



New Perspectives on Difficult Asthma; Sex and Age of Asthma-Onset Based Phenotypes

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Title: New Perspectives on Difficult Asthma; Sex and Age of Asthma-Onset Based

Phenotypes

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ABSTRACT:

Background: Asthma is a diverse condition that differs with age and sex. However, it remains unclear how sex, age of asthma-onset, and/or their interaction, influence clinical expression of more problematic adult “difficult” asthma.

Objectives: To better understand the clinical features of difficult asthma within a real-world clinical setting using novel phenotypic classification, stratifying subjects by sex and age of asthma-onset.

Methods: Participants in a longitudinal difficult asthma clinical cohort study (Wessex AsThma CoHort of difficult asthma; WATCH), United Kingdom, (n=501) were stratified into 4 difficult asthma phenotypes based on sex and age of asthma-onset (early<18-years or adult≥18-years) and characterised in relation to clinical and pathophysiological features.

Results: The cohort had more female participants (65%) but had similar proportions of participants with early or adult-onset disease. Early-onset female disease was commonest (35%), highly atopic, with good spirometry and strong associations to some physical comorbidities but highest psychophysiologic comorbidities. Adult-onset females also had considerable psychophysiologic comorbidities, highest obesity, and were least atopic. Amongst male subjects, proportionately more had adult-onset disease. Early-onset male disease was rarest (14%) but associated with worst lung function, high smoking, atopy and fungal sensitisation. Despite shortest disease duration, adult-onset males had highest use of maintenance oral corticosteroid, poor lung function and highest FeNO in spite of highest smoking prevalence.

Conclusion: This study shows that sex, age of asthma-onset, and their interactions influence different clinical manifestations of difficult asthma and identifies a greater risk for lung

70 function loss and oral corticosteroid dependency associated with smoking in adult-onset male
 71 subjects.

72 **Hig**

- **What is already known about this topic?**

Asthma shows differing sex associations across the life-course, with male predominance in childhood switching to female predominance in adulthood. How such disease associations relate to more difficult asthma in adulthood is unclear.

- **What does this article add to our knowledge?**

This real-world study shows that stratifying difficult asthma by sex and age of asthma-onset identifies clinically important phenotypes that are currently poorly recognised including more common early-onset female, and more severe adult-onset male, difficult asthma.

- **How does this study impact current management guidelines?**

This study describes clinical features of difficult asthma from a new phenotypic perspective. By characterising these novel phenotypes, and their multimorbid nature, this study can guide better identification and management of patients with difficult asthma.

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89 : age of onset, comorbidity, difficult asthma, lung function, phenotypes, sex, smoking

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91 ABBREVIATIONS:

- 92 ABPA Allergic Bronchopulmonary Aspergillosis
- 93 ACQ Asthma Control Questionnaire
- 94 BD Bronchodilator
- 95 BDP Beclomethasone
- 96 BMI Body Mass Index
- 97 CF Cystic Fibrosis
- 98 COPD Chronic Obstructive Pulmonary Disease
- 99 DLCO Diffusing Capacity of Lung for Carbon Monoxide
- 100 EGPA Eosinophilic Granulomatosis with Polyangitis
- 101 FeNO Fractional Exhaled Nitrogen Oxide
- 102 FEF 25-75% Forced expiratory flow between 25-75% exhalation
- 103 FEV1 Forced Expiratory Volume in 1 second
- 104 FVC Forced Vital Capacity
- 105 GORD Gastroesophageal reflux
- 106 ILO Intermittent Laryngeal Dysfunction
- 107 HADS Hospital Anxiety and Depression Score
- 108 HRCT High resolution computed tomography
- 109 ICU Intensive Care Unit
- 110 IgE Immunoglobulin E
- 111 OCS Oral corticosteroids
- 112 KCO Diffusing Capacity of Lung for Carbon Monoxide corrected for alveolar volume
- 113 SAFS Severe Asthma with Fungal Sensitisation
- 114 SPT Skin prick test
- 115 SNOT 22 Sinonasal Outcome Test

INTRODUCTION

Asthma is a diverse condition with different characteristics across the life-course. It is more prevalent and problematic in males during childhood but following puberty becomes a predominantly female symptomatic disease in adulthood¹⁻⁵. Potential contributing factors to these age-related changing sex associations include remission of childhood asthma in boys and asthma development in adolescent girls⁴. Postulated mechanisms for these processes include protective effects of male (androgenic) sex hormones and potentially sex-specific deleterious effects of female sex hormones⁶⁻⁸. Such concepts are supported by changes in asthma prevalence with menarche⁸⁻⁹ and menopause⁸⁻¹⁰. Additional important contributory mechanisms include differences in innate and adaptive immune responses in males and females during reproductive life¹¹. Other environmental or lifestyle factors, like smoking exposure/habit, may plausibly influence these disease patterns too⁵. In that context, some studies have demonstrated associations between smoking and asthma in females but not males¹², while others have associated older onset asthma with male smokers¹³. Conversely, obesity shows clear association to incident asthma in females across the life-course¹⁴.

Studies have shown both childhood and adult-onset patterns of adult severe asthma¹⁵⁻¹⁸, but it is widely regarded that adult severe asthma is commoner in females, with severe asthma cohort studies consistently showing female predominance¹⁵⁻¹⁸. Contrary to traditional understanding of asthma-sex associations across the life-course, studies also point to both clusters of childhood-onset female asthma and adult-onset male severe asthma⁵. However, it remains unclear how sex and age of asthma-onset influence models of the more commonly encountered clinical challenge of adult difficult asthma.

Most asthmatics can be treated effectively but 5-10% suffer from “difficult asthma”, with poor disease control and disproportionately high socio-economic costs¹⁹⁻²¹. Difficult asthma describes asthma in which co-morbidities, inadequate treatment, suboptimal inhaler technique

and/or poor adherence impede good asthma control. This broad definition also encompasses a subset of patients with truly severe, treatment refractory, asthma that remain sub-optimally controlled despite optimised treatment of both asthma and contributory factors¹⁹⁻²⁴. Better insight of how sex and age of asthma-onset relate to difficult asthma could support more personalised characterisation of that problematic condition, offering a path to better outcomes. Here we describe influences of sex and age of onset on the nature of adult difficult asthma within a clinical cohort; the Wessex AsThma CoHort of difficult asthma (WATCH) Study.

METHODS

WATCH Data Collection

WATCH is an ongoing clinical cohort of patients with difficult asthma based at University Hospitals Southampton NHS Foundation Trust (UHSFT), Southampton, United Kingdom (UK). All patients managed with British Thoracic Society Step “high dose therapies” and/or “continuous or frequent use of oral corticosteroids”²⁵ in the Adult or Transitional Regional Asthma Clinic at UHSFT are invited to participate. Briefly, research data capture is aligned with the extensive clinical characterisation required of a commissioned National Health Service (NHS) Specialist Centre for Severe Asthma²⁶. Data acquisition at enrolment includes detailed clinical, health and disease-related questionnaires, anthropometry, allergy skin prick testing (SPT), lung function testing, radiological imaging (in a subset) and collection of biological samples (blood, and urine). Brief longitudinal updates of data are obtained annually. A detailed outline of study protocol and methodology is published elsewhere²⁷. The study was approved by West Midlands – Solihull Research Ethics Committee (REC reference: 14/WM/1226). Here, we present data at enrolment from the first 501 WATCH patients.

Statistical Analysis

Statistical analysis was performed using SPSS 25 (NY, USA), GraphPad Prism 7 (La Jolla California, USA) and R (Vienna, Austria). Quantitative variables are presented as mean plus standard deviation and categorical variables as frequencies (percentages).

