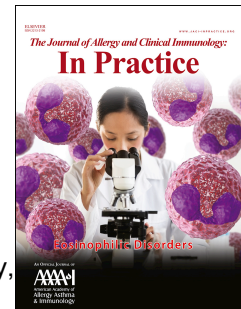


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The Clinical Implications of *Aspergillus Fumigatus* Sensitization in Difficult-To-Treat Asthma Patients

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Title:

**The Clinical Implications of Aspergillus Fumigatus Sensitization in Difficult-To-Treat
Asthma Patients**

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ABSTRACT:

Background: Fungal sensitivity has been associated with severe asthma outcomes.

However, the clinical implication of *Aspergillus fumigatus* (*A.fumigatus*) sensitization in difficult-to-treat (or difficult) asthma is unclear.

Objectives: To characterize the clinical implications of *A.fumigatus* sensitization in a large difficult asthma cohort.

Methods: Participants who underwent both skin prick (SPT) and specific IgE testing to *A.fumigatus* (n=318) from the longitudinal real-life Wessex AsThma CoHort of difficult asthma (WATCH), UK, were characterized by *A.fumigatus* sensitization (either positive SPT or specific IgE) and Allergic Bronchopulmonary Aspergillosis (ABPA) status using clinical/pathophysiological disease measures.

Results: *A.fumigatus* sensitization was found in 23.9% (76/318) of difficult asthma patients. Compared to *A.fumigatus* non-sensitized subjects, those with sensitization were significantly more often male (50% v 31%), older (58-years) with longer asthma duration (33-years), higher maintenance oral corticosteroid (m-OCS) (39.7%) and asthma biologic use (27.6%), raised current/maximum $\log_{10}$ total IgE+1 (2.43/2.72IU/L), worse pre-bronchodilator airflow obstruction (FEV_1 62.2%predicted, FEV_1/FVC 61.2%, $FEF_{25-75\%}$ 30.9%pred.), frequent radiological bronchiectasis (40%), but had less psychophysiologic comorbidities. ABPA diagnosis was associated with higher treatment needs and stronger eosinophilic signals. Factors independently associated with *A.fumigatus* sensitization in difficult asthma included m-OCS use (OR=3.34) and maximum $\log_{10}$ total IgE+1 (OR=4.30), whilst for ABPA, included m-OCS use (OR=6.98), maximum $\log_{10}$ total IgE+1 (OR=4.65) and radiological bronchiectasis (OR=4.08).

Conclusion: *A.fumigatus* sensitization in difficult asthma identifies a more severe form of airways disease associated with greater morbidity, treatment need, and airways dysfunction/damage, but fewer psychophysiologic comorbidities. Screening of *A.fumigatus* status should be an early element in the comprehensive assessment of difficult asthma patients.

Highlights Box:

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

A.fumigatus sensitivity has been linked to worse asthma outcomes through adverse-associated clinical phenotypes including Allergic Bronchopulmonary Aspergillosis. However, the clinical relevance and burden of *A.fumigatus* sensitization within the real-life adult difficult asthma population is unknown.

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

Stratification of a UK real-life difficult asthma cohort by *A.fumigatus* sensitization identified a more severe airways disease state with few of the comorbidities commonly observed in difficult asthma.

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

This study highlights that *A.fumigatus* sensitization status should be a core early assessment in difficult asthma patients that could then facilitate management measures to potentially prevent lung function impairment and development of structural airways damage.

The WATCH study is registered through ClinicalTrials.gov; Identifier: NCT03996590

KEY WORDS: Aspergillus fumigatus, fungal sensitization, SAFS, ABPA, difficult asthma,
lung function

ABBREVIATIONS:

ABPA Allergic Bronchopulmonary Aspergillosis
ACQ Asthma Control Questionnaire
BD Bronchodilator
BMI Body Mass Index
FeNO Fractional Exhaled Nitric Oxide
FEF_{25-75%} Forced expiratory flow between 25-75% exhalation
FEV₁ Forced Expiratory Volume in 1 second
FVC Forced Vital Capacity
GORD Gastro-oesophageal Reflux Disease
HADS Hospital Anxiety and Depression Scale
HRCT High-Resolution Computed Tomography
ICU Intensive Care Unit
IgE Immunoglobulin E
IL-5 Interleukin-5
m-OCS Maintenance oral corticosteroid
OCS Oral corticosteroid
SAFS Severe Asthma with Fungal Sensitization
SPT Skin prick test

INTRODUCTION

An evolving understanding of asthma as a clinically diverse heterogeneous collection of phenotypes has led to the recognition of more severe forms of asthma¹⁻³. In that context, clinical phenotypes characterized by sensitization to fungal allergens like *Aspergillus fumigatus* (*A.fumigatus*) have been associated with worse asthma severity^{4,5}. Sensitization to *A.fumigatus* has been associated with a spectrum of states from “Severe Asthma with Fungal Sensitization” (SAFS) to Allergic Bronchopulmonary Aspergillosis (ABPA)⁶. The global prevalence of such “Allergic Fungal Airway Disease” is unclear but it has been estimated that 4.8 million people with asthma may have ABPA worldwide⁷. A previous meta-analysis estimated *A.fumigatus* sensitization in around 28% of people with asthma in general, of whom 40% had ABPA⁸. ABPA was generally commoner in developing countries in that study⁸. Notably, *A.fumigatus* sensitization and exposure have been linked to adverse asthma outcomes including poor disease control, higher treatment needs, greater healthcare utilization, potential mortality-risk, impaired lung function and bronchiectasis⁹⁻²⁰.

Around 5-10% of asthmatics have “difficult-to-treat asthma”, also known as “difficult asthma”, defined as problematic asthma where poor control is related to contributory factors such as comorbidities, suboptimal treatment, poor medication adherence and poor inhaler technique^{21,22}. Difficult asthma imposes significant healthcare and economic burden and is far more prevalent than severe treatment-resistant asthma where such factors have been addressed yet asthma control remains poor²³. While the association of *A.fumigatus* sensitization with severe asthma is recognized, the impact of *A.fumigatus* sensitization in the more widely encountered clinical group of difficult asthma has not been clearly described. Better understanding of the clinical importance of *A.fumigatus* sensitization in difficult asthma could support improved personalised management strategies and clinical

outcomes. To address this need, herein we characterize the clinical implications of *A.fumigatus* sensitization in a real-life United Kingdom (UK) clinical cohort of adult difficult asthma; the Wessex AsThma CoHort of difficult asthma (WATCH) study.

