Original Article

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

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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 recognized 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 characterizing these novel phenotypes, and their multimorbid nature, this study can guide better identification and management of patients with difficult asthma.

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 characterized 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 with some physical comorbidities but highest psychophysiologic comorbidities. Adult-onset females also had considerable psychophysiologic comorbidities and 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 sensitization. Despite shortest disease duration, adult-onset males had highest use of maintenance oral corticosteroid, poor lung function, and highest fractional exhaled nitrogen oxide in spite of highest smoking prevalence.

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Abbreviations used
ABPA- Allergic bronchopulmonary aspergillosis
ACQ6- 6-Item Asthma Control Questionnaire
ANOVA- Analysis of variance
BD- Bronchodilator
BMI- Body mass index
BTS- British Thoracic Society
COPD- Chronic obstructive pulmonary disease
FeNO- Fractional exhaled nitrogen oxide
FEV_1- Forced expiratory volume in 1 second
FVC- Forced vital capacity
GORD- Gastroesophageal reflux disease
IOWBC- Isle of Wight Whole Population Birth Cohort
NHS- National Health Service
NSAID- Nonsteroidal anti-inflammatory drug
OCS- Oral corticosteroid
SAFS- Severe asthma with fungal sensitization
SARP- Severe Asthma Research Program
SPT- Skin prick test
UBIOPRED- Unbiased BIOmarkers in PREDiction of respiratory disease outcomes
UHSFT- University Hospitals Southampton NHS Foundation Trust
WATCH- Wessex AsThma CoHort of difficult asthma

CONCLUSIONS: 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 function loss and oral corticosteroid dependence associated with smoking in adult-onset male subjects.

Key words: *Age of onset; Comorbidity; Difficult asthma; Lung function; Phenotypes; Sex; Smoking*

Asthma is a diverse condition with different characteristics across the life course. It is more prevalent and problematic in males during childhood but after puberty becomes a predominantly female symptomatic disease in adulthood.[1-5] Potential contributing factors to these age-related changing sex associations include remission of childhood asthma in boys and asthma development in adolescent girls.[4] Postulated mechanisms for these processes include protective effects of male (androgenic) sex hormones and potentially sex-specific deleterious effects of female sex hormones.[6-8] Such concepts are supported by changes in asthma prevalence with menarche[8,9] and menopause.[8-10] Additional important contributory mechanisms include differences in innate and adaptive immune responses in males and females during reproductive life.[11] Other environmental or lifestyle factors, such as smoking exposure/habit, may plausibly influence these disease patterns too.[5] In that context, some studies have demonstrated associations between smoking and asthma in females but not males,[12] whereas others have associated older onset asthma with male smokers.[13] Conversely, obesity shows clear association with incident asthma in females across the life course.[14]

Studies have shown both childhood- and adult-onset patterns of adult severe asthma,[15-18] but it is widely regarded that adult severe asthma is commoner in females, with severe asthma cohort studies consistently showing female predominance.[15-18] Contrary to a 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 asthma.[5] 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% to 10% suffer from "difficult asthma," with poor disease control and disproportionately high socioeconomic costs.[19-21] Difficult asthma describes asthma in which comorbidities, 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 remains suboptimally controlled despite optimized treatment of both asthma and contributory factors.[19-24] Better insight of how sex and age of asthma onset relate to difficult asthma could support more personalized characterization 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 National Health Service (NHS) Foundation Trust (UHSFT), Southampton, United Kingdom. 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 characterization required of a commissioned NHS Specialist Centre for Severe Asthma.[26] 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 elsewhere.[27] 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 version 25 (IBM Corp, Armonk, NY), GraphPad Prism 7 (GraphPad Software, La Jolla, CA), and R (R Foundation, Vienna, Austria). Quantitative variables are presented as mean plus standard deviation and categorical variables as frequencies (percentages).

We defined 4 phenotypes using 2 binary variables: sex (male, female) and age of asthma diagnosis (early <18 years, adult >18 years). Age of asthma diagnosis was highly correlated with age of reported disease onset (see text in this article's Online Repository at www.jaci-inpractice.org). The interaction between sex and age of diagnosis for quantitative variables was tested with a 2-way analysis of variance (ANOVA). If the interaction was significant, a 1-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 realized with R software, using the *glm* function for ANOVA and logistic regression models and *glm.nb* for negative binomial

models. Data modeling checks were undertaken for model verification. If the 1-factor model was better than 2-factor model (by stepwise selection), the significant effect was shown from the 1-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 $<.05$ was regarded statistically significant.