We defined four phenotypes using two binary variables: sex (male, female) and age of asthma diagnosis (early <18years, adult \geq 18 years). Age of asthma diagnosis was highly correlated with age of reported disease onset (see online repository text). The interaction between sex and age of diagnosis for quantitative variables was tested with a two-way ANOVA. If the interaction was significant, a one-way ANOVA was applied to each factor separately. The same strategy was applied to both count and binary variables but using

negative binomial models and logistic models, respectively. These analyses were realised with R software, using the *glm* function for ANOVA and logistic regression models and *glm.nb* for negative binomial models. Data modelling checks were undertaken for model verification. If the one-factor model was better than two-factors model (by stepwise selection), the significant effect was shown from the one-factor model. Significant effects are presented as a difference of means for quantitative variables, rate ratio for count variables, and odds ratio for binary variables, each with 95% confidence intervals. A p value of <0.05 was regarded statistically significant.

RESULTS

Representativeness of WATCH Cohort to the Difficult Asthma Clinic

Patients not enrolled in WATCH but attending the UHSFT Difficult Asthma clinic were compared to enrolment data from the WATCH cohort (online repository text; Table E1). There were no statistically significant differences between WATCH and non-WATCH patients for sex or smoking status but median age of WATCH patients was 1-year younger. There was no statistically significant difference for patients receiving biological therapies but maintenance oral corticosteroid (OCS) use was significantly higher in WATCH patients.

WATCH Cohort Description

Of 501 cohort subjects, 2/3 (65.3%) were female with a mean study enrolment age of 50.6-years and age of asthma-onset of 23.6-years (Table 1). The commonest physical comorbidities ever reported (diagnostic definitions; Table E2) were rhinitis, GORD (gastro-oesophageal reflux disease) and obesity with high prevalence also of psychophysiologic (anxiety, depression, dysfunctional breathing and intermittent laryngeal dysfunction) comorbidity. Half the cohort (47.6%) had ever smoked, (current smokers = 5.6%). At enrolment, in the preceding 12 months, 43.6% of the cohort had required multiple (≥ 3) courses of rescue or increased maintenance OCS, 29.9% were on maintenance OCS (mean dose = 12.0 mg/day), and 29.0% had been hospitalised due to asthma. Furthermore, 17.6% were on biological asthma therapies and 28.2% had ever had an Intensive Care asthma admission (Table 1). Mean ACQ6 (Asthma Control Questionnaire) was 2.5. Two-thirds (68.0%; 266/391) were atopic on SPT. Mean post-bronchodilator FEV1/FVC ratio was obstructive at 66.4%.

Age of Onset and Sex Stratified Analyses

Demographic Characteristics

The cohort was equally split between early (<18-years) and adult (\geq 18-years) onset disease (48.7% and 51.3% respectively). Age at study enrolment was significantly greater in males than females regardless of age of asthma-onset (Table 2) while females were more predominant both in early (71.3%) and adult-onset disease (59.5%). Females had proportionately more early (53.2%) than adult-onset disease (46.8%) but males had more adult (59.8%) than early-onset disease (40.2%). When stratified by age of onset and sex into four groups, 34.7% were early-onset female, 30.5% were adult-onset female, 20.8% were adult-onset male and 14% were early-onset male.

Males were younger at diagnosis than females among early-onset disease but older among adult-onset disease. Males were also significantly taller and heavier than female counterparts regardless of age of onset (Table E3). Age of onset and sex did not separately affect BMI (Body Mass Index) though their interaction led to significantly higher BMI in female than male adult-onset asthma (32.5 v 29.1). Female adult-onset subjects had highest obesity prevalence (Table 2). Obesity ($\text{BMI} \geq 30$) was significantly affected by age of onset with a sex stratified interaction. While obesity prevalence was significantly lower in adult than early-onset asthmatic males it showed opposing patterns in females. Ever smoking history was significantly higher for both male and adult-onset status.

Comorbidity Characteristics

Rhinitis, GORD and sleep apnoea were equally common across the 4 groups and did not differ significantly by sex or age of asthma-onset (Table 3). Conversely, fungal sensitive disease (Allergic Bronchopulmonary Aspergillosis [ABPA]/Severe Asthma with Fungal Sensitivity [SAFS]) was significantly greater in males than females and early-onset than adult-onset disease. Clinically diagnosed non CF-bronchiectasis was significantly associated

with male sex regardless of age of asthma-onset. Radiological bronchiectasis or emphysema on HRCT scan did not show significant association to sex or age of onset (Table 4).

Several physical (salicylate [Non-Steroidal Anti-Inflammatory drug; NSAID] sensitivity, sulphite sensitivity, latex allergy) and psychophysiologic (depression, anxiety, dysfunctional breathing and intermittent laryngeal dysfunction) disorders were significantly associated with female sex regardless of age of asthma-onset. History of bariatric surgery was also significantly associated with female sex (overall prevalence; 1.65%, sex difference $p = 0.007$). Regardless of sex, significant age of onset associations were noted for eczema (more prevalent in early-onset asthma), COPD and eosinophilic granulomatosis with polyangiitis (EGPA) (both more prevalence in adult-onset asthma).

Objective Disease Phenotype Characteristics

Atopic status and Total IgE were significantly influenced by age of onset, being greatest in early-onset groups with no sex differences (Table 4). Conversely, skin test positivity to aspergillus was significantly associated with male sex regardless of age of onset. Peripheral eosinophil counts at enrolment did not differ significantly by age or sex but FeNO was significantly higher in adult-onset groups regardless of sex.

Sex significantly influenced post-bronchodilator (BD) spirometry with significantly lower FEV1, FVC, and FEV1/FVC predicted values in males than females (Figure 1 and Table E4).

A significant interaction between sex and age of onset ($p = 0.002$) was shown for both FEV1 and FVC which were higher for adult-onset compared to early-onset males but no different in females (Figure 1; Table E4). Neither age or sex affected transfer factor (DLCO/KCO) measures at enrolment (Table 4). We found no differences in FEV1 between ever smokers and never smokers within each phenotype based on reported current, past or never smoking status. Thus, whilst smoking prevalence differed between phenotypes, the simple parameter

of ever smoking status did not significantly account for differences in FEV1 between these groups.(Figure 2; full data in Table E5).

Disease-Related Questionnaire Characteristics

ACQ6 was significantly affected by interaction of sex and age of onset with lowest (best) values in adult-onset males. HADS (Hospital Anxiety and Depression Score), Nijmegen score, Hull cough score and SNOT-22 score were significantly higher in females regardless of age of asthma-onset (Table 5).

Treatment & Healthcare Utilisation Characteristics

Maintenance OCS use was highest in male adult-onset disease reflecting a significant interaction between male sex and age of onset ($p=0.014$); no such associations were observed in females (Table E6 and Table E7). Maintenance OCS use and dosage, number of rescue OCS courses and use of biological therapies did not differ by phenotype. Ever needing ICU admission and history of intubation for asthma was greater in early-onset disease ($p=0.001$) irrespective of sex but recent hospitalisations were equally prevalent across phenotypes (Table E6 and E7).

Summary Of Age of onset/ Sex Phenotypes

Summary characterization of the 4 age of onset/ sex phenotypes is displayed in Figure 3.