METHODS

WATCH Data Collection

WATCH (n=501, at point of analysis) is a prospective clinical cohort of adult difficult asthma patients at University Hospital Southampton NHS Foundation Trust (UHSFT), UK. All patients managed with British Thoracic Society Step “high-dose therapies” and/or “continuous or frequent use of oral steroids”²⁴ in the Adult or Transitional Regional Difficult Asthma Clinic at UHSFT were invited to participate. Data acquisition at enrolment from April 2015-March 2019 included detailed clinical, health and disease-related questionnaires, anthropometry, allergy skin prick testing (SPT), lung function testing, radiological imaging (small subset), biological samples (blood/urine) and induced sputum in a subgroup. A detailed outline of study protocol/methodology is published elsewhere²⁵. The study received Research Ethics Committee approval (REC reference: 14/WM/1226). Here, we present analysis of WATCH study enrolment data from 318 patients who underwent both *A.fumigatus* SPT (ALK-Abello, Denmark) and specific immunoglobulin E (IgE) testing within the preceding 10-years. This subgroup exhibited comparable characteristics to the overall WATCH cohort (n=501; Table E1). Mean wheal SPT diameter of ≥ 3 mm greater than the negative control defined positive *A.fumigatus* skin test sensitization. *A.fumigatus*-specific IgE ≥ 0.35 kU/L defined positive specific IgE sensitization. ABPA was defined by physician clinical diagnosis based on conventional criteria^{26,27}, as were other comorbidities (Table E2).

Our aims were 3-fold: First, to characterize the nature and clinical impact of the *A.fumigatus* sensitized phenotype within a difficult asthma cohort using WATCH study enrolment data.

Secondly, to characterize the nature and clinical impact of ABPA. Finally, to characterize how *A.fumigatus* sensitized subjects differ by diagnosed ABPA status.

Statistical Analysis

Statistical analysis was performed using SPSS 26 (NY, USA) and GraphPad Prism 9.1.2 (La Jolla, California, USA). To address our aims, analysis was performed with 3 sets of comparisons.

1. *A.fumigatus* sensitized (n=76) versus non-sensitized patients (n=242) in those where both SPT and specific IgE were performed (n=318).
2. A clinical diagnosis of ABPA (n=21) versus no ABPA (n=290) in patients who underwent *A.fumigatus* SPT and specific IgE testing, and had ABPA status recorded (n=311).
3. A clinical diagnosis of ABPA (n=21) versus no ABPA (n=55) in patients with positive *A.fumigatus* sensitization (n=76).

Continuous variables are presented as mean (standard deviation) for parametric data, and median (interquartile range) for non-parametric data, including minimum-maximum values. Categorical variables are displayed as frequencies (percentages). Independent sample T-test and Mann-Whitney U tests were applied to continuous variables with normal and skewed distribution respectively. For categorical variables, Fisher's exact and Chi-squared tests were performed for binary variables and one-way ANOVA for comparison of multiple groups. Backward stepwise binary logistic regression models using factors with trends for significance ($P < 0.1$) at univariate analysis were applied to identify factors independently associated with *A.fumigatus* sensitisation and/or ABPA. A P -value of < 0.05 was regarded statistically significant.

RESULTS

The WATCH cohort showed good stability during the reported observation period (April 2015 - March 2019) with retention of 86.4% of enrolled subjects during that interval. Of the 318 WATCH subjects who underwent both SPT and specific IgE testing for *A.fumigatus* sensitization, 15.4% had positive SPT to *A.fumigatus*, 17.6% had positive *A.fumigatus*-specific IgE, and 23.9% had *A.fumigatus* sensitization at either SPT or specific IgE (Table 1). Of subjects with *A.fumigatus* sensitization, 38.1% (29/76) were dual sensitized on both SPT and specific IgE.

Characterization of the A.fumigatus Sensitized Difficult Asthma Phenotype

A.fumigatus sensitized subjects were more often male, significantly older with longer asthma duration than non-sensitized subjects (Table 1). Conversely, no differences were observed in age of asthma onset, body mass index (BMI) and smoking status.

Acute oral corticosteroid (OCS) courses and prophylactic antibiotic use did not differ significantly by *A.fumigatus* sensitization status. Use of maintenance OCS (m-OCS), asthma biologics (omalizumab/mepolizumab) and the anti-fungal itraconazole were significantly greater in sensitized subjects (Table 1). Asthma hospitalizations in the past year were significantly greater in non-sensitized subjects.

Asthma Control Questionnaire-6 (ACQ6) score was significantly better in *A.fumigatus* sensitized subjects although 69.9% had suboptimal asthma control (ACQ6 ≥ 1.50) (Table 1). Nijmegen score, a measure of dysfunctional breathing, was significantly worse in non-sensitized subjects, among whom 49.4% had a score ≥ 23 . Hospital Anxiety and Depression Scale (HADS) Anxiety-component scores were also significantly worse in non-sensitized

subjects. Salicylate sensitivity (26.5% vs. 7.9%, $P=0.001$) and psychophysiologic comorbidities; dysfunctional breathing (57.8% vs. 34.7%, $P=0.001$), and anxiety or depression (52.2% vs. 31.0%, $P=0.002$), were significantly commoner in non-sensitized subjects (Table E3). Physical comorbidities including rhinitis, gastro-oesophageal reflux disease (GORD), obesity (BMI ≥ 30) and eczema did not differ significantly with *A.fumigatus* sensitization (Figure 1 and Table E3).

Serum log₁₀ total IgE+1 taken at +/- 6-months from enrolment, maximum log₁₀ total IgE+1 (highest IgE value recorded over 10-years preceding enrolment), plus both *A.fumigatus*-specific IgE and IgG were significantly greater in *A.fumigatus* sensitized subjects (Table 2). While blood eosinophil and neutrophil counts at enrolment did not significantly differ between groups, maximum blood eosinophil and neutrophil counts in the preceding 10-years were significantly greater in sensitized subjects. Airway inflammometry measurements including fractional exhaled nitric oxide (FeNO) and % sputum eosinophils were not significantly associated with *A.fumigatus* sensitization in the subgroup who underwent both *A.fumigatus* sensitization testing and sputum induction (n= 134). Percentage sputum neutrophils were significantly higher in *A.fumigatus* sensitized subjects. Furthermore, radiological bronchiectasis (central +/- other) and mucus plugging on high-resolution computed tomography (HRCT) scan were significantly commoner in sensitized subjects.

Pre-bronchodilator (BD) spirometry measurements were only available in a minority of subjects as many were unable to abstain from bronchodilators. Pre-BD forced expiratory volume in 1-second (FEV₁) (62.2 %predicted vs. 73.2 %pred., $P=0.031$), FEV₁/forced vital capacity (FVC) ratio (61.2% vs. 68.3%, $P=0.025$) and forced expiratory flow between 25-75%

exhalation (FEF_{25-75%}) (30.9 %pred. vs. 46.8 %pred., $P=0.005$) were significantly lower in sensitized subjects (Figure 2 and Table E4). Similarly, (post-BD) FEV₁/FVC and FEF_{25-75%} measures undertaken in clinic were also significantly worse in sensitized subjects (Table E4). Lastly, backward stepwise binary logistic regression models (Comparison 1; Table 5) identified *A.fumigatus* sensitization to be independently associated with higher maximum log₁₀ total IgE+1 and increased m-OCS use but decreased prevalence of psychological comorbidity, salicylate sensitivity and asthma hospitalizations in the past year. As HRCT data was available for only 57.5% cases, regression models were rerun without HRCT variables (bronchiectasis/mucus plugging) increasing the model to 79.9% cases. However, exclusion of HRCT variables from the regression model gave similar findings to the original model (Table 5).