RESULTS

Representativeness of the WATCH cohort to the difficult asthma clinic

Patients not enrolled in WATCH but attending the UHSFT Difficult Asthma clinic were compared with enrolment data from the WATCH cohort (see text and Table E1 in this article's Online Repository at www.jaci-inpractice.org). There were no statistically significant differences between WATCH and non-WATCH patients for sex or smoking status, but the median age of WATCH patients was 1 year less. 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, two-thirds (65.3%) were female with a mean study enrolment age of 50.6 years and age of asthma onset of 23.6 years (Table I). The commonest physical comorbidities ever reported (diagnostic definitions; Table E2, available in this article's Online Repository at www.jaci-inpractice.org) were rhinitis, gastroesophageal reflux disease (GORD), and obesity with high prevalence also of psychophysiologic (anxiety, depression, dysfunctional breathing, and intermittent laryngeal dysfunction) comorbidity. Half of 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 ($\geq$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 hospitalized due to asthma. Furthermore, 17.6% were on biological asthma therapies and 28.2% had ever had an intensive care asthma admission (Table I). The mean 6-Item Asthma Control Questionnaire (ACQ6) score was 2.5. Two-thirds (68.0%; 266 of 391) were atopic on SPT. The mean post-bronchodilator (BD) forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio was obstructive at 66.4%.

Age of onset and sex-stratified analyses

Demographic characteristics. The cohort was equally split between early- ($<$18 years) and adult-onset ($\geq$18 years) 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 II), whereas 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 4 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, available in this article's Online Repository at www.jaci-inpractice.org). Age of onset and sex did not separately affect body mass index (BMI), though their interaction led to a significantly higher BMI in female than male adult-onset asthma (32.5 vs 29.1). Female adult-onset subjects had the highest obesity prevalence (Table II). Obesity (BMI $\geq$30) was significantly affected by age of onset with a sex-stratified interaction. Although 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 III). Conversely, fungal sensitive disease (allergic bronchopulmonary aspergillosis [ABPA]/severe asthma with fungal sensitization [SAFS]) was significantly greater in males than females and early-onset than adult-onset disease. Clinically diagnosed non−cystic fibrosis bronchiectasis was significantly associated with male sex regardless of age of asthma onset. Radiological bronchiectasis or emphysema on high-resolution computed tomography scan did not show significant association with sex or age of onset (Table IV).

Several physical (salicylate [nonsteroidal anti-inflammatory drug: NSAID] sensitivity, sulfite 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 = .007). Regardless of sex, significant age of onset associations were noted for eczema (more prevalent in early-onset asthma), and chronic obstructive pulmonary disease (COPD) and eosinophilic granulomatosis with polyangiitis (both more prevalent 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 IV). 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 fractional exhaled nitrogen oxide (FeNO) was significantly higher in adult-onset groups regardless of sex.

Sex significantly influenced post-BD spirometry with significantly lower FEV_1, FVC, and FEV_1/FVC predicted values in males than females (Figure 1; Table E4, available in this article's Online Repository at www.jaci-inpractice.org). A significant interaction between sex and age of onset (P = .002) was shown for both FEV_1 and FVC, which were higher for adult-onset compared with early-onset males but no difference in females (Figure 1; Table E4, available in this article's Online Repository at www.jaci-inpractice.org). Neither age nor sex affected transfer factor (diffusing capacity of lung for carbon monoxide/diffusing capacity of lung for carbon monoxide corrected for alveolar volume) measures at enrolment (Table IV). We found no differences in FEV_1 between ever smokers and never smokers within each phenotype based on reported current, past, or never smoking status. Thus, although smoking prevalence differed between phenotypes, the simple parameter of ever smoking

TABLE I. Summary characteristics of the overall WATCH cohort at enrolment

	Valid cases data available	Mean (SD)	% (N)
Demographics			
Female	501 (100%)		65.3% (327)
Age at study enrolment (y)	501 (100%)	50.6 (15.8)	
Age at asthma diagnosis	479 (95.6%)	23.6 (20.5)	
BMI (kg/m^2)	495 (98.8%)	30.9 (7.23)	
Obese (BMI >30 kg/m^2)	495 (98.8%)		48.3% (239)
Current or ex-smokers	500 (99.8%)		47.6% (238)
Comorbidities			
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)
Sulfite sensitivity†	493 (98.4%)		7.7% (38)
Salicylate sensitivity†	495 (98.8%)		25.1% (124)
EGPA			1.0% (5)
Sleep apnoea			7.2% (35)
Health care utilization			
≥1 asthma-related ICU visits ever	500 (99.8%)		28.2% (141)
≥1 asthma hospital admission (last 12 mo)	497 (99.2%)		29.0% (144)
≥3 rescue oral corticosteroids (last 12 mo)	448 (89.4%)		43.6% (240)
Treatment			
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)
Blood test results			
Eosinophil count (10^9 cells/L)	455 (90.8%)	0.3 (0.33)	
Total IgE (iu/mL)	384 (76.6%)	378 (1336)	
Lung function test results			
$FeNO_{50}$ (ppb)	390 (77.8%)	30.8 (34.43)	
Post-BD FEV_1 (%)	341 (68.1%)	75.6 (22.79)	
Post-BD FEV_1/FVC (ratio)	341 (68.1%)	66.4 (14.62)	
DLCO (%)	198 (39.5%)	99.7 (17.97)	
Skin prick tests			
Positive to any aeroallergen (≥3 mm)	391 (78.0%)		68.0% (266/391)
Positive to aspergillus (≥3 mm)	355 (70.9%)		15.8% (56)
Questionnaires			
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)	

Quantitative variables expressed as mean (SD) and categorical variables as n (%).