DISCUSSION

To our knowledge, this is the first description of a clinical cohort of difficult asthma patients using a simple phenotypic stratification based on their sex and age of asthma-onset. WATCH cohort participants showed high asthma morbidity and comorbidities, consistent with the concept of difficult asthma. The cohort had a higher proportion of females but equal proportions of early and adult-onset disease. Males developed asthma younger than females among the early-onset asthmatics but later within the adult-onset groups, suggesting biphasic, age-related associations for male difficult asthma. The identified phenotypes differed in respect of lung function, FeNO, atopic status, fungal sensitisation, smoking status, oral corticosteroid needs and both physical and psychophysiologic comorbidities. This highlights the heterogeneous nature of difficult asthma in relation to age of asthma-onset and/or sex. Such understanding may have important clinical implications.

Differential associations of sex and age of onset with aspects of Difficult Asthma

Our observations are consistent with female predominance reported in three out of four secondary care clusters in the Leicester study¹⁵, all five clusters in BTS Difficult Asthma Registry¹⁷ and SARP¹⁶ studies, and in three out of four clusters in UBIOPRED¹⁸. Using a different approach, we identified both early and adult-onset forms of male difficult asthma, with males disproportionately more likely to have adult-onset disease. Whether such patterns represent a distinctive feature of difficult compared to milder asthma is unclear. Of note, within SARP III, regardless of disease severity, childhood-onset asthma demonstrated male predominance²⁸. Comparison to milder asthmatics in the Isle of Wight Whole Population Birth Cohort (IOWBC)²⁹ and also in our mild adult asthma study cohort (Table E8; online repository text) suggests that there may indeed be different associations of sex for mild and difficult asthma. Previous severe asthma cluster studies also reported varied age of onset/sex relationships. In the Leicester study, three secondary care clusters were childhood-onset/

female predominant and the one adult-onset cluster predominantly male¹⁵. Of the three Leicester primary care clusters, two were adult-onset female predominant while the childhood-onset cluster was male predominant. In SARP, three clusters were childhood and two adult-onset (all female predominant)¹⁶. In the BTS Registry four clusters were adult-onset (all female predominant)¹⁷. UBIOPRED reported two childhood and two adult-onset severe asthma clusters with male and female predominant groups in each¹⁸. Such variation may reflect both population and methodological/ classification differences.

In our study, males had impaired spirometry accompanied by a significant age-related interaction whereby early-onset males had lowest FEV₁ and FVC. Those findings in early-onset male difficult asthma may represent effects of longer disease duration, associated with more pronounced airway remodelling, fixed airflow limitation and consequent air trapping^{30,31}. They also align with findings of persistently low lung function trajectories established in early life that track longitudinally³²⁻³⁵. However, our findings for males were not seen in female early-onset subjects whose disease duration was also long. Timing of disease onset, before or after pubertal growth spurt, and parallel/ subsequent environmental exposures might impact on lung function to account for such apparent sex differences. Our early-onset male asthmatics showed raised smoking prevalence, which may have contributed to their impaired adult lung function. While smoking uptake in early-onset male asthmatics is contrary to conventional expectation, it mirrors prior descriptions of smoking uptake in asthma patients in EGEA and IOWBC studies^{36,37}. This, therefore, identifies an important focus for improved clinical management. Adult-onset males also had higher smoking prevalence and poorer lung function than female counterparts despite shortest disease duration. However, while adult-onset females had higher smoking prevalence than early-onset females, their lung function was not significantly worse, questioning how much smoking additionally influenced lung function differences between early and adult-onset

females. One limitation of our dataset is the lack of more detailed information on smoking duration and consumption levels (ie pack year history). Therefore our findings that ever smoking status did not add significantly to the effects of age of onset and sex upon lung function remain speculative and should be interpreted with caution. Unfortunately our dataset lacks the depth to assess causal association of smoking with observed lung function differences. Future assessment of these phenotypes should seek to assess this point using detailed smoking information to give clarity on the nature of that potential association.

Salicylate (NSAID) sensitive asthma is known to be more severe and we found that to be more prevalent in females, confirming existing understanding³⁸. The absence of a positive formal drug challenge for diagnosis of this state is a potential limitation in our study that might raise concerns of overdiagnosis in our data. However patient reported symptoms in the presence of an appropriate clinical phenotype have been previously shown to align to high likelihood of positive aspirin challenge³⁸. While generally regarded as associated with adult-onset asthma, we also demonstrated it among early-onset females. That aligns with recent reports of early-onset forms of this phenotype that merit awareness³⁹. Our findings associating sulphite sensitivity with females are less well recognised⁴⁰. Fungal sensitivity is also a hallmark of more severe asthma and we found that ABPA/SAFS and aspergillus were commonest in males⁴¹. That is also not well documented in the literature where either no sex, or female predominance have generally been reported^{42,43}. Highest prevalence occurred in early-onset male asthma contrasting with findings of later-onset fungal disease in other populations⁴³. Much interest has recently focused on associations of obesity with more problematic asthma¹⁴. In this study, we confirmed high prevalence of obesity in difficult asthma, which was significantly influenced by interaction of sex with age of asthma-onset. Our findings of greater obesity prevalence in females with difficult asthma are consistent with other severe asthma cohorts and likely multifactorial in origin^{15-18,28}. Opposing obesity

prevalence for adult-onset asthmatic males and females in WATCH highlight potential sex-stratified mechanistic differences for adult-onset difficult asthma⁴⁴.

Psychophysiologic comorbidity was common in WATCH and showed female predominance, with depression and anxiety more common in females. A potentially complex interplay of chronic inflammation, sex hormones and psychosocial factors may influence such associations⁴⁵. Dysfunctional breathing and intermittent laryngeal obstruction also showed a female predominance and high prevalence in our cohort, consistent with other studies^{46,47}. Psychophysiologic comorbidity has been frequently noted in adult-onset female severe asthma clusters, including cluster 2 in the BTS Registry¹⁷, cluster T4 in U-BIOPRED¹⁸ and cluster 2 in the Leicester secondary care cluster¹⁵. Such clusters manifest disproportionately high symptom expression for degree of airway pathophysiology, suggesting a multicomponent framework for their breathlessness^{15,17,18}. In WATCH, whilst confirming high psychophysiologic comorbidity among a similar adult-onset female group, highest prevalence actually occurred in early-onset females who also had strong pathophysiological disease signals. Individuals with longer asthma duration might plausibly manifest psychophysiologic comorbidity as a consequence of detriment from their prolonged airways disease though seemingly more so in females.

Relevance and Implications of WATCH Phenotypes

Presentation to secondary or tertiary care with difficult asthma is often decades after disease onset. Greater awareness of asthmatics at risk for more difficult disease outcomes should support earlier identification and more targeted treatment, potentially alleviating decades of suffering from poorly controlled disease. In that regard, comparing to preceding analyses using unbiased data modelling, WATCH early-onset male difficult asthmatics are not clearly distinguished in the Leicester¹⁵, SARP¹⁶, BTS Registry¹⁷ or UBIOPRED¹⁸ studies but share

features with childhood-onset male severe asthmatics in SARP III²⁸. Significant airflow limitation shows them worthy of attention and likely to benefit from focused efforts to prevent smoking uptake. WATCH adult-onset female difficult asthmatics shared features with previously described clusters including cluster T4 in UBIOPRED¹⁸, cluster 3 in SARP¹⁶ and cluster 2 in the BTS Registry¹⁷. Early-onset female difficult asthma was the commonest grouping in WATCH and resembled aspects of cluster 1 in the BTS Registry¹⁷, clusters 1 and 3 in the Leicester secondary care cohort¹⁵ and clusters 1 and 2 in SARP¹⁶. It is therefore important to recognise that a fair proportion of difficult/severe asthma in adult females originates in early life. Consequently, it is worth considering if better recognition and management of childhood asthma in girls might reduce later disease morbidity.