Characterization of the ABPA Difficult Asthma Phenotype

A total of 311 subjects with both *A.fumigatus* SPT and specific IgE testing had a documented ABPA diagnosis status. Of these, 21 subjects (6.8%) had a clinical diagnosis of ABPA (Table 3). ABPA subjects were significantly older with longer asthma duration. No significant differences were seen in sex, BMI, smoking status or age at asthma onset. Use of m-OCS and itraconazole at enrolment was significantly greater in ABPA subjects. However, healthcare utilization, asthma biologics use, and acute OCS and antibiotic requirements were not significantly different between groups (Table 3).

ACQ6 was significantly worse in non-ABPA subjects, but HADS and Nijmegen scores did not differ between groups (Table 3). Psychological comorbidities and salicylate sensitivity were significantly more prevalent in subjects without ABPA (Figure 1 and Table E5, $P=0.042$ and $P=0.010$ respectively), but no significant differences were noted for other comorbidities.

Serum log₁₀ total IgE+1, maximum log₁₀ total IgE+1 plus *A.fumigatus*-specific IgE were significantly greater in ABPA subjects (Table 4). Furthermore, significantly lower current but higher maximum blood eosinophil counts in the preceding 10-years were observed in ABPA subjects, of whom 81.8% had a peripheral eosinophilia $\geq 0.4 \times 10^9/L$. Blood neutrophil counts and airway inflammometry did not differ. A significantly greater proportion of ABPA subjects had radiological bronchiectasis, mucus plugging and ground glass shadowing (Table 4). Spirometry did not significantly differ with ABPA status (Table E6).

Lastly, logistic regression models comparing ABPA status (Comparison 2; Table 5) demonstrated that m-OCS use, higher maximum log₁₀ total IgE+1 levels and radiological bronchiectasis were independently associated with an ABPA diagnosis. When the regression model was rerun without HRCT variables, similar independent associations for ABPA with m-OCS use and higher maximum log₁₀ total IgE+1 levels were found.

Stratification of A.fumigatus Sensitized Difficult Asthma by ABPA Status

Clinical characterization of *A.fumigatus* sensitized subjects (n =76) with (n =21; 27.6%) and without (n =55; 72.4%) an ABPA diagnosis (Table E7) was also performed.

Demographic, asthma-related history and healthcare utilization characteristics were similar between groups. Significant findings among ABPA subjects included greater use of m-OCS and itraconazole (Table E7, both $P<0.001$), plus higher current/maximum log₁₀ total IgE+1 levels, *A.fumigatus*-specific IgE, blood eosinophils at enrolment, and radiological bronchiectasis plus mucus plugging (Table E8, $P=0.027$, $P=0.005$, $P<0.001$, $P=0.027$, $P=0.003$ and $P=0.009$ respectively). In contrast, disease-related questionnaires, comorbidities and spirometry (Table E7, E9 and E10) did not vary between groups.

261 Lastly, logistic regression modelling identified independent associations of m-OCS use and
262 higher maximum $\log_{10}$ total IgE+1 levels with ABPA status in *A.fumigatus* sensitized subjects
263 (Comparison 3; Table 5). These associations remained when the model was rerun without
264 HRCT data.

265

DISCUSSION

This study provides clinically relevant insight into the implications of *A.fumigatus* sensitization and a diagnosis of ABPA within a UK adult clinical cohort of difficult asthma. In that regard, our definition of difficult asthma aligned with the corresponding GINA classification²¹. Stratification of subjects using *A.fumigatus* sensitization identified an important more severe disease phenotype within difficult asthma; the “*A.fumigatus* difficult asthma phenotype”. That represented a more severe airways disease state characterized by greater morbidity, treatment needs, elevated inflammatory signals, lung function impairment and structural airway damage but limited other comorbidities commonly seen in difficult asthma. Within this phenotype those diagnosed as ABPA showed most severe disease and substantial treatment needs. These findings highlight the clinical importance and implications of assessing *A.fumigatus* sensitization among patients with difficult asthma; a group known to have high healthcare needs.

Our study found that 1 in 4 patients with difficult asthma in a UK setting had *A.fumigatus* sensitization. That falls at the lower end of the prevalence range (15-48%) found in a previous worldwide meta-analysis of 20 studies reporting *A.fumigatus* sensitization across a range of asthmatic populations and severities⁸. It is plausible that *A.fumigatus* sensitization, SAFS and ABPA show geographical variation due to different environmental and climatic factors as well as possible genetic population differences and it is noteworthy that such conditions show higher prevalence in many developing countries^{8,28-30}. Differences in prevalence findings between studies may also reflect differences in the diagnostic tools used to define *A.fumigatus* sensitization. We used a combination of longitudinally available SPT or specific IgE sensitization to define *A.fumigatus* sensitization, since it is recognized that there may be discordance between SPT and specific IgE assessments of *A.fumigatus*

sensitization in up to 25% of subjects³¹. Indeed, we found that of subjects with either SPT or specific IgE sensitization, only 38% showed positive sensitization on both testing modalities. Our reported prevalence of 6.8% for ABPA in a UK difficult asthma population is greater than an estimated global prevalence of 2.5%⁷. It is though at the lower end of ABPA prevalence reported in a recent meta-analysis of fungal asthma studies conducted in Africa³⁰ and generally lower than recently reported studies from India²⁹.

Factors associated with *A.fumigatus* sensitization in the setting of asthma and ABPA remain poorly understood. In the present study of difficult asthma patients, *A.fumigatus* sensitization (but not ABPA diagnosis) showed male predominance which has not been widely reported before. One study of an adult severe asthma clinic in Singapore showed non-significant trends for male predominance in those with *A.fumigatus* sensitization¹¹. Otherwise, previously female or no sex predominance for *A.fumigatus* sensitization and/or ABPA have been demonstrated in studies of more severe asthma groups in both paediatric¹², and adult^{28,32,33,34} settings. Another notable finding in our difficult asthma population was that both *A.fumigatus* sensitized and ABPA diagnosed subjects were significantly older. Furthermore, their median age of ~60-years was older than the previously described range of 35-50-years for *A.fumigatus* sensitized asthmatics^{9,11,28,32-34}.

Also, a significantly longer asthma duration was observed in both *A.fumigatus* sensitized and ABPA subjects. That is consistent with recent findings from India that both severe adult asthma and longer asthma duration were independent predictors of *A.fumigatus* sensitivity³⁴. Though we observed trends for younger age of asthma onset in *A.fumigatus* sensitized difficult asthma and ABPA, these associations did not reach statistical significance. We recently described “age of onset-sex” stratified phenotypes in the wider WATCH cohort (n= 501) where significantly greater prevalence of *A.fumigatus* sensitization, ABPA and

bronchiectasis were found in the male early-onset (<18-years) atopic asthma phenotype who had longest disease duration³⁵. Our findings differ from many prior severe asthma observational studies where adult-onset asthma with a shorter disease duration was predominant in *A.fumigatus* sensitized individuals^{9,11,20,32-34}. However, at least one prior study has associated earlier onset asthma (<16-years) with having fungal sensitization⁹. Furthermore, recent studies have highlighted findings of fungal sensitization among childhood asthmatics that is associated with poor lung function, high treatment needs and potential persistent disease^{10,12,36}. Such patients may subsequently align with our recently described early-onset male adult difficult asthmatics³⁵. Early origins of adult airways disease are emerging with recognition of persistently low lung function trajectories established in early life that track longitudinally into adulthood³⁷⁻³⁹. We previously showed that both asthma and smoking impact such lung function trajectories in adolescence/early adulthood⁴⁰. The influence of early fungal sensitization in such pathways also merits consideration.