ABPA, Allergic bronchopulmonary aspergillosis; *ACQ6*, 6-Item Asthma Control Questionnaire; *BD*, bronchodilator; *BDP*, beclomethasone; *BMI*, body mass index; *DLCO*, diffusing capacity of lung for carbon monoxide; *EGPA*, eosinophilic granulomatosis with polyangiitis; *$FENO_{50}$*, fractional exhaled nitric oxide at expiratory rate of 50 mL/s in parts per billion (ppb); *FEV_1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *GORD*, gastroesophageal reflux disease; *HADS*, Hospital Anxiety (A) and Depression (D) Score; *ICU*, intensive care unit; *OCS*, oral corticosteroid; *SAFS*, severe asthma fungal sensitization; *SD*, standard deviation; *SNOT22*, Sino-Nasal Outcome Test 22; *WATCH*, Wessex AsThma CoHort of difficult asthma.

*Determined clinically using evidence of relevant serological and radiological information guided by conventional clinical diagnostic criteria (eg, Denning et al[28]).

†Determined clinically based on compatible history of reaction on exposure and consistent clinical phenotypes.

TABLE II. 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) $P < .001$	8.18 (5.68; 10.68) $P < .001$
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 $P < .001$ (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 $P = .047$ (see below)	
Missing cases	2	2	2	0		
Obese† (BMI > 30) (%)	48.53%	49.42%	31.37%	58.17%	Interaction effect $P = .006$ (see below)	
Missing cases	2	2	2	0		
Never smokers,† (%)	42.86%	65.52%	37.50%	51.97%	1.56 (1.09; 2.25) $P = .015$	2.1 (1.44; 3.08) $P < .001$
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)	$P < .001$	28.73 (26.47; 30.99)	$P < .001$
BMI*	−1.1 (−2.83; 0.63)	ns	1.63 (−0.08; 3.34)	ns
Obese†	0.48 (0.26; 0.91)	$P = .024$	1.42 (0.92; 2.21)	ns

BMI, Body mass index; *ns*, not significant; *SD*, standard deviation.

*Quantitative variables expressed as mean (SD). Early onset <18 years; adult onset ≥18 years. Adult onset and male effects explored by a 2-way analysis of variance (ANOVA) and expressed as the difference of means (95% confidence intervals). For age at diagnosis and BMI, where a significant interaction result was found, a 1-way ANOVA of late onset for each gender is performed.

†Categorical 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 obesity, where a significant interaction result was found, a logistic regression model of late onset for each sex is performed.

status did not significantly account for differences in FEV_1 between these groups (Figure 2; full data in Table E5, available in this article's Online Repository at www.jaci-inpractice.org).

Disease-related questionnaire characteristics. ACQ6 was significantly affected by the interaction of sex and age of onset with lowest (best) values in adult-onset males. Hospital Anxiety and Depression Score, Nijmegen score, Hull cough score, and Sino-Nasal Outcome Test-22 score were significantly higher in females regardless of age of asthma onset (Table V).

Treatment and health care utilization characteristics. Maintenance OCS use was highest in male adult-onset disease reflecting a significant interaction between male sex and age of onset ($P = .014$); no such associations were observed in females (Tables E6 and E7, available in this article's Online Repository at www.jaci-inpractice.org). Maintenance OCS use and dosage, number of rescue OCS courses, and use of biological therapies did not differ by phenotype. Ever-needing intensive care unit admission and history of intubation for asthma were greater in early-onset disease ($P = .001$) irrespective of sex, but recent hospitalizations were equally prevalent across phenotypes (Tables E6 and E7, available in this article's Online Repository at www.jaci-inpractice.org).

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 patients with difficult asthma 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 sensitization, smoking status, OCS 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 3 of 4 secondary care clusters in the Leicester study,[15] all 5 clusters in British Thoracic Society (BTS) Difficult Asthma Registry[17] and Severe Asthma Research Program (SARP)[16] studies, and in 3 of 4 clusters in Unbiased BIOmarkers in PREDiction of respiratory disease outcomes (UBIOPRED).[18] 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 with milder asthma is unclear. Of note, within SARP III, regardless of disease severity, childhood-onset asthma demonstrated male predominance.[29] Comparison with milder asthmatics in the Isle of Wight Whole Population Birth Cohort