The adult-onset male difficult asthmatic observed in WATCH is poorly acknowledged in clinical practice. Evolving into more difficult disease shortly after onset, as judged by the short disease duration in WATCH, they had the worst lung function, high smoking prevalence and high maintenance OCS use. Overlaps of asthma with COPD are now well recognised and it could be speculated that this group represents such disease duality⁴⁸, yet while diagnosed COPD was significantly associated with older age of onset it was not significantly associated with male sex in WATCH. Of note, adult-onset males did not show significantly greater radiological emphysema or impairment of gas transfers. Furthermore, despite their smoking history they had highest FeNO levels (a biomarker that is normally suppressed by cigarette smoke) and trends for highest peripheral eosinophils, both signs of T2-high inflammation. Given their other disease features their low ACQ scores may actually represent relative symptom under-perception which is previously reported in males^{49,50}. Neither SARP¹⁷, ECRHS II⁵¹ nor UBIOPRED¹⁸ studies clearly identified this group. However, a similar group was seen as cluster 4 in the Leicester secondary care cluster that showed male predominance, raised FeNO, higher eosinophilia, lower lung function and oral

corticosteroid dependency¹⁵. Though differing in some characteristics, male adult-onset troublesome asthma is noted as phenotype F in the EGEA2 Study⁵¹, cluster 2 in the Seinäjoki Adult Asthma Study (SAAS)¹³ and cluster 6 in the Taiwanese Adult Asthma Cohorts study⁵². Cluster 4 in the BTS Registry, whilst not male predominant, showed highest male prevalence in that study alongside adult-onset, higher smoking and impaired lung function¹⁷.

Strengths and limitations

An important strength of this study is that the WATCH cohort represents an extensively characterized real-life difficult asthma clinic population. Patients are drawn from many locations across a large geographical area across Southern England, effectively making the study multi-site. The WATCH participants showed levels of morbidity comparable to previous Severe Asthma cohorts¹⁵⁻¹⁸. However, WATCH specifically focuses on the more common clinical entity of difficult rather than severe asthma and therefore potentially has wider clinical applicability. As with any study, there are limitations. WATCH is a pragmatic study aligned to clinic attendance and therefore there is some missing data though that is not substantial. Because entry into the study is entirely voluntary, we cannot exclude that some phenotypes were more likely to enrol. Age of onset data is collected at enrolment into WATCH and is, therefore, prone to an element of recall bias, a common issue in all severe or difficult asthma studies. Our definition of early-onset is <18yrs, merging childhood and adolescence, which has the potential to oversimplify differential influence of sex on asthma in earlier life. Nevertheless, this age cut off results in a clear definition of adult-onset disease mirroring paediatric/ adult respiratory care transition and is, therefore, clinically applicable. The use of clinical diagnoses to define comorbidities might also be criticised but reflects real-life clinical practice. Finally, our study population is largely Caucasian, representative of the locality. Our findings need replication in other populations to assess wider applicability.

Conclusion

This study depicts a diverse nature to difficult asthma as a multicomponent problem with numerous comorbidities. Assessment based on age of disease onset and sex shows that these factors, and sometimes their interaction, are relevant to different clinical manifestations of difficult asthma. That perspective highlights patient groups that are currently poorly recognised in clinical practice. In particular, early-onset female and adult-onset male difficult asthma phenotypes need recognition to improve their outcomes and future research should focus further on the mechanisms underlying their clinical symptoms.

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631

632 **Table 1 Summary Characteristics of the Overall WATCH Cohort at Enrolment.**

	<i>Valid Cases Data Available</i>	<i>Mean (SD)</i>	<i>% (N)</i>
<i>Demographics</i>			
Female	501 (100%)		65.3% (327)
Age at Study Enrolment (years)	501 (100%)	50.6 (15.8)	
Age at Asthma Diagnosis	479 (95.6%)	23.6 (20.5)	
BMI (kg/m²)	495 (98.8%)	30.9 (7.23)	
Obese (BMI > 30 kg/m²)	495 (98.8%)		48.3% (239)
Current or Ex Smokers	500 (99.8%)		47.6% (238)
<i>Co-Morbidities</i>			
Rhinitis	446 (89.0%)		67.5% (301)
Eczema	495 (98.8%)		26.1% (129)
ABPA or SAFS[†]	493 (98.4%)		6.9% (34)
Bronchiectasis	495 (98.8%)		14.1% (70)
GORD	486 (97.0%)		64.8% (315)
Depression	454 (90.6%)		36.8% (167)
Anxiety	451 (90.0%)		32.8% (148)
Dysfunctional Breathing	476 (95.0%)		48.7% (232)
Intermittent Laryngeal Dysfunction	447 (89.2%)		14.5% (65)
Sulphite Sensitivity*	493 (98.4%)		7.7% (38)
Salicylate Sensitivity*	495 (98.8%)		25.1% (124)
EGPA			1.0% (5)
Sleep Apnoea			7.2% (35)
<i>Healthcare Utilisation</i>			
≥1 Asthma Related ICU Visits ever	500 (99.8%)		28.2% (141)
≥1 Asthma Hospital Admission (last 12 months)	497 (99.2%)		29.0% (144)
≥3 Rescue Oral Corticosteroids (last 12 months)	448 (89.4%)		43.6% (240)

<i>Treatment</i>			
Inhaled Corticosteroid Dose (BDP equivalent; ucg)	412 (82.2%)	2593.41 (985.27)	
Maintenance Oral Corticosteroid	475 (94.8%)		30.5% (145)
OCS Dose (for those on maintenance oral corticosteroid; mg)	140 (27.9%)	12.03 (8.49)	
Biologic Therapy	495 (98.8%)		17.6% (87)
<i>Blood Test Results</i>			
Eosinophil Count (10⁹ cells/L)	455 (90.8%)	0.3 (0.33)	
Total IgE (iu/mL)	384 (76.6%)	378 (1336)	
<i>Lung Function Test Results</i>			
FeNO50 (ppb)	390 (77.8%)	30.8 (34.43)	
Post BD FEV1 (%)	341 (68.1%)	75.6 (22.79)	
Post BD FEV1/FVC (ratio)	341 (68.1%)	66.4 (14.62)	
DLCO (%)	198 (39.5%)	99.7 (17.97)	
<i>Skin Prick Tests</i>			
Positive to any Aeroallergen (≥3mm)	391 (78.0%)		68.0% (266/391)
Positive to Aspergillus (≥3mm)	355 (70.9%)		15.8% (56)
<i>Questionnaires</i>			
ACQ6 Score (good control <1.5)	467 (93.2%)	2.5 (1.36)	
Epworth Score (normal <11)	424 (84.6%)	8.3 (5.5)	
HADS A Score (normal<8)	418 (83.4%)	7.06 (4.78)	
HADS D Score (normal <8)	418 (83.4%)	5.41 (4.39)	
Hull Cough Score (normal <14)	378 (75.4%)	26.2 (15.68)	
Nijmegen Score (normal <23)	373 (74.5%)	22.2 (12.4)	
SNOT22 Score (normal <8)	324 (64.7%)	35.2 (21.35)	

Table 1. Quantitative variables expressed as mean (SD) and Categorical variables as n(%). Abbreviations: BMI = Body Mass Index, ABPA = Allergic Bronchopulmonary Aspergillosis, SAFS = Severe Asthma Fungal Sensitisation, GORD = Gastro-Oesophageal Reflux Disease, EGPA = Eosinophilic Granulomatosis with Polyangiitis, ICU = Intensive Care Unit, BDP = Beclomethasone, OCS = Oral Corticosteroid, IgE = Immunoglobulin E, FENO50 = Fractional Exhaled Nitric Oxide at Expiratory Rate of 50ml/s in parts per billion (ppb), Post BD = post bronchodilator, FEV1 = Forced Expiratory Volume in 1 second, FVC = Forced Vital Capacity, DLCO = Diffusing Capacity of Lung for Carbon Monoxide, ACQ6 = 6 Item Asthma Control Questionnaire, HADS = Hospital Anxiety (A) and Depression (D) Score, SNOT22 = SinoNasal Outcome Test 22. * Determined clinically based on compatible history of reaction on exposure and consistent clinical phenotypes. † Determined clinically using evidence of relevant serological and radiological information guided by conventional clinical diagnostic criteria (eg reference 41).