Our findings that *A.fumigatus* sensitized difficult asthma subjects had significantly impaired pre-bronchodilator spirometry with greater airflow limitation and small airways obstruction echo prior findings of impaired lung function in *A.fumigatus* sensitized asthmatics^{9,17-20}. So too do our findings of increased prevalence of radiological bronchiectasis at HRCT chest scan in difficult asthma patients with *A.fumigatus* sensitization and with ABPA¹⁸⁻²⁰. Collectively, this highlights potentially significant detrimental pathophysiological consequences of *A.fumigatus* airways disease even among a population of difficult asthma where other significant phenotypes may also be expected to exert detrimental pathophysiological effects¹⁻³. In our study, inflammatory measures (blood eosinophils and neutrophils, sputum eosinophils plus FeNO) showed limited cross-sectional association to *A.fumigatus*

sensitization or ABPA status. This may reflect the impact of high treatment levels that these patients were taking at the time of those assessments (high-dose inhaled steroids, m-OCS, omalizumab (anti-IgE) or mepolizumab (anti-IL-5)). We recently demonstrated that longitudinal assessment of parameters like blood eosinophils can provide added insight into the inflammatory endotypes of difficult asthma⁴¹. Applying that approach to our present analysis confirmed historical evidence of significantly elevated blood eosinophils in cases with *A.fumigatus* sensitization and ABPA. That supports the concept that inflammatory indices may have been suppressed and effectively masked by high treatment levels at a single time point assessment like WATCH study enrolment. Nevertheless, sputum neutrophils were significantly greater in *A.fumigatus* sensitized difficult asthmatics which along with evidence of historical maximum blood neutrophil counts may reflect the mixed inflammatory nature of allergic fungal airways disease that has been previously described^{6,20,42}. That we did not see as pronounced sputum changes in ABPA subjects as previously reported⁴² may again reflect treatment effects.

A notable feature of our *A.fumigatus* sensitized patients was the high level of asthma treatment that they required compared to other difficult asthmatics. Both *A.fumigatus* sensitized and ABPA subjects had higher requirements for m-OCS and anti-fungal treatments. Furthermore, *A.fumigatus* sensitized patients had greater need for asthma biologics. Both anti-fungal and biologic approaches in ABPA have proven efficacy^{43,44} and such high treatment needs are consistent with prior reports for fungal sensitized asthma¹¹⁻¹². What our study demonstrates is that this differential association of treatment need with *A.fumigatus* sensitization pertains even within a population of more difficult asthmatics.

Associations between *A.fumigatus* sensitization and frequent asthma exacerbations, hospitalization and ICU admissions have previously been reported¹³⁻¹⁵. This was not apparent in our cohort except with respect to ABPA status in *A.fumigatus* sensitized subjects who had non-significant trends for more ICU visits. So, we did not clearly corroborate recent reports associating ABPA with risk of ICU admission and intubation¹⁵. That we did not see more pronounced signals of morbidity may partly reflect the fact that the WATCH cohort represents a high morbidity population with more difficult asthma, limiting differences in adverse outcomes between subgroups. However, it may also again reflect the high levels of treatment being taken by *A.fumigatus* sensitized patients in our cohort that may have mitigated against more severe asthma outcomes. Potentially aligning with this latter concept, we noted that asthma control (ACQ6) was significantly better in both *A.fumigatus* sensitized and ABPA subjects. Perhaps for similar reasons, asthma hospitalization was commoner in non-sensitized subjects.

Difficult asthma can be regarded as a multimorbidity state that is typified by the presence of asthma alongside numerous aggravating comorbidities, both physical (e.g. rhinitis, GORD, obesity, salicylate sensitivity) and psychophysiologic (e.g. dysfunctional breathing, intermittent laryngeal dysfunction, depression, anxiety). We have previously demonstrated this model of difficult asthma within the WATCH cohort³⁵. In this study we found significantly lower prevalence of psychophysiologic comorbidities such as dysfunctional breathing and anxiety and/or depression in *A.fumigatus* sensitized subjects plus lower psychological comorbidity in ABPA subjects. Alongside their pathophysiological findings, that consolidates the impression that *A.fumigatus* sensitization identifies a purer severe airways disease endotype within the difficult asthma population. The significantly lower prevalence of salicylate (aspirin-exacerbated respiratory disease) sensitivity in both

A.fumigatus sensitized and ABPA subjects may reflect the commoner association of salicylate sensitivity with later rather than early-onset asthma phenotypes⁴⁵.

We demonstrated that difficult asthma subjects diagnosed with ABPA showed greater disease severity in terms of higher treatment needs, greater prevalence of bronchiectasis and higher serological markers including total IgE and blood eosinophils. That is consistent with existing knowledge of the ABPA phenotype and emphasizes the importance of assessing for this diagnosis in patients with difficult asthma⁴⁻⁶. However, making a diagnosis of ABPA is not always straightforward⁴⁶ even though diagnostic criteria have evolved over the past 40-years^{4,26,27,47,48}. As has been recently suggested, a more generic term of “Allergic Fungal Airway Disease” (AFAD) may provide a simpler framework of understanding⁵. In the future, adoption of novel tools such as recombinant antigen testing⁴⁹ may facilitate simpler diagnostic processes.

Our study had limitations. The real-life setting of the WATCH study meant it was prone to some missing data and recall bias, but these points did not significantly limit findings. The use of clinical diagnoses to define ABPA and other comorbidities may be criticized but is again reflective of real-life clinical practice. Also, our WATCH cohort is largely Caucasian and should be viewed in the context of the UK population studied. Nevertheless, it raises useful insights for consideration in other populations. Further studies are necessary in other communities to assess for the wider applicability of our findings. We focused our present analysis on impact of *A.fumigatus* sensitization in difficult asthma rather than wider fungal allergens given the thermotolerant nature of *A.fumigatus*, which enables airway colonisation and potentially unique pathological pathways compared to non-thermotolerant fungi that act as pure inhalant allergens⁵. This narrower perspective might be viewed as a

limitation, but when similarly assessed in the WATCH study sensitization to non-colonising fungi like *Alternaria* and *Cladosporium* did not associate with outcomes in difficult asthma patients (data not shown). This may infer that the different pathological and immunogenic properties of fungal species may confer different effects in difficult asthma. This observation is potentially clinically relevant given that sensitization to these other fungi is included in criteria to define entities like SAFS, AFAD and Allergic Bronchopulmonary Mycosis^{4,6,50}. Again future work should assess this point further. A key strength of our study is that the WATCH cohort represents a real-life difficult asthma clinic population. We were also able to define *A.fumigatus* sensitization in subjects using both SPT and blood testing thus providing a wider perspective on sensitization status. Another strength was the large size of the assessed cohort and extensive characterization available which enabled novel assessment of *A.fumigatus* sensitization in the context of the multimorbid state of difficult asthma.