TABLE III. 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%	ns		ns	
Missing cases	7	16	9	23				
Eczema*	38.57%	39.41%	11.65%	15.13%	0.25 (0.16; 0.38)	$P < .001$	ns	
Missing cases	0	4	1	1				
ABPA/SAFS*	14.49%	8.24%	6.73%	2.00%	0.33 (0.14; 0.69)	$P = .003$	2.27 (1.11; 4.68)	$P = .025$
Missing cases	1	4	0	3				
Bronchiectasis*	23.19%	8.19%	19.23%	13.25%	ns		2.18 (1.30; 3.66)	$P = .003$
Missing cases	1	3	0	2				
GORD*	63.77%	63.47%	67.37%	67.79%	ns		ns	
Missing cases	1	7	3	4				
COPD*	10.14%	3.49%	17.31%	12.58%	2.78 (1.47; 5.59)	$P < .001$	ns	
Missing cases	1	2	0	4				
Depression*	27.87%	47.44%	24.74%	37.14%	ns		0.49 (0.32; 0.75)	$P = .001$
Missing cases	9	18	7	13				
Anxiety*	28.57%	40.38%	21.88%	33.82%	ns		0.57 (0.36; 0.87)	$P = .010$
Missing cases	7	18	8	17				
Dys. breathing*	41.79%	59.01%	40.00%	46.62%	ns		0.63 (0.43; 0.93)	$P = .019$
Missing cases	3	13	4	5				
ILO*	9.52%	17.65%	8.99%	16.90%	ns		0.49 (0.25; 0.89)‡	$P = .018$
Missing cases	7	21	15	11				
Sulfite sensitivity*	2.90%	12.43%	4.85%	6.58%	ns		0.40 (0.16; 0.87)‡	$P = .020$
Missing cases	1	5	1	1				
Salicylate sensitivity*	10.29%	28.90%	13.59%	35.10%	ns		0.30 (0.18; 0.49)‡	$P < .001$
Missing cases	2	1	1	2				
EGPA*	0	0	2.88%	1.33%	n/a†		ns	
Missing cases	1	4	0	3				
Sleep apnoea*	10.61%	6.43%	8.82%	5.33%	ns		ns	
Missing cases	4	3	2	3				

ABPA, Allergic bronchopulmonary aspergillosis; *COPD*, chronic obstructive pulmonary disease; *Dys*, dysfunctional; *EGPA*, eosinophilic granulomatosis with polyangiitis; *GORD*, gastroesophageal reflux disease; *ILO*, intermittent laryngeal dysfunction; *ns*, not significant; *SAFS*, severe asthma fungal sensitization.

*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).

†Unable to express odds ratio as frequency for early onset is 0.

‡Nonadjusted estimated odds ratio because the 1-factor model was better than the 2-factor model (by stepwise selection), but very similar to the adjusted estimated odds ratio.

(IOWBC)[30] and also in our mild adult asthma study cohort (see Table E8 and text in this article's Online Repository at www.jaci-inpractice.org) 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, 3 secondary care clusters were childhood-onset/female predominant and the one adult-onset cluster predominantly male.[15] Of the 3 Leicester primary care clusters, 2 were adult-onset female predominant, whereas the childhood-onset cluster was male predominant. In SARP, 3 clusters were childhood and 2 adult-onset (all female predominant).[16] In the BTS Registry, 4 clusters were adult-onset (all female predominant).[17] UBIOPRED reported 2 childhood- and 2 adult-onset severe asthma clusters with male and female predominant groups in each.[18] 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 FEV_1 and FVC. Those findings in early-onset male difficult asthma may represent the effects of longer disease duration, associated with more pronounced airway remodeling, fixed airflow limitation, and consequent air trapping.[31,32] They also align with findings of persistently low lung function trajectories established in early life that track longitudinally.[33-36] 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. Although smoking uptake in early-onset male asthmatics is contrary to conventional expectation, it mirrors prior descriptions of smoking uptake in patients with asthma in Epidemiological study on the Genetics and Environment of Asthma and IOWBC studies.[37,38] This, therefore, identifies an important focus for improved clinical management. Adult-onset males also had a higher smoking prevalence and poorer lung function than female counterparts despite shortest disease duration. However, although adult-onset females had a higher smoking prevalence

TABLE IV. Objective characterization 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)	Adult onset effect		Male effect	
Blood eosinophil* (10^9 cells/L)	0.25 (0.21)	0.26 (0.38)	0.31 (0.38)	0.24 (0.28	ns		ns	
Missing cases	9	17	6	15				
Total Serum IgE* (iu/mL)	638 (988)	485 (2073)	74 (665)	141 (266)	−291.27 (−557.38; −25.16)‡	$P = .032$	ns	
Missing cases	19	38	24	36				
$FeNO_{50}$* (ppb)	22.91 (24.64)	25.40 (28.77)	41.49 (41.44)	32.56 (36.49)	11.15 (4.33; 17.96)	$P = .001$	ns	
Missing cases	16	44	17	34				
DLCO* (%pred)	86.31 (19.04)	91.01 (15.33)	85.74 (22.49)	87.17 (18.28)	ns		ns	
Missing cases	44	102	69	88				
KCO* (%pred)	105 (18)	99 (15)	101 (22)	97 (18)	ns		ns	
Missing cases	44	102	69	88				
Positive SPT†	83.64%	76.92%	60.76%	54.39%	0.36 (0.23; 0.55)‡	$P < .001$	ns	
Missing cases	15	31	25	39				
Aspergillus + SPT†	28.85%	14.17%	18.67%	8.91%	ns		2.41 (1.34; 4.37)	$P = .004$
Missing cases	18	47	29	52				
HRCT bronchiectasis	26.83%	24.1%	22.86%	22.78%	ns		ns	
Missing cases	29	91	34	74				
HRCT emphysema	2.33%	7.32%	8.7%	13.58%	ns		ns	
Missing cases	27	92	35	72				