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644 **Table 2 Demographic Characteristics of Age of onset/ Sex Phenotypes.**

	Male Early Onset (n=70)	Female Early Onset (n=174)	Male Adult Onset (n=104)	Female Adult Onset (n=153)	Adult Onset Effect		Male Effect	
*Age (at Enrolment) Mean (SD)	49.97 (15.45)	40.51 (14.85)	61.92 (11.25)	54.77 (12.26)	13.48 (11.09 ; 15.86)	$p<0.001$	8.18 (5.68 ; 10.68)	$p<0.001$
Missing cases	0	0	0	0				
*Age at Diagnosis Mean (SD)	4.27 (4.74)	6.66 (5.98)	46.98 (14.16)	35.39 (13.49)	Interaction effect $p<0.001$ (see below)			
Missing cases	6	7	6	3				
*BMI (mean SD)	30.11 (5.86)	30.87 (8.22)	29.01 (5.49)	32.50 (7.42)	Interaction effect $p=0.047$ (see below)			
Missing cases	2	2	2	0				
†Obese (BMI>30) %	48.53%	49.42%	31.37%	58.17%	Interaction effect $p=0.006$ (see below)			
Missing Cases	2	2	2	0				
†Never Smokers %	42.86%	65.52%	37.50%	51.97%	1.56 (1.09 ; 2.25)	$p=0.015$	2.1 (1.44 ; 3.08)	$p<0.001$
Missing cases	0	0	0	1				
					Effect of Late onset for Male		Effect of Late Onset for Female	
*Age at Diagnosis					42.71 (39.12 ; 46.31)	$p<0.001$	28.73 (26.47 ; 30.99)	$p<0.001$
*BMI					-1.1 (-2.83 ; 0.63)	ns	1.63 (-0.08 ; 3.34)	ns
†Obese					0.48 (0.26 ; 0.91)	$p=0.024$	1.42 (0.92 ; 2.21)	ns

645 Table 2. *Quantitative variables expressed as Mean (SD). Early-onset <18-years; Adult-onset ≥18-years. Adult Onset and Male Effects explored by two way ANOVA and expressed as difference
646 of means (95% confidence intervals). For Age at Diagnosis and BMI, where a significant interaction result was found, a one way ANOVA of late onset for each gender is performed. †Categorical
647 variables expressed as percentages within each group. Adult Onset and Male Effects explored by logistic regression models and expressed as an odds ratio (95% confidence intervals). For
648 Obesity, where a significant interaction result was found, a logistic regression model of late onset for each sex is performed. Abbreviations: BMI = body mass index, ns = not significant.

649

650 Table 3 Common Comorbidities of Age of onset/ Sex Phenotypes.

	Male Early Onset (n=70)	Female Early Onset (n=174)	Male Adult Onset (n=104)	Female Adult Onset (n=153)	Adult Onset Effect		Male Effect	
*Rhinitis	69.84%	68.35%	67.37%	65.38%		<i>ns</i>		<i>ns</i>
Missing cases	7	16	9	23				
*Eczema	38.57%	39.41%	11.65%	15.13%	0.25 (0.16 ; 0.38) °	<i>p</i> <0.001		<i>ns</i>
Missing cases	0	4	1	1				
*ABPA/SAFS	14.49%	8.24%	6.73%	2.00%	0.33 (0.14 ; 0.69)	<i>p</i> =0.003	2.27 1.11 ; 4.68)	<i>p</i> =0.025
Missing cases	1	4	0	3				
*Bronchiectasis	23.19%	8.19%	19.23%	13.25%		<i>ns</i>	2.18 (1.30 ; 3.66)	<i>p</i> =0.003
Missing Cases	1	3	0	2				
*GORD	63.77%	63.47%	67.37%	67.79%		<i>ns</i>		<i>ns</i>
Missing cases	1	7	3	4				
*COPD	10.14%	3.49%	17.31%	12.58%	2.78 (1.47 ; 5.59)	<i>p</i> <0.001		<i>ns</i>
Missing cases	1	2	0	4				
*Depression	27.87%	47.44%	24.74%	37.14%		<i>ns</i>	0.49 (0.32 ; 0.75)	<i>p</i> =0.001
Missing cases	9	18	7	13				
*Anxiety	28.57%	40.38%	21.88%	33.82%		<i>ns</i>	0.57 (0.36 ; 0.87)	<i>p</i> =0.010
Missing cases	7	18	8	17				
*Dys. Breathing	41.79%	59.01%	40.00%	46.62%		<i>ns</i>	0.63 (0.43 ; 0.93)	<i>p</i> =0.019
Missing cases	3	13	4	5				
*ILO	9.52%	17.65%	8.99%	16.90%		<i>ns</i>	0.49 (0.25 ; 0.89) ‡	<i>p</i> =0.018
Missing cases	7	21	15	11				
*Sulphite Sensitivity	2.90%	12.43%	4.85%	6.58%		<i>ns</i>	0.40 (0.16 ; 0.87) ‡	<i>p</i> =0.020
Missing cases	1	5	1	1				
*Salicylate Sensitivity	10.29%	28.90%	13.59%	35.10%		<i>ns</i>	0.30 (0.18 ; 0.49) ‡	<i>p</i> <0.001
Missing cases	2	1	1	2				
*EGPA	0	0	2.88%	1.33%		n/a†		<i>ns</i>
Missing cases	1	4	0	3				
*Sleep Apnoea	10.61%	6.43%	8.82%	5.33%		<i>ns</i>		<i>ns</i>
Missing cases	4	3	2	3				

651 *Table 3 *Categorical variables expressed as percentages within each group. Early-onset <18-years; Adult-onset ≥18-years. Adult Onset and Male Effects explored by logistic regression models*
652 *and expressed as an odds ratio (95% confidence intervals). Abbreviations: ABPA = Allergic Bronchopulmonary Aspergillosis, SAFS = Severe Asthma Fungal Sensitisation, GORD = Gastro-*
653 *Oesophageal Reflux Disease, COPD = Chronic Obstructive Pulmonary Disease, Dys. = Dysfunctional, ILO – Intermittent Laryngeal Dysfunction, EGPA = Eosinophilic Granulomatosis with*
654 *Polyangiitis. † unable to express odds ratio as frequency for early-onset is 0, ‡non adjusted estimated odds ratio because the one-factor model was best than two-factors model (by stepwise*
655 *selection), but very similar as adjusted estimated odds ratio, ns = not significant.*

656

657 **Table 4 Objective characterisation test results for Age of onset/ Sex Phenotypes.**