In conclusion, *A.fumigatus* sensitization in difficult asthma patients identifies a more severe form of airways disease associated with older age but longer duration of disease, male sex, lung function impairment, bronchiectasis, higher inflammatory parameters and greater treatment needs but less psychophysiologic comorbidities. A diagnosis of ABPA carried worse prognosis. Early identification and screening of *A.fumigatus* status in difficult asthma patients should be a core part of their assessment. It could then direct more personalized treatments that preserve lung function, prevent progression to irreversible structural disease and associated morbidity.

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FIGURE LEGENDS**Figure 1 A-B: Comorbidity Characteristics Stratified by *A.fumigatus* Sensitization and Diagnosis of ABPA**

*Figure 1. Comorbidity Characteristics Stratified by A. fumigatus Sensitization Status and Diagnosis of ABPA: (A) Comorbidities stratified by A. fumigatus sensitization status. (B) Comorbidities stratified by diagnosis of ABPA. * $p \leq 0.05$, ** $p \leq 0.01$ and all other results not significant. Chi-squared and Fisher's exact tests applied for categorical variables. A full breakdown of results and statistics available in Supplementary Table E3 and E5.*

Figure 2 A-D: Pre-Bronchodilator Lung Function Characteristics Stratified by *A. fumigatus* sensitization

*Figure 2. Pre-Bronchodilator Spirometry Values Stratified by A.fumigatus Sensitization Status: A.fumigatus Sensitized vs. Non-sensitized. (A) Pre-BD FEV₁ %predicted. (B) Pre-BD FVC %predicted. (C) Pre-BD FEV₁/FVC ratio (%). (D) FEF_{25-75%} %predicted. ns=not significant, * $p \leq 0.05$, ** $p \leq 0.01$. T-test applied for parametric continuous variables and Mann-Whitney test for non-parametric data. A full breakdown of results and statistics available in Supplementary Table E4.*

605 **Table 1. Clinical characteristics of *A. fumigatus* sensitized vs. non-sensitized patients**

Variables	Overall	Sensitized	Non-sensitized	P-value
Subjects N	318	76	242	
Demographics				
Sex n (%)				
Female	204 (64.2)	38 (50.0)	166 (68.6)	0.003
Male	114 (35.8)	38 (50.0)	76 (31.4)	
Age at Enrolment (years)				
Median (IQ) Min-Max	51.5 (25.0) 17.0-85.0	58.0 (16.0) 18.0-81.0	50.0 (26.0) 17.0-85.0	0.001
Ethnicity				
Caucasian	294 (92.5)	70 (92.1)	224 (92.6)	1.000
Not Caucasian	24 (7.5)	6 (7.9)	18 (7.4)	
Body Mass Index (kg/m ²)				
Median (IQ) Min-Max	29.7 (9.7) 17.6-53.3	28.3 (7.4) 19.2-53.3	29.8 (10.5) 17.6-52.3	0.349
Smoking History n (%)				
Never	163 (51.3)	33 (43.4)	130 (53.7)	0.207
Current	16 (5.0)	3 (3.9)	13 (5.4)	
Ex	139 (43.7)	40 (52.6)	99 (40.9)	
Asthma-related History				
Age of Asthma Onset (years)				
Median (IQ) Min-Max	19.0 (34.0) 0-75.0	12.0 (40.0) 0-75.0	21.0 (32.0) 0-69.0	0.076
Asthma Duration (years)				
Median (IQ) Min-Max	23.5 (25.0) 0-83.0	33.0 (31.0) 0-74.0	22.0 (24.0) 0-83.0	<0.001
Missing	14	1	13	
Healthcare Utilization				
Asthma-related ICU Visits				
Median (IQ) Min-Max	0 (1) 0-15	0 (0) 0-6	0 (1) 0-15	0.167
Intubated Ever n (%)				
Yes	39 (12.3)	9 (11.8)	30 (12.4)	0.898
Hospitalizations in past 12 months				
Median (IQ) Min-Max	0 (1) 0-10	0 (0) 0-3	0 (1) 0-10	0.001
Missing	2	0	2	
OCS Courses in past 12 months				
Median (IQ) Min-Max	3.0 (4.0) 0-16.0	3.0 (3.0) 0-12.0	3.0 (4.0) 0-16.0	0.511
Missing	37	8	29	
Medication				
Maintenance OCS n/N (%)	94/314 (29.9)	29/73 (39.7)	65/241 (27.0)	0.037
Biologics at enrolment n (%)	56 (17.6)	21 (27.6)	34 (14.0)	0.006
Biologics after enrolment n (%)	86 (27.0)	24 (31.6)	69 (28.5)	0.608
Itraconazole n (%)	16 (5.0)	15 (19.7)	1 (0.4)	<0.001*
Macrolides n (%)	68 (21.4)	14 (18.4)	54 (22.3)	0.470
Doxycycline n (%)	31 (9.7)	7 (9.2)	24 (9.9)	0.856
Disease-related Questionnaires				
ACQ6 Score				
Median (IQ) Min-Max	2.50 (2.00) 0-6.00	2.20 (1.70) 0-5.70	2.50 (2.00) 0-6.00	0.006
Missing	26	3	23	
ACQ6 Score ≥ 1.50 n/N (%)	229/292 (78.4)	51/73 (69.9)	178/219 (81.3)	0.040
HADS-A Score				
Median (IQ) Min-Max	6.0 (6.0) 0-19.0	5.0 (6.0) 0-18.0	7.0 (6.0) 0-19.0	0.044
Missing	50	3	47	
HADS-A Score ≥ 11.0 n/N (%)	59/268 (22.0)	13/73 (17.8)	46/195 (23.6)	0.309
HADS-D Score				
Median (IQ) Min-Max	4.0 (6.0) 0-20.0	4.0 (5.0) 0-16.0	5.0 (7.0) 0-20.0	0.129
Missing	52	3	49	
HADS-D Score ≥ 11.0 n/N (%)	35/266 (13.2)	7/73 (9.6)	28/193 (14.5)	0.290
Nijmegen Score				
Median (IQ) Min-Max	22.0 (17.0) 0-57.0	20.0 (19.0) 0-42.0	22.0 (17.0) 0-57.0	0.048
Missing	87	17	70	
Nijmegen Score ≥ 23.0 n/N (%)	108/231 (46.8)	23/59 (39.0)	85/172 (49.4)	0.166

606 Table 1. Continuous variables are represented as median and interquartile range (IQ) with minimum, maximum and missing values shown. Categorical variables as frequency and percentages (n (%)). Mann Whitney tests applied for non-parametric continuous variables and Chi-squared tests for categorical variables with application of Fishers Exact Test (*) in cases with low cell counts. P-values < 0.05 are significant (in bold). Biologics at/after enrolment include Omalizumab (anti-IgE) and Mepolizumab (anti-interleukin-5). Abbreviations: ICU= intensive care unit, OCS= oral corticosteroids, ACQ6= Asthma Control Questionnaire, HADS-A= Hospital Anxiety and Depression Scale-Anxiety component, HADS-D= Hospital Anxiety and Depression Scale-Depression component.