BD, Bronchodilator; *DLCO*, diffusing capacity of lung for carbon monoxide; *$FENO_{50}$*, fractional exhaled nitric oxide at expiratory rate of 50 mL/s in parts per billion (ppb); *FEV_1*, forced expiratory volume in 1 s; *HRCT*, high-resolution computed tomography chest; *KCO*, diffusing capacity of lung for carbon monoxide corrected for alveolar volume; *ns*, not significant; *SD*, standard deviation; *SPT*, skin prick test (to standard panel of aeroallergens).

*Quantitative variables expressed as mean (SD). Early onset <18 years; adult onset ≥18 years. Adult onset and male effects explored by a 2-way analysis of variance (ANOVA) and expressed as the difference of means (95% confidence intervals). For Post-BD FEV_1 %pred, where a significant interaction result was found, a 1-way ANOVA of late onset for each sex is performed.

†Categorical 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).

‡Nonadjusted estimated odds ratio because the 1-factor model was better than the 2-factor model (by stepwise selection), but very similar to the adjusted estimated odds ratio.

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 on 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 the existing understanding.[39] 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 challenge.[39] Although 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 awareness.[40] Our findings associating sulfite sensitivity with females are less well recognized.[41] Fungal sensitivity is also a hallmark of more severe asthma, and we found that ABPA/SAFS and aspergillus sensitivity were commonest in males.[28] That is also not well documented in the literature where either no sex or female predominance has generally been reported.[42,43] The highest prevalence occurred in early-onset male asthma contrasting with findings of later-onset fungal disease in other populations.[43] Much interest has recently focused on associations of obesity with more problematic asthma.[14] In this study, we confirmed a high prevalence of obesity in difficult asthma, which was significantly influenced by the 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.[15-18,29] Opposing obesity prevalence for adult-onset asthmatic males and females in WATCH highlights potential sex-stratified mechanistic differences for adult-onset difficult asthma.[44]

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 associations.[45] 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 Registry,[17] cluster T4 in U-BIOPRED,[18] and cluster 2 in the Leicester secondary care cluster.[15] Such clusters manifest disproportionately high symptom expression for degree of airway pathophysiology, suggesting a multicomponent framework for their

