to smoking pack years, medication adherence and small sputum sample size. Similarly, lung function characteristics compared pre-bronchodilator values in the mild asthma cohort with post-bronchodilator values in the difficult asthma cohort, reflecting the real-world limitation of withholding regular inhaler therapy in a high-risk population. A key strength of our study is the identical methodology used in both cohorts allowing detailed comparisons. Moreover, this study provides one of the most comprehensive assessments of mild asthma and its phenotype. Replication in other diverse ethnic populations is warranted given both cohorts were mainly Caucasian. Similarly, validation of our findings in other mild asthma cohorts is essential but currently there are no populations with similar data variables readily available for use as comparators.

In conclusion, this study extensively characterised the phenotypic nature of the EOSA mild asthma cohort. Mild asthma is characterised as a female-predominant, early-onset, significantly multimorbid disease with a high prevalence of current smokers, atopy and T2-high inflammation. The nature of mild asthma has not previously been well described. Identifying a mild asthma phenotype with the characterisation presented warrants further attention in clinical practice as it affords a framework with which to better understand mild asthma and offers steps to address factors that might limit potential progression to more complex severe diseases including early smoking cessation intervention and addressing multimorbidity.

Abbreviations

A. fumigatus, Aspergillus fumigatus; ABPA, Allergic bronchopulmonary aspergillosis; ACQ-6, Asthma control questionnaire-6; BD, Bronchodilator; BDP equiv., Beclomethasone dipropionate equivalent/day; BEC, Blood eosinophil

count; BMI, Body mass index; BRC, Biomedical Research Centre; BTS, British Thoracic Society; DHAAC, David Hide Asthma & Allergy Centre; COPD, Chronic obstructive pulmonary disease; EOSA, Epigenetics of Severe Asthma; EQ5D-5L, EuroQoL 5D-5L questionnaire; FeNO, Fractional exhaled nitrogen oxide; FEF_{25-75%}, Forced expiratory flow between 25 and 75% exhalation; FEV₁, Forced expiratory volume in 1 s; FVC, Forced vital capacity; GINA, Global Initiative for Asthma; GORD, Gastro-oesophageal reflux disease; HADS-A, Hospital anxiety and depression scale – anxiety subscale; HADS-D, Hospital anxiety and depression scale – depression subscale; HRQoL, Health-related quality of life; ICS, Inhaled corticosteroid; ICU, Intensive care unit; IgE, Immunoglobulin E; IOW, Isle of Wight; IOWBC, Isle of Wight Whole Population Birth Cohort; LABA, Long-acting beta-agonist; mOCS, Maintenance oral corticosteroid; NIHR, National Institute for Health and Care Research <https://www.nihr.ac.uk/>; NRAD, National Review of Asthma Deaths; OCS, Oral corticosteroid; ppb, Parts per billion; SAFS, Severe asthma with fungal sensitisation; SGRQ, St George's respiratory questionnaire; SNOT22, Sino-nasal outcome test-22; SPT, Skin prick test; T2, Type 2; UHSFT, University Hospital Southampton NHS Foundation Trust; VAS, Visual analogue scale; WATCH, Wessex AsThma CoHort of difficult asthma.

Data Sharing Statement

We confirm that data accessed complied with relevant data protection and privacy regulations *with reference to the General Data Protection Regulations 2018*.

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Disclosure

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