607 **Table 2. Objective characteristics of *A. fumigatus* sensitized vs. non-sensitized patients**

Variables	Overall	Sensitized	Non-sensitized	P-value
Subjects N	318	76	242	
Blood				
Log ₁₀ (Total IgE+1) (+/-6 months) (IU/L)				
Median (IQ)	1.96 (1.11)	2.43 (0.97)	1.78 (1.02)	<0.001
Min, Max	0, 3.63	0, 3.51	0, 3.63	
Missing	64	13	51	
Log ₁₀ (Max. Total IgE+1) (IU/L)				
Median (IQ)	2.16 (1.11)	2.72 (0.92)	2.03 (1.06)	<0.001
Min, Max	0, 4.31	1.09, 4.31	0, 3.83	
Missing	1	0	1	
<i>A. fumigatus</i> -specific IgE (IU/L)				
Median (IQ)	0.00 (0.00)	1.04 (2.51)	0.00 (0.00)	<0.001
Min, Max	0.00 100.00	0.00, 100.00	0.00, 0.34	
<i>A. fumigatus</i> -specific IgG (mg/L)				
Median (IQ)	18.7 (22.7)	23.9 (32.8)	17.8 (19.9)	0.046
Min, Max	0.0, 190.0	0.0, 153.0	2.4, 190.0	
Missing	123	27	96	
Blood Eosinophils (10 ⁹ /L) (+/-6 months)				
Median (IQ)	0.20 (0.20)	0.20 (0.30)	0.20 (0.20)	0.960
Min, Max	0, 2.70	0, 1.50	0, 2.70	
Missing	23	6	17	
Max. Blood Eosinophils (10 ⁹ /L)				
Median (IQ)	0.40 (0.60)	0.60 (0.90)	0.40 (0.50)	0.017
Min, Max	0, 4.50	0, 4.50	0, 3.80	
Max. Blood Eosinophils $\geq 0.4 \times 10^9/L$ n (%)	184 (57.9)	53 (69.7)	131 (54.1)	0.016
Blood Neutrophils (10 ⁹ /L) (+/-6 months)				
Median (IQ)	5.6 (3.0)	5.8 (3.5)	5.6 (2.9)	0.837
Min, Max	2.1, 24.0	2.6, 16.6	2.1, 24.0	
Missing	23	6	17	
Max. Blood Neutrophils (10 ⁹ /L)				
Median (IQ)	9.5 (6.5)	10.6 (6.5)	9.3 (6.1)	0.031
Min, Max	2.8, 34.3	4.1, 24.1	2.8, 34.3	
Airway Inflammometry				
FeNO (ppb)				
Median (IQ)	19.0 (29.4)	18.0 (28.8)	19.0 (30.2)	0.901
Min, Max	0, 216.0	0, 189.0	0, 216.0	
Missing	78	10	68	
Sputum Eosinophils (%)				
Median (IQ)	1.50 (8.39)	2.56 (7.88)	1.50 (8.80)	0.572
Min, Max	0, 66.25	0, 66.25	0, 60.25	
Missing	184	35	149	
Sputum Neutrophils (%)				
Median (IQ)	43.06 (42.72)	50.75 (40.90)	40.50 (35.75)	0.005
Min, Max	1.50, 96.75	3.75, 96.75	1.50, 88.75	
Missing	184	35	149	
HRCT Chest Imaging				
Bronchiectasis n/N (%)	41/183 (22.4)	20/50 (40.0)	21/133 (15.8)	0.001
Mucus plugging n/N (%)	20/183 (10.9)	10/50 (20.0)	10/133 (7.5)	0.016
Ground glass shadowing n/N (%)	25/184 (13.6)	10/50 (20.0)	15/134 (11.2)	0.121
Bronchial wall thickening n/N (%)	82/184 (44.6)	21/50 (42.0)	61/134 (45.5)	0.740

608 Table 2. Continuous variables are represented as median and interquartile range (IQ) for non-parametric data and mean (SD) for
609 parametric data. Minimum, maximum and missing values are shown. Categorical variables as frequency and percentages (n (%)).
610 Mann Whitney tests applied for non-parametric continuous variables and T-test for parametric data. Chi-squared tests for
611 categorical variables. P-values < 0.05 are significant (in bold). Abbreviations: IgE= immunoglobulin E, Max.= maximum, IgG=
612 immunoglobulin G, FeNO= fractional exhaled nitric oxide, HRCT= high resolution computed tomography.

Table 3. Clinical characteristics of WATCH difficult asthma patients with or without a diagnosis of ABPA

Variables	Overall	ABPA	No ABPA	P-value
Subjects N	311	21	290	
Demographics				
Sex n (%)				
Female	199 (64.0)	10 (47.6)	189 (65.2)	0.106
Male	113 (36.0)	11 (52.4)	101 (34.8)	
Age at Enrolment (years)				
Median (IQ) Min-Max	52.0 (25.0) 17.0-85.0	61.0 (16.0) 34.0-77.0	51.0 (25.0) 17.0-85.0	0.027
Ethnicity				
Caucasian	287 (92.3)	18 (85.7)	269 (92.8)	0.213*
Not Caucasian	24 (7.7)	3 (14.3)	21 (7.2)	
Body Mass Index (kg/m ²)				
Median (IQ) Min-Max	29.7 (9.7) 17.6-53.3	27.8 (7.2) 19.2-38.4	29.8 (9.9) 17.6-53.3	0.067
Smoking History n (%)				
Never	160 (51.4)	10 (47.6)	150 (51.7)	0.514
Current	13 (4.2)	0 (0)	13 (4.5)	
Ex	139 (44.7)	11 (52.4)	127 (43.8)	
Asthma-related History				
Age of Asthma Onset (years)				
Median (IQ) Min-Max	19.5 (34.0) 0-75.0	11.0 (34) 0-75.0	21.0 (33.0) 0-73.0	0.221
Asthma Duration (years)				
Median (IQ) Min-Max	23.0 (25.0) 0-83.0	35.0 (25.0) 0-59.0	22.0 (26.0) 0-83.0	0.002
Missing	13	0	13	
Healthcare Utilization				
Asthma-related ICU Visits				
Median (IQ) Min-Max	0 (1) 0-15	0 (1) 0-6	0 (1) 0-15	0.429
Intubated Ever n (%)				
Yes	39 (12.5)	5 (23.8)	34 (11.7)	0.160*
Hospitalizations in past 12 months				
Median (IQ) Min-Max	0 (1) 0-10	0 (0) 0-3	0 (1) 0-10	0.362
OCS Courses in past 12 months				
Median (IQ) Min-Max	3.0 (4.0) 0-16.0	4.0 (3.0) 0-8.0	3.0 (4.0) 0-16.0	0.643
Missing	37	3	34	
Medication				
Maintenance OCS n/N (%)	93/307 (30.3)	16 (76.2)	77/286 (26.9)	<0.001
Biologics at enrolment n (%)	52 (16.7)	7 (33.3)	45 (15.5)	0.061*
Biologics after enrolment n (%)	92 (29.6)	7 (33.3)	85 (29.3)	0.696
Itraconazole n (%)	16 (5.1)	14 (67.3)	2 (0.7)	<0.001
Macrolides n (%)	68 (21.9)	7 (33.3)	61 (21.0)	0.183*
Doxycycline n (%)	31 (10.0)	4 (19.0)	27 (9.3)	0.144*
Disease-related Questionnaires				
ACQ6 Score				
Median (IQ) Min-Max	2.50 (1.9) 0-6.00	2.05 (1.90) 0-3.70	2.50 (1.90) 0-6.00	0.049
Missing	25	1	24	
ACQ6 Score ≥ 1.50 n/N (%)	224/286 (78.4)	12/20 (60.0)	212/266 (79.7)	0.050*
HADS-A Score				
Median (IQ) Min-Max	6.0 (6.0) 0-19.0	5.0 (5.0) 0-18.0	7.0 (6.0) 0-19.0	0.149
Missing	49	3	46	
HADS-A Score ≥ 11.0 n/N (%)	57/262 (21.8)	2/18 (11.1)	55/244 (22.5)	0.378*
HADS-D Score				
Median (IQ) Min-Max	4.0 (5.8) 0-20.0	4.0 (5.0) 0-11.0	4.5 (6.0) 0-20.0	0.255
Missing	51	3	48	
HADS-D Score ≥ 11.0 n/N (%)	33/260 (12.7)	2/18 (11.1)	31/242 (12.8)	1.000*
Nijmegen Score				
Median (IQ) Min-Max	22.0 (17.0) 0-57.0	20.5 (17.0) 0-39.0	22.0 (17.0) 0-57.0	0.191
Missing	85	3	82	
Nijmegen Score ≥ 23.0 n/N (%)	104/226 (46.1)	6/18 (33.3)	98/208 (47.1)	0.390