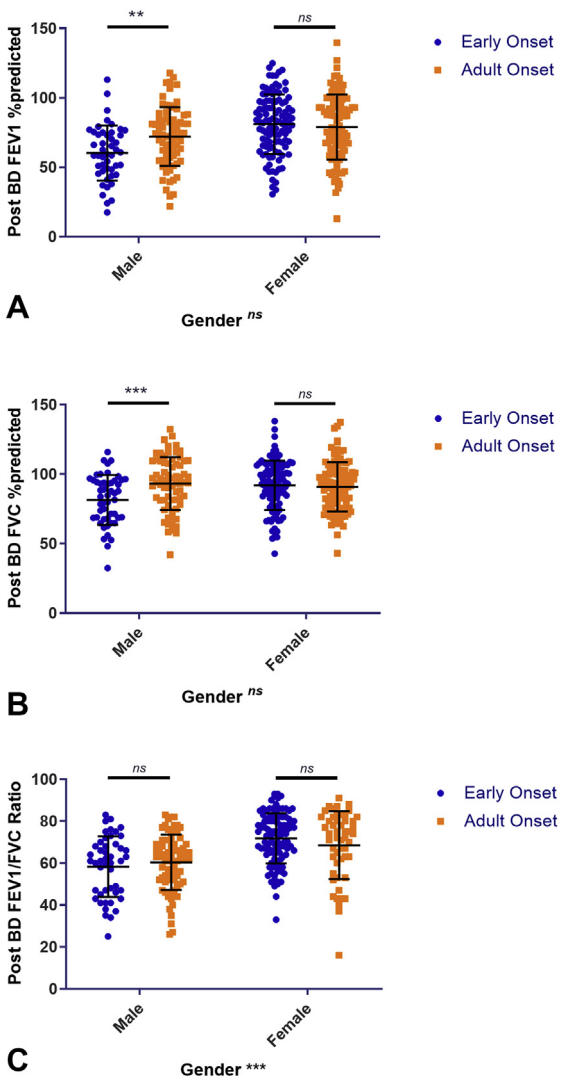

FIGURE 1. Post-bronchodilator lung function characteristics for age of onset/sex phenotypes. Post-bronchodilator spirometry values for each phenotype: Early onset <18 years; adult onset ≥18 years. (**A**) Post-BD FEV_1 % predicted, (**B**) post-BD FVC % predicted, and (**C**) post-BD FEV_1/FVC ratio. An interaction effect by a 2-way ANOVA is seen in post-BD FEV_1 % predicted, $^{**}P = .002$. Post hoc 1-way ANOVA demonstrates an effect of age of diagnosis in males but not females. An interaction effect by a 2-way ANOVA is seen in post-BD FVC % predicted, $^{**}P = .002$. Post hoc 1-way ANOVA demonstrates an effect of age of diagnosis in males but not females. ***In post-BD FEV_1/FVC ratio and post-BD $FEF_{25-75\%}$ predicted, there is a significant difference between male and female, $P < .001$ and $P < .001$, respectively. A full breakdown of these statistics is available in Table E4 (available in this article's Online Repository at www.jaci-inpractice.org). ANOVA, Analysis of variance; BD, bronchodilator; $FEF_{25-75\%}$, forced expiratory flow between 25% and 75% exhalation; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ns, not significant.

breathlessness.[15,17,18] In WATCH, although confirming high psychophysiologic comorbidity among a similar adult-onset female group, the 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, compared with preceding analyses using unbiased data modeling, WATCH early-onset male difficult asthmatics are not clearly distinguished in the Leicester,[15] SARP,[16] BTS Registry,[17] or UBIOPRED[18] studies but share features with childhood-onset male severe asthmatics in SARP III.[29] 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 UBIOPRED,[18] cluster 3 in SARP,[16] and cluster 2 in the BTS Registry.[17] Early-onset female difficult asthma was the commonest grouping in WATCH and resembled aspects of cluster 1 in the BTS Registry,[17] clusters 1 and 3 in the Leicester secondary care cohort,[15] and clusters 1 and 2 in SARP.[16] It is therefore important to recognize 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 asthmatics observed in WATCH are 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 recognized, and it could be speculated that this group represents such disease duality,[48] yet although 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 underperception that is previously reported in males.[49,50] Neither SARP,[17] European Community Respiratory Health Survey II,[51] nor UBIOPRED[18] 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 OCS dependence.[15] Although differing in some characteristics, male adult-onset troublesome asthma is noted as phenotype F in the Epidemiological study on the Genetics and Environment of Asthma 2 Study,[51] cluster 2 in the Seinäjoki Adult Asthma Study[13] and

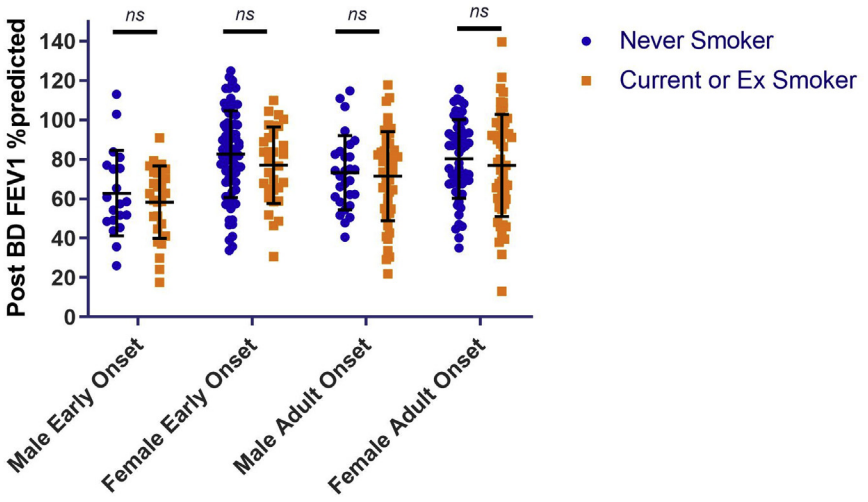

FIGURE 2. Post-bronchodilator FEV_1 % predicted values for each phenotype stratified by smoking history. Early onset <18 years; adult onset ≥18 years. *BD*, Bronchodilator; *FEV_1*, forced expiratory volume in 1 s; *ns*, not significant.

TABLE V. 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 $P = .014$ (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)†	<.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)†	$P = .013$
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)†	$P < .001$
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)†	$P < .001$
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)†	$P = .003$
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)		$P = .009$		0.09 (−0.21; 0.39)		ns

ACQ, Asthma Control Questionnaire; *HADS*, Hospital Anxiety (A) and Depression (D) Score; *ns*, not significant; *SNOT*, Sino-Nasal Outcome Test.
*Quantitative variables expressed as mean (standard deviation). Early onset <18 years; adult onset ≥18 years. Adult onset and male effects explored by a 2-way analysis of variance (ANOVA) and expressed as difference of means (95% confidence intervals). For ACQ6, where a significant interaction result was found, a 1-way ANOVA of late onset for each sex is performed.
†Nonadjusted estimated odds ratio because the 1-factor model was better than the 2-factor model (by stepwise selection), but very similar to the adjusted estimated odds ratio.