	Male Early Onset (n=70)	Female Early Onset (n=174)	Male Adult Onset (n=104)	Female Adult Onset (n=153)	<i>Adult Onset Effect</i>		<i>Male Effect</i>	
*Blood Eosinophil (10⁹ cells/L)	0.25 (0.21)	0.26 (0.38)	0.31 (0.38)	0.24 (0.28)		<i>ns</i>		<i>ns</i>
<i>Missing cases</i>	9	17	6	15				
*Total Serum IgE (iu/mL)	638 (988)	485 (2073)	74 (665)	141 (266)	-291.27 (-557.38 ; -25.16) ‡	<i>p=0.032</i>		<i>ns</i>
<i>Missing cases</i>	19	38	24	36				
*FeNO50 (ppb)	22.91 (24.64)	25.40 (28.77)	41.49 (41.44)	32.56 (36.49)	11.15 (4.33 ; 17.96)	<i>p=0.001</i>		<i>ns</i>
<i>Missing cases</i>	16	44	17	34				
*DLCO (%pred)	86.31 (19.04)	91.01 (15.33)	85.74 (22.49)	87.17 (18.28)		<i>ns</i>		<i>ns</i>
<i>Missing cases</i>	44	102	69	88				
*KCO (%pred)	105 (18)	99 (15)	101 (22)	97 (18)		<i>ns</i>		<i>ns</i>
<i>Missing cases</i>	44	102	69	88				
†Positive SPT	83.64%	76.92%	60.76%	54.39%	0.36 (0.23 ; 0.55) ‡	<i>p<0.001</i>		<i>ns</i>
<i>Missing cases</i>	15	31	25	39				
†Aspergillus + SPT	28.85%	14.17%	18.67%	8.91%		<i>ns</i>	2.41 (1.34 ; 4.37)	<i>p=0.004</i>
<i>Missing cases</i>	18	47	29	52				
HRCT Bronchiectasis	26.83%	24.1%	22.86%	22.78%		<i>ns</i>		<i>ns</i>
<i>Missing cases</i>	29	91	34	74				
HRCT Emphysema	2.33%	7.32%	8.7%	13.58%		<i>ns</i>		<i>ns</i>
<i>Missing cases</i>	27	92	35	72				

658 Table 4 *Quantitative variables expressed as Mean (SD). Early-onset <18-years; Adult-onset ≥18-years. Adult Onset and Male Effects explored by two way ANOVA and expressed as difference
659 of means (95% confidence intervals). For PostBD FEV1 %pred, where a significant interaction result was found, a one way ANOVA of late onset for each sex is performed. †Categorical variables
660 expressed as percentages within each group. Adult Onset and Male Effects explored by logistic regression models and expressed as an odds ratio (95% confidence intervals). Abbreviations: IgE
661 = Immunoglobulin E, FENO50 = Fractional Exhaled Nitric Oxide at Expiratory Rate of 50ml/s in parts per billion (ppb), DLCO = Diffusing Capacity of Lung for Carbon Monoxide, KCO = Diffusing

662 *Capacity of Lung for Carbon Monoxide corrected for alveolar volume, SPT = skin prick test (to standard panel of aeroallergens), HRCT = High Resolution CT Chest. ‡ non adjusted estimated odds*
663 *ratio because the one-factor model was best than two-factors model (by stepwise selection), but very similar as adjusted estimated odds ratio. ns = not significant.*

664

665 **Table 5 Self Report Questionnaire Scores for Age of onset/ Sex Phenotypes.**

	Male Early Onset (n=70)	Female Early Onset (n=174)	Male Adult Onset (n=104)	Female Adult Onset (n=153)	Adult Onset Effect		Male Effect	
*ACQ6	2.59 (1.34)	2.59 (1.29)	2.03 (1.36)	2.68 (1.38)	Interaction effect p=0.014 (see below)			
Missing cases	3	9	10	12				
*Epworth	9.05 (5.56)	8.44 (5.31)	7.42 (5.35)	8.49 (5.78)		ns		ns
Missing cases	12	25	14	26				
*HADS A	6.55 (4.86)	7.59 (4.77)	5.52 (4.10)	7.77 (4.92)		ns	-1.74 (-2.68 ; -0.80) †	p<0.001
Missing cases	10	28	15	23				
*HADS D	5.34 (3.93)	5.06 (4.46)	5.10 (4.25)	6.05 (4.51)		ns		ns
Missing Cases	11	29	15	20				
*HADS Total	11.83 (7.85)	12.64 (8.48)	10.62 (7.90)	13.84 (8.50)		ns	-2.11 (-3.77 ; -0.45) †	p=0.013
Missing cases	12	31	15	25				
*Hull Cough	21.80 (12.48)	27.26 (15.64)	21.71 (14.84)	29.92 (16.57)		ns	-6.78 (-10.04 ; -3.53) †	p<0.001
Missing cases	14	45	29	35				
*Nijmegen	20.76 (11.75)	23.76 (11.85)	17.91 (12.98)	24.08 (12.29)		ns	-4.82 (-7.41 ; -2.23) †	p<0.001
Missing cases	16	38	26	48				
*SNOT 22	30.60 (19.98)	37.56 (21.82)	30.21 (18.61)	37.71 (22.47)		ns	-7.25 (-12.12 ; -2.39) †	p=0.003
Missing cases	23	50	42	62				
					Effect of Late onset for Male		Effect of Late Onset for Female	
ACQ6					-0.56 (-0.98 ; -0.14)	p=0.009	0.09 (-0.21 ; 0.39)	ns

666 Table 5 *Quantitative variables expressed as Mean (SD). Early-onset <18-years; Adult-onset ≥18-years. Adult Onset and Male Effects explored by two way ANOVA and expressed as difference
667 of means (95% confidence intervals). For ACQ6, where a significant interaction result was found, a one way ANOVA of late onset for each sex is performed. Abbreviations: ACQ = Asthma
668 Control Questionnaire, HADS = Hospital Anxiety and Depression Score, A = Anxiety, D = Depression, SNOT = SinoNasal Outcome Test, †non adjusted estimated odds ratio because the one-factor
669 model was best than two-factors model (by stepwise selection), but very similar as adjusted estimated odds ratio. ns = not significant

FIGURE LEGENDS

Figure 1 A-D: Post Bronchodilator Lung Function Characteristics for Age of Onset/Sex Phenotypes

*Figure 1 Post Bronchodilator Spirometry Values for each phenotype: Early-onset <18-years; Adult-onset ≥18-years. A = Post BD FEV1 % predicted, B = Post BD FVC % predicted, C = Post BD FEV1/FVC Ratio, D = Post BD FEF 25-75 % predicted. An interaction effect by two way ANOVA is seen in Post BD FEV1 % predicted ** $p=0.002$. Post hoc one way ANOVA demonstrates an effect of age of diagnosis in males but not females. An interaction effect by two ANOVA is seen in Post BD FVC % predicted ** $p=0.002$. Post hoc one way ANOVA demonstrates an effect of age of diagnosis in males but not females. ****In Post BD FEV1/FVC Ratio and Post BD FEF 25-75 % predicted there is a significant difference between male and female, $p<0.001$ and $p<0.001$ respectively. A full breakdown of these statistics is available in Table E4 online repository text.*

Figure 2 Post Bronchodilator FEV1% predicted values for each phenotype stratified by smoking history

Figure 2 Post Bronchodilator FEV1% predicted values for each phenotype stratified by smoking history, ns = not significant, Early-onset <18-years; Adult-onset ≥18-years

Figure 3 Summary Characteristics of Difficult Asthma Age of Onset/Sex Phenotypes in the WATCH Cohort.

Figure 3 Summary of the four phenotypes in the WATCH Cohort of Difficult Asthma. The size of each quadrant is proportional to their prevalence within the WATCH cohort, Early-onset <18-years; Adult-onset ≥18-years

New Perspectives on Difficult Asthma; Sex and Age of Asthma-Onset Based Phenotypes - Supplementary Data

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Age of Onset vs Age of Diagnosis

Age of onset of symptoms and age of diagnosis are both self-reported variables. These were reported to be identical in 267 of 382 cases (69.9%) and thus highly correlated ($r_s = 0.932$, $p < 0.001$).