Table 3. Continuous variables are represented as median and interquartile range (IQ) with minimum, maximum and missing values shown. Categorical variables as frequency and percentages (n (%)). Mann Whitney tests applied for non-parametric continuous variables and Chi-squared tests for categorical variables with application of Fishers Exact Test (*) in cases with low cell counts. P-values < 0.05 are significant (in bold). Biologics at/after enrolment include Omalizumab (anti-IgE) and Mepolizumab (anti-interleukin-5). Abbreviations: ABPA= Allergic Bronchopulmonary Aspergillosis, ICU= intensive care unit, OCS= oral corticosteroids, ACQ6= Asthma Control Questionnaire, HADS-A= Hospital Anxiety and Depression Scale-Anxiety component, HADS-D= Hospital Anxiety and Depression Scale-Depression component.

Table 4. Objective characteristics of WATCH difficult asthma patients with or without a diagnosis of ABPA

Variables	Overall	ABPA	No ABPA	P-value
Subjects N	311	21	290	
Blood				
Log ₁₀ (Total IgE+1) (+/-6 months) (IU/L)				
Median (IQ)	1.96 (1.13)	2.76 (0.96)	1.91 (1.07)	<0.001
Min, Max	0, 3.63	0, 3.51	0, 3.63	
Missing	62	2	60	
Log ₁₀ (Max. Total IgE+1) (IU/L)				
Median (IQ)	2.15 (1.12)	2.98 (0.80)	2.13 (1.07)	<0.001
Min, Max	0, 4.31	1.24, 4.31	0, 3.83	
Missing	1	0	1	
A. fumigatus-specific IgE (IU/L)				
Median (IQ)	0 (0)	9.30 (19.84)	0 (0)	<0.001
Min, Max	0, 100.00	0, 100.00	0, 22.50	
A. fumigatus-specific IgG (mg/L)				
Median (IQ)	18.7 (22.9)	31.2 (53.7)	18.7 (22.4)	0.233
Min, Max	0, 190.0	0, 153.0	0, 190.0	
Missing	119	6	113	
Blood Eosinophils (10 ⁹ /L) (+/-6 months)				
Median (IQ)	0.20 (0.20)	0.10 (0.20)	0.20 (0.20)	0.043
Min, Max	0, 2.70	0, 1.50	0, 2.70	
Missing	23	1	22	
Max. Blood Eosinophils (10 ⁹ /L)				
Median (IQ)	0.40 (0.60)	0.90 (1.30)	0.40 (0.60)	0.029
Min, Max	0, 4.50	0, 2.70	0, 4.50	
Max. Blood Eosinophils $\geq 0.4 \times 10^9/L$ n (%)	182 (58.3)	18 (81.8)	164 (56.6)	0.020
Blood Neutrophils (10 ⁹ /L) (+/-6 months)				
Median (IQ)	5.6 (3.0)	6.5 (3.1)	5.6 (3.0)	0.185
Min, Max	2.1, 24.0	3.9, 16.6	2.1, 24.0	
Missing	23	1	22	
Max. Blood Neutrophils (10 ⁹ /L)				
Median (IQ)	9.4 (6.5)	10.7 (6.5)	9.3 (6.4)	0.116
Min, Max	2.8, 34.3	6.2, 21.8	2.8, 34.3	
Airway Inflammometry				
FeNO (ppb)				
Median (IQ)	19.0 (29.3)	18.5 (54.3)	19.0 (28.3)	0.766
Min, Max	0, 216.0	2.7, 164.7	0, 216.0	
Missing	76	3	73	
Sputum Eosinophils (%)				
Median (IQ)	1.50 (8.55)	2.03 (8.31)	1.50 (8.83)	0.914
Min, Max	0, 66.25	0, 60.25	0, 66.25	
Missing	180	7	173	
Sputum Neutrophils (%)				
Median (IQ)	43.06 (42.72)	43.82 (52.88)	42.88 (40.56)	0.809
Min, Max	1.50, 96.75	7.75, 93.50	1.50, 96.75	
Missing	180	7	173	
HRCT Chest Imaging				
Bronchiectasis n/N (%)	41/182 (22.5)	13/20 (65.0)	28/162 (17.3)	<0.001*
Mucus plugging n/N (%)	20/182 (11.0)	8/20 (40.0)	12/162 (7.4)	<0.001*
Ground glass shadowing n/N (%)	25/183 (13.7)	7/20 (35.0)	18/163 (11.0)	0.009*
Bronchial wall thickening n/N (%)	82/183 (44.8)	9/20 (45.0)	73/163 (44.8)	1.000

Table 4. Continuous variables are represented as median and interquartile range (IQ) for non-parametric data and mean (SD) for parametric data. Minimum, maximum and missing values are shown. Categorical variables as frequency and percentages (n (%)). Mann Whitney tests applied for non-parametric continuous variables and T-test for parametric data. Chi-squared tests for categorical variables with application of Fishers Exact Test (*) in cases with low cell counts. P-values < 0.05 are significant (in bold). Abbreviations: ABPA= Allergic Bronchopulmonary Aspergillosis, IgE= immunoglobulin E, Max.= maximum, IgG= immunoglobulin G, FeNO= fractional exhaled nitric oxide, HRCT= high resolution computed tomography.