cluster 6 in the Taiwanese Adult Asthma Cohorts study.[52] Cluster 4 in the BTS Registry, although not male predominant, showed the highest male prevalence in that study alongside adult-onset, higher smoking, and impaired lung function.[17]

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 multisite. The WATCH participants showed levels of morbidity comparable with previous Severe Asthma cohorts.[15-18] 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

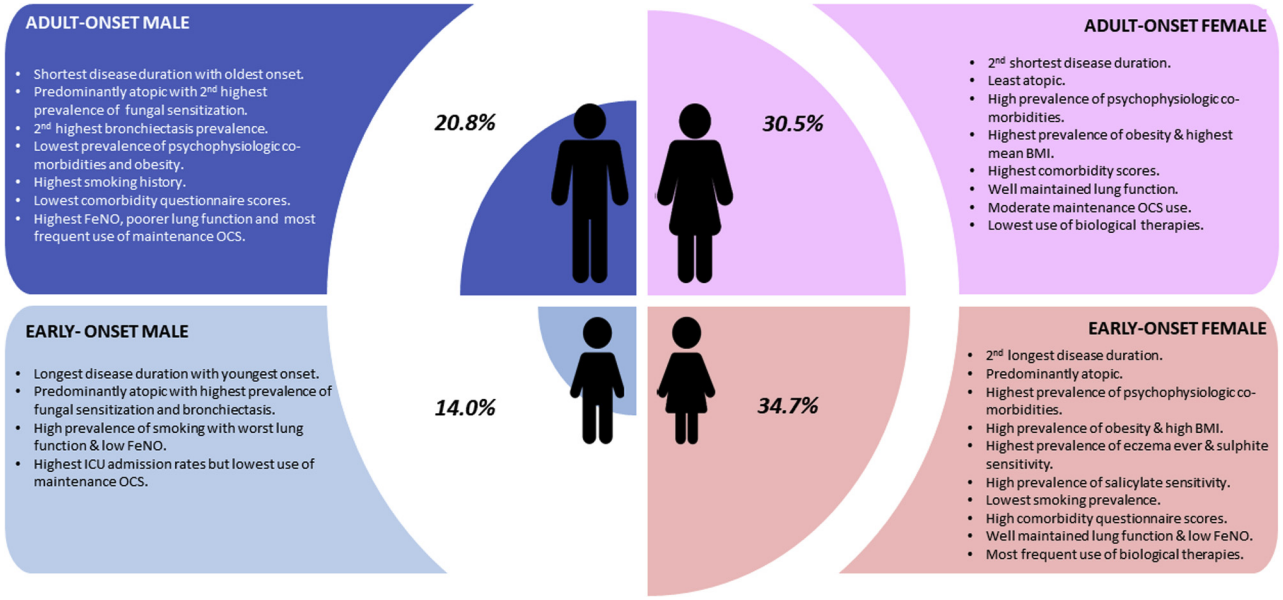

FIGURE 3. Summary characteristics of difficult asthma age of onset/sex phenotypes in the WATCH sohort. Summary of the 4 phenotypes in the WATCH cohort of difficult asthma. The size of each quadrant is proportional to their prevalence within the WATCH cohort. Early onset <18 years; adult onset ≥18 years. *BMI*, Body mass index; *FeNO*, fractional exhaled nitrogen oxide; *ICU*, intensive care unit; *OCS*, oral corticosteroid; *WATCH*, Wessex AsThma CoHort of difficult asthma.

entry into the study is entirely voluntary, we cannot exclude that some phenotypes were more likely to enroll. Age of onset data are collected at enrolment into WATCH and are, therefore, prone to an element of recall bias, a common issue in all severe or difficult asthma studies. Our definition of early-onset is <18 years, merging childhood and adolescence, which has the potential to oversimplify the differential influence of sex on asthma in earlier life. Nevertheless, this age cutoff results in a clear definition of adult-onset disease mirroring pediatric/adult respiratory care transition and is, therefore, clinically applicable. The use of clinical diagnoses to define comorbidities might also be criticized 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.

CONCLUSIONS

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 recognized 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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ONLINE REPOSITORY

AGE OF ONSET VERSUS 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 ($rs = 0.932$, $P < .001$).

COMPARISON OF WATCH AND NON-WATCH PATIENTS

In January 2018, the University Hospitals Southampton Difficult Asthma Clinic was responsible for 980 patients. From this list, 598 patients were not participating in the Wessex AsThma CoHort of difficult asthma (WATCH) study at that time. Sixty-four patients (6.5%) did not meet Step 4/5 criteria. Ninety 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 oral corticosteroid and biologics use) from clinic letters. Complete data were only available for 408 patients (represented below). We compared these patients with all WATCH patients enrolled up until March 2019.