Comparison of WATCH and Non WATCH patients.

In January 2018, the UHS Difficult Asthma Clinic was responsible for 980 patients. From this list 598 patients were not participating in the WATCH Study at that time. 64 patients (6.5%) did not meet Step 4/5 criteria. 90 patients (16.9% of eligible patients) went on to join the WATCH study. From the remaining 444 patients, we collected data on age and gender from their demographic details and smoking status and treatment details (maintenance OCS and biologics use) from clinic letters. Complete data was only available for 408 patients (represented below). We compared these patients with all WATCH patients enrolled up until Mar 2019.

Table E1: Comparison of WATCH and Non-WATCH Patient Characteristics

	WATCH (472)	Not WATCH (408)	p value
Age at enrolment median (IQR)	52.00 (26)	53.00 (22)	$p < 0.05$
Gender (% female)	65.0%	66.2%	ns
Smoking Status (% never)	52.1%	51.7%	ns
Maintenance OCS (%)	30.1%	20.1%	$p < 0.001$
Biologics (%)	16.9%	15.2%	ns

Table E1 Notes: Includes only those patients with complete data for all variables. Continuous variables expressed as Median (IQR) and compared across groups by Mann Whitney U test. Categorical variables expressed as percentages and compared across groups by Chi Square. OCS = oral corticosteroids. ns = not significant

39 **Table E2: Diagnostic Criteria Used in Clinical Practice for Comorbidities**

Rhinitis	Physician clinical diagnosis
Eczema	Physician clinical diagnosis
ABPA or SAFS [†]	Determined clinically using evidence of relevant serological and radiological information guided by conventional clinical diagnostic criteria (eg reference 41).
Bronchiectasis	Objective evidence (Radiological Features on any CT imaging of Chest including but not exclusive to HRCT)
COPD	Physician clinical diagnosis
GORD	Physician clinical diagnosis
Depression	Physician clinical diagnosis
Anxiety	Physician clinical diagnosis
Dysfunctional Breathing	Physician clinical diagnosis (supported by abnormal Nijmegen score)
Intermittent Laryngeal Dysfunction	Physician clinical diagnosis
Sulphite Sensitivity*	Physician clinical diagnosis based on compatible history of reaction on exposure and consistent clinical phenotypes
Salicylate Sensitivity*	Physician clinical diagnosis based on compatible history of reaction on exposure and consistent clinical phenotypes
EGPA	Physician clinical diagnosis based on objective evidence (serum results, radiological features, biopsy findings)
Sleep Apnoea	Physician clinical diagnosis (confirmed by sleep study)

40 *Table E2 Notes:*41 *COPD = Chronic Obstructive Pulmonary Disease, GORD = Gastro-oesophageal reflux disease, EGPA = Eosinophilic*42 *Granulomatosis with Polyangiitis*

43 **Table E3: Height Comparisons for Age of onset/Sex Phenotypes**

	Male Early Onset (n=70)	Female Early Onset (n=174)	Male Adult Onset (n=104)	Female Adult Onset (n=153)	Adult Onset Effect		Male Effect		
*Height (cm)	172.35 (7.6)	162.88 (6.58)	173.72 (6.49)	161.07 (6.99)	Interaction effect $p<0.001$ (see below)				
Missing cases	2	2	2	0					
					Effect of Late onset for Male		Effect of Late Onset for Female		
*Height					1.36 (-0.77 ; 3.5)	ns	-1.81 (-3.29 ; -0.34)	$p<0.05$	

44 Table E3 Notes: *Quantitative variables expressed as Mean (SD). Early-onset <18-years; Adult-onset ≥ 18 -years. Adult Onset and Male Effects explored by two way ANOVA and expressed as
 45 difference of means (95% confidence intervals). ns = not significant

46 **Table E4: Post Bronchodilator (BD) Spirometry for Age of onset/Sex Phenotypes**

	Male Early Onset (n=70)	Female Early Onset (n=174)	Male Adult Onset (n=104)	Female Adult Onset (n=153)	Adult Onset Effect		Male Effect	
*PostBD FEV1 (%pred)	60.03 (19.92)	81.25 (21.10)	72.86 (20.84)	78.79 (23.61)	Interaction effect p=0.002 (see below)			
Missing Cases	20	65	33	42				
*Post BD FEV1/FVC (%pred)	58.18 (14.38)	71.78 (11.76)	60.54 (13.12)	68.42 (15.44)		ns	-10.42 (-13.49 ; -7.36)	p<0.001
Missing cases	20	65	33	42				
Post BD FVC (%pred)	81.49 (17.89)	91.96 (17.78)	93.2 (19.07)	90.84 (17.68)	Interaction effect p=0.002 (see below)			
Missing Cases	20	65	33	43				
					Effect of Late onset for Male		Effect of Late Onset for Female	
Post BD FEV1 %pred					12.83 (5.43 ; 20.24)	p=0.001		ns
Post BD FVC %pred					11.71 (4.98 ; 18.44)	p<0.001		ns

Table E4 Notes: *Quantitative variables expressed as Mean (SD). Early-onset <18-years; Adult-onset ≥18-years. Adult Onset and Male Effects explored by two way ANOVA and expressed as difference of means (95% confidence intervals). For PostBD FEV1 %pred, where a significant interaction result was found, a one way ANOVA of late onset for each sex is performed. ns = not significant

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Table E5: Effect of Smoking History on *PostBD FEV1 (%pred) on Phenotypes

	Male Childhood Onset	Female Childhood Onset	Male Adult Onset	Female Adult Onset
Never Smoker	62.5 (21.2)	83.1 (21.9)	74.0 (18.8)	79.8 (20.1)
<i>Valid cases</i>	21	75	27	57
Current/Ex Smoker	58.2 (19.1)	77.3 (19.0)	72.2 (22.2)	76.8 (26.4)
<i>Valid cases</i>	29	34	44	53
	ns	ns	ns	ns

Table E5 Notes: *Quantitative variables expressed as Mean (SD). Early-onset <18-years; Adult-onset ≥18-years.

Table E6: Healthcare Utilisation and Treatment Requirements for Age of onset/ Sex Phenotypes.

	Male Childhood Onset (n=70)	Female Childhood Onset (n=174)	Male Adult Onset (n=104)	Female Adult Onset (n=153)	Adult Onset Effect		Male Effect	
*Mean ICS Dose (BDP equivalent; ucg)	2578.84 (916.93)	2573.12 (967.58)	2449.17 (970.46)	2531.12 (1028.86)	-205.6 (-395.51 ; -15.69) °	p=0.034		ns
<i>Missing cases</i>	15	37	14	23				
#Maintenance OCS	21.88%	29.09%	37.62%	31.03%		ns		ns
	6	9	3	8				
*Mean Maintenance OCS Dose (mg)	13.64 (9.03)	12.71 (8.88)	10.7 (6.62)	11.94 (9.55)		ns		ns
	56	127	66	112				
#Biologic Therapy	18.84%	20.35%	18.27%	13.33%		ns		ns
<i>Missing cases</i>	1	2	0	3				
§>1 ICU Visit ever	35.71%	32.76%	26.92%	20.26%	0.49 (0.32 ; 0.75)	p=0.001		ns
<i>Missing Cases</i>	0	1	0	0				
§1> Hospitalisations	24.29%	31.03%	28.85%	30.72%		ns		ns

Missing cases	0	3	0	1				
^{\$} 3 ⁺ OCS Courses	41.43%	45.98%	51.92%	50.32%				
Missing cases	9	20	12	12		ns		ns

Table E6 Notes: *Quantitative variables expressed as Mean (SD). #Categorical variables expressed as percentages within each group. Early-onset <18-years; Adult-onset ≥18-years. Adult Onset and Male Effects explored by logistic regression models and expressed as an odds ratio (95% confidence intervals). For Maintenance OCS, where a significant interaction result was found, a logistic regression model of late onset for each sex is performed. ^{\$}Count variables expressed as percentages of summary of post hoc defined categories – a full breakdown of each count is available in Table E6. Adult Onset and Male Effects explored by negative binomial models and expressed as rate ratios (95% confidence intervals). Abbreviations: ICS = inhaled corticosteroid, BDP = Beclomethasone, OCS = oral corticosteroid, ICU = intensive care unit, ° non adjusted estimated odds ratio because the one-factor model was best than two-factors model (by stepwise selection), but very similar as adjusted estimated odds ratio. ns = not significant.