Table 5. Logistic regression models assessing associated factors for *A. fumigatus* sensitization and ABPA in difficult asthma

Comparisons	Models	Clinical Variables	P-value	OR	95% CI
1. <i>A. fumigatus</i> sensitized vs. non-sensitized subjects	Model 1	Maintenance OCS use	0.011	3.34	1.32-8.49
		Maximum Log ₁₀ Total IgE+1	<0.001	4.30	2.18-8.46
		Hospitalization in past 12 months	0.012	0.42	0.22-0.83
		Psychological comorbidity	0.004	0.21	0.08-0.61
		Salicylate sensitivity	0.011	0.13	0.03-0.63
	Model 2	Maintenance OCS use	0.023	2.32	1.12-4.77
		Maximum Log ₁₀ Total IgE+1	<0.001	4.60	2.67-7.94
		Hospitalization in past 12 months	0.012	0.54	0.34-0.87
		Psychological comorbidity	0.033	0.45	0.22-0.94
		Salicylate sensitivity	0.004	0.19	0.06-0.59
2. Diagnosis of ABPA in WATCH cohort	Model 1	Maintenance OCS use	0.005	6.98	1.81-26.98
		Maximum Log ₁₀ Total IgE+1	0.002	4.65	1.79-12.07
		Bronchiectasis on HRCT	0.027	4.08	1.18-14.15
	Model 2	Maintenance OCS use	<0.001	9.42	2.80-19.68
3. Diagnosis of ABPA in <i>A. fumigatus</i> sensitized subjects	Model 1	Maximum Log ₁₀ Total IgE+1	<0.001	7.46	2.83-19.70
		Maintenance OCS use	0.001	16.36	3.04-88.16
	Model 2	Maximum Log ₁₀ Total IgE+1	0.018	5.06	1.32-19.47
		Maintenance OCS use	<0.001	13.30	3.17-55.72
		Maximum Log ₁₀ Total IgE+1	0.006	5.21	1.59-17.05

Table 5. P-values < 0.05 are significant. Abbreviations: OR= odds ratio, 95% CI= 95% confidence intervals, OCS= oral corticosteroids, IgE= immunoglobulin E, HRCT =high resolution computed tomography chest, ABPA= Allergic Bronchopulmonary Aspergillosis. Psychological comorbidity is defined as anxiety +/- depression.

Comparison 1.: Model 1 consists of 149/318 (46.9%) cases and includes the variables male sex, age at enrolment, maintenance OCS use, asthma hospitalization in the past 12 months at enrolment, ACQ6 score, max. log₁₀ total IgE+1 in past 10-years, max. blood eosinophil count in past 10-years, max. blood neutrophil count in past 10-years, bronchiectasis on HRCT, mucus plugging on HRCT and comorbidities (psychological comorbidity, dysfunctional breathing and salicylate sensitivity). Model 2 consists of 254/318 (79.9%) cases and includes variables used for Model 1 except bronchiectasis and mucus plugging on HRCT.

Comparison 2.: Model 1 consists of 152/311 (48.9%) cases and includes the variables age at enrolment, BMI, maintenance OCS use, ACQ6 score, max. log₁₀ total IgE+1 in past 10-years, max. blood eosinophil count in past 10-years, bronchiectasis on HRCT and psychological comorbidity. Model 2 consists of 256/311 cases (82.3%) cases and includes variables used for Model 1 except bronchiectasis on HRCT.

Comparison 3.: Model 1 consists of 47/76 cases (61.8%) and includes the variables asthma-related ICU visits, maintenance OCS use, max. log₁₀ total IgE+1 in past 10-years, blood eosinophil count within 6 months of enrolment and bronchiectasis on HRCT. Model 2 consists of 70/76 (92.1%) cases and includes variables used in Model 1 except bronchiectasis on HRCT.

Figure 1.

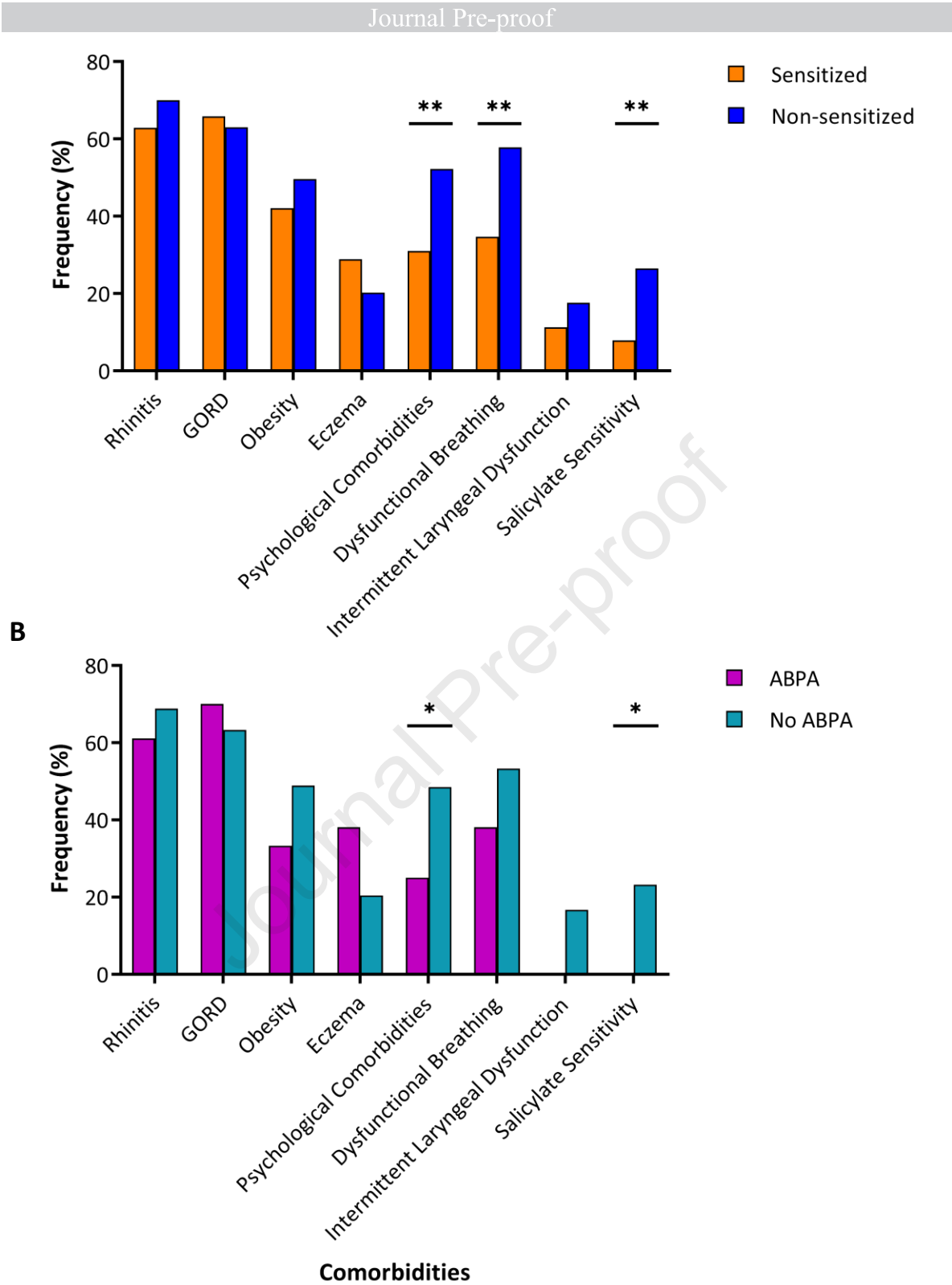


Figure 2.