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 first 26 years (birth, 1, 2, 4, 10, 18, and 26 years) enabling thorough characterization of the cohort utilizing 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 steps 1-3). The Epigenetics of Severe Asthma (EOSA) 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, United Kingdom.

To explore the unexpected finding of disproportionately less male early-onset difficult asthma we also assessed the sex distribution among mild asthmatics over the first 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 first 18 years, there was an equal sex distribution, whereas 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 three-fourths of males with mild asthma had early-onset disease. Such observations should not be overinterpreted but suggest possible differential relationships of male sex with age of disease onset for mild and difficult asthma, which warrant future research focus.

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)	<.05
Gender (% female)	65.0	66.2	ns
Smoking status (% never)	52.1	51.7	ns
Maintenance OCS (%)	30.1	20.1	<.001
Biologics (%)	16.9	15.2	ns

Includes only those patients with complete data for all variables. Continuous variables expressed as median (IQR) and compared across groups by the Mann-Whitney *U* test. Categorical variables expressed as percentages and compared across groups by χ^2.
IQR, Interquartile range; *ns*, not significant; *OCS*, oral corticosteroid; *WATCH*, Wessex AsThma CoHort of difficult asthma.

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, Denning et al[E1])
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
Sulfite 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)

ABPA, Allergic bronchopulmonary aspergillosis; *COPD*, chronic obstructive pulmonary disease; *CT*, computed tomography; *EGPA*, eosinophilic granulomatosis with polyangiitis; *GORD*, gastroesophageal reflux disease; *HRCT*, high-resolution computed tomography chest; *SAFS*, severe asthma fungal sensitization.

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 $P < .001$ (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)		$P < .05$

ns, Not significant; *SD*, standard deviation.
*Quantitative variables expressed as mean (SD). Early onset <18 years; adult onset ≥18 years. Adult onset and male effects explored by a 2-way analysis of variance and expressed as the difference of means (95% confidence intervals).

TABLE E4. Postbronchodilator (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
Post-BD FEV_1* (%pred)	60.03 (19.92)	81.25 (21.10)	72.86 (20.84)	78.79 (23.61)	Interaction effect $P = .002$ (see below)	
Missing cases	20	65	33	42		
Post-BD FEV_1/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) $P < .001$
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 $P = .002$ (see below)	
Missing cases	20	65	33	43		

	Effect of late onset for male		Effect of late onset for female
Post-BD FEV_1 %pred	12.83 (5.43; 20.24)	$P = .001$	ns
Post-BD FVC %pred	11.71 (4.98; 18.44)	$P < .001$	ns

BD, Bronchodilator; *FEV_1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *ns*, not significant; *SD*, standard deviation.
*Quantitative variables expressed as mean (SD). Early onset <18 years; adult onset ≥18 years. Adult onset and male effects explored by a 2-way analysis of variance (ANOVA) and expressed as the difference of means (95% confidence intervals). For post-BD FEV_1 %pred, where a significant interaction result was found, a 1-way ANOVA of late onset for each sex is performed.

TABLE E5. Effect of smoking history on post-BD FEV_1* (%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)
Valid cases	21	75	27	57
Current/ex-smoker	58.2 (19.1)	77.3 (19.0)	72.2 (22.2)	76.8 (26.4)
Valid cases	29	34	44	53
	ns	ns	ns	ns

ns, Not significant; *SD*, standard deviation.
*Quantitative variables expressed as mean (SD). Early onset <18 years; adult onset ≥18 years.

TABLE E6. Health care utilization 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)§	$P = .034$	ns
Missing cases	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
Missing cases	1	2	0	3			
≥1 ICU visit ever‡	35.71%	32.76%	26.92%	20.26%	0.49 (0.32; 0.75)	$P = .001$	ns
Missing cases	0	1	0	0			
≥1 hospitalizations‡	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%		ns	ns
Missing cases	9	20	12	12			

BDP, Beclomethasone; *ICU*, intensive care unit; *ICS*, inhaled corticosteroid; *ns*, not significant; *OCS*, oral corticosteroid; *SD*, standard deviation.
*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. Adult onset and male effects explored by negative binomial models and expressed as rate ratios (95% confidence intervals).
§Nonadjusted estimated odds ratio because the 1-factor model was better than the 2-factor model (by stepwise selection), but very similar to the adjusted estimated odds ratio.

TABLE E7. Detailed health care utilization/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
Hospitalizations				
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

Count variables expressed as percentages for each category. Early onset <18 years; adult onset ≥18 years.
ICU, Intensive care unit; *OCS*, oral corticosteroid.

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 (y)	50.6 (15.8)		18.0 (0.6)	38.3 (12.6)	
	Early onset	Adult onset	Early onset (ever asthmatic in first 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		

Early onset <18 years; adult onset ≥18 years.
EOSA, Epigenetics of Severe Asthma study, mild cohort; *IOWBC*, Isle of Wight Whole Population Birth Cohort; *WATCH*, Wessex AsThma CoHort of difficult asthma.

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