Table E7: Detailed Healthcare Utilisation/ Steroid Data for Age of onset/Sex Phenotypes

		Male Early Onset (n=70)	Female Early Onset (n=174)	Male Adult Onset (n=104)	Female Adult Onset (n=153)
ICU Visit Count	0	45 (64.29%)	116 (67.05%)	76 (73.08%)	122 (79.74%)
	1	12 (17.14%)	23 (13.29%)	19 (18.27%)	11 (7.19%)
	2 - 35	13 (18.57%)	34 (19.65%)	9 (8.65%)	20 (13.07%)
	Missing	0	1	0	0
Hospitalisations	0	53 (75.71%)	120 (70.18%)	74 (71.15%)	106 (69.74%)
	1	10 (14.29%)	19 (11.11%)	16 (15.38%)	18 (11.84%)
	2 – 20	7 (10%)	32 (18.71%)	14 (13.46%)	28 (18.42%)
	Missing	0	3	0	1
OCS Courses	0	13 (21.31%)	28 (18.18%)	21 (22.83%)	25 (17.73%)
	1	9 (14.75%)	28 (18.18%)	10 (10.87%)	23 (16.31%)
	2	10 (16.39%)	18 (11.69%)	7 (7.61%)	16 (11.35%)
	3	9 (14.75%)	17 (11.04%)	18 (19.57%)	22 (15.6%)
	4 – 20	20 (32.79%)	63 (40.91%)	36 (39.13%)	55 (39.01%)
	Missing	9	20	12	12

Table E7 Notes: Count variables expressed as percentages for each category. Early-onset <18-years; Adult-onset ≥18-years.

Mild Asthma Cohorts

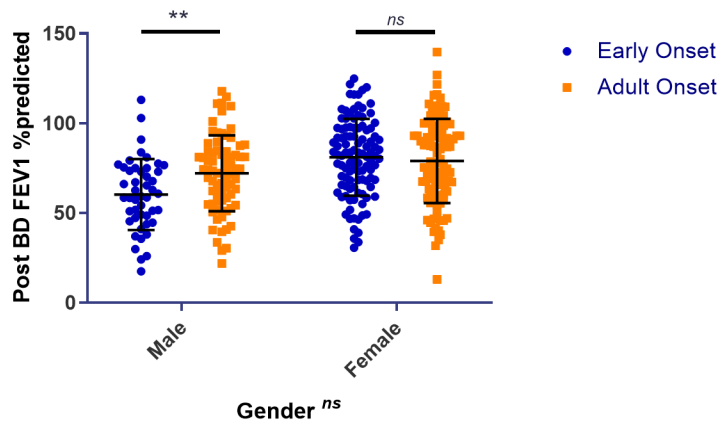
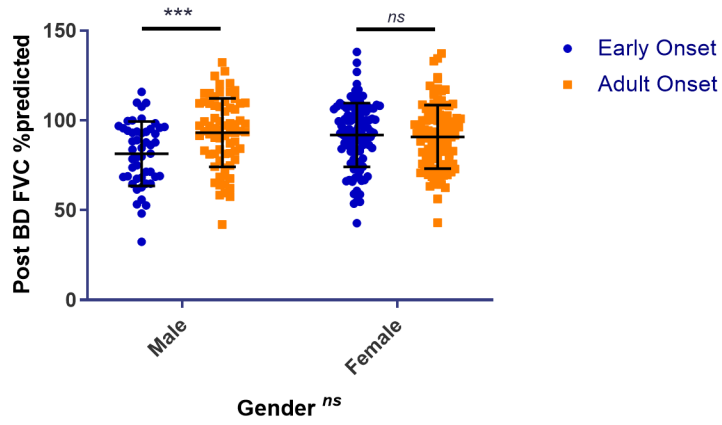
The Isle of Wight Whole Population Birth Cohort (IOWBC) (n=1456) was established in 1989 to prospectively study the natural history of asthma and allergy through the life course. Follow-up at the David Hide Asthma and Allergy Research Centre, Isle of Wight has been conducted at regular intervals in the 1st 26-years (birth, 1, 2, 4, 10, 18 and 26-years) enabling thorough characterisation of the cohort utilising questionnaires, lung function testing, bronchial challenge testing, skin prick testing and blood testing. Now aged 30-years the cohort is estimated to include around 130 current mild asthmatics (BTS Step 1-3). The EOSA (Epigenetics of Severe Asthma) mild asthma cohort comprises 69 participants with mild asthma (BTS Step 1 or 2). These were drawn from either the IOWBC that has been followed to age 26-years to date or from clinics/ community recruitment on the Isle of Wight, UK.

To explore the unexpected finding of disproportionately less male early-onset difficult asthma we also assessed the sex distribution among mild asthmatics over the 1st 18-years of life in our IOWBC. Findings are shown in Table E6. Among 359 IOWBC subjects with early-onset mild asthma present at any point in the 1st 18-years there was an equal sex distribution while for IOWBC subjects with current mild asthma at 18-years there was moderate (55.4%) female predominance. The IOWBC has only been followed to 26-years precluding further assessment of relationships of sex to adult-onset asthma. We therefore also compared WATCH findings with a further small cohort (EOSA) of mild asthmatic volunteers (n=69) that included older subjects. There we found that a similar distribution of age of onset pertained in mild females as for the WATCH cohort. However contrasting with WATCH findings for difficult asthma, in that study $\frac{3}{4}$ of males with mild asthma had early-onset disease. Such observations should not be over-interpreted but suggest possible differential relationships of male sex with age of disease onset for mild and difficult asthma, which warrant future research focus.

Table E8: Age of onset and Sex Associations for Difficult and Mild Asthma Cohorts

	WATCH Study – Difficult Asthma (N= 501)		IOWBC – Mild Asthma (Overall cohort = 1456)	EOSA Cohort – Mild Asthma (N=69)	
Mean Age (years)	50.6 (15.8)		18.0 (0.6)	38.3 (12.6)	
	Early-Onset	Adult-onset	Early-Onset (Ever Asthmatic in 1st 18-years; N = 359)	Early-Onset	Adult-onset
%Male	40.2%	59.8%	50.7%	74.1%	25.9%
%Female	53.2%	46.8%	49.3%	53.9%	46.2%
			Early-Onset (Currently Asthmatic at 18-years; N =231)		
%Male			44.6%		
%Female			55.4%		

Table E8 Notes: Early-onset <18-years; Adult-onset ≥18-years. WATCH study = Wessex AsThma CoHort of difficult asthma, IOWBC = Isle of Wight Whole Population Birth Cohort, EOSA = Epigenetics of Severe Asthma study, mild cohort.

A**B****C**