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The role of inflammation in anxiety and depression in the European U-BIOPRED asthma cohorts

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ABSTRACT

Background: Growing evidence indicates high comorbid anxiety and depression in patients with asthma. However, the mechanisms underlying this comorbid condition remain unclear. The aim of this study was to investigate the role of inflammation in comorbid anxiety and depression in three asthma patient cohorts of the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) project.

Methods: U-BIOPRED was conducted by a European Union consortium of 16 academic institutions in 11 European countries. A subset dataset from subjects with valid anxiety and depression measures and a large blood biomarker dataset were analysed, including 198 non-smoking patients with severe asthma (SAn), 65 smoking patients with severe asthma (SAs), 61 non-smoking patients with mild-to-moderate asthma (MMA), and 20 healthy non-smokers (HC). The Hospital Anxiety and Depression Scale was used to measure anxiety and depression and a series of inflammatory markers were analysed by the SomaLogic v3 platform (SomaLogic, Boulder, Colo). ANOVA and the Kruskal-Wallis test were used for multiple-group comparisons as appropriate.

Results: There were significant group effects on anxiety and depression among the four cohort groups ($p < 0.05$). Anxiety and depression of SAn and SAs groups were significantly higher than that of MMA and HC groups ($p < 0.05$). There were significant differences in serum IL6, MCP1, CCL18, CCL17, IL8, and Eotaxin among the four

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groups ($p < 0.05$). Depression was significantly associated with IL6, MCP1, CCL18 level, and CCL17; whereas anxiety was associated with CCL17 only ($p < 0.05$).

Conclusions: The current study suggests that severe asthma patients are associated with higher levels of anxiety and depression, and inflammatory responses may underlie this comorbid condition.

1. Introduction

Asthma is a major chronic health problem affecting over 300 million worldwide which causes a significant social and financial burden (Del Giacco et al., 2016). It is not only associated with increased physical comorbidity, but also with increased psychological distress (Goodwin et al., 2003a). The fundamental characteristic of asthma is sudden and unexpected attacks of impaired breathing, with a strong affective component that can cause anxiety. Data from epidemiological surveys show a high prevalence of anxiety in asthma patients: up to 30% in children and adolescents and 34% in adults (Katon et al., 2004; Weiser, 2007). People with asthma are up to six times more likely than the general population to experience anxiety (Thomas et al., 2011), which can present at all three stages of asthma: onset, progression, and exacerbation (Edwards et al., 2017). Different characteristics and forms of anxiety have been identified in asthma, which vary in intensity and situation (ten Thoren and Petermann, 2000). In addition, psychological distress is found to be associated with bronchoconstriction of the airways (ten Brinke et al., 2001). There is evidence that individuals with asthma have twice the risk of developing depressive symptoms as compared with those who do not have asthma (Rosenkranz and Davidson, 2009). This was further highlighted in our recent systematic review and meta-analysis (Ye et al., 2021). In secondary care populations, up to 50% of patients with asthma have been reported to have clinically significant depressive symptoms and over a third of asthmatic outpatients have been found to have a major depressive episode (Hasegawa et al., 2012). Comorbid anxiety and depression can lead to poor asthma control, symptomatic exacerbation, lower quality of life, and an increased utilization of emergency services (Richardson et al., 2006; McCauley et al., 2007).

Growing evidence indicates impaired inflammatory responses linked to asthma, depression, and anxiety independently (Zhu et al., 2016). However, the mechanisms underlying comorbid anxiety and depression with asthma remain unclear. One theory suggests that this association is linked to the complex psycho-neuro-immunological pathways involving mainly pro-inflammatory cytokines and the imbalance towards the Th2 T-cell response (Del Giacco et al., 2016). Cytokines modulate inflammatory responses which are involved in both asthma and affective disorders (Jiang et al., 2014). The CD4 Th2 immune response and its associated cytokines (interleukin (IL)-4, IL-5, and IL-13) are known to play an important role in the pathogenesis of allergic asthma. On the other hand, reports have shown that cytokines such as IL-6, tumor necrosis factor-alpha (TNF- α), IL-10, and monocyte chemoattractant protein-1/CCL2 are associated with anxiety and depression (Köhler et al., 2018; Rosenblat and McIntyre, 2017).

The aim of this study was to investigate the role of inflammation in comorbid anxiety and depression in asthma patients using a subset of data from the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) cohorts. We hypothesized that a shared inflammatory mechanism may underlie comorbid anxiety and depression in asthma patients. The European Asthma Research and Innovation Partnership (EARIP) Work Package has highlighted stress and psychological factors as amongst the key mechanisms involved in asthma onset, progression and exacerbation (Edwards et al., 2017). However, research into the mechanisms underlying comorbid anxiety and depression in asthma is limited due to relatively small sample size, lack of controls in the study design, and limited selection of inflammatory markers measured (Ye et al. 2021). In order to gain a better understanding of the biological mechanisms underpinning the co-morbidity of asthma and

anxiety and depression, we examined associations between pathobiological biomarkers and behavioural measures of anxiety and depression in the largest European asthma cohort.

2. Material and methods

2.1. U-BIOPRED cohorts

U-BIOPRED is a European Union consortium of 16 academic institutions in 11 European countries recruiting adult asthmatic patients and healthy volunteers with the objective of improving the understanding of asthma disease mechanisms using a systems biology approach (Shaw et al., 2015). The study was approved by the ethics committee for each participating clinical institution and adhered to the standards set by International Conference on Harmonisation and Good Clinical Practice. It is registered on [ClinicalTrials.gov](https://www.clinicaltrials.gov) (identifier: NCT01982162). All participants gave written informed consent. The U-BIOPRED adult cohort comprises 509 patients with mild-to-moderate and severe asthma, with additional sub-classification based on smoking history, and 101 non-asthmatic control subjects.

2.2. Participants

We used a subset of subjects with valid anxiety and depression measurements. Data from 198 non-smoking patients with severe asthma (SAn), 65 smoking patients with severe asthma (SAs), 61 non-smoking patients with mild-to-moderate asthma (MMA), and 20 healthy non-smokers (HC) were analysed in our study. The full descriptions of the different groups were reported in a previous report (Shaw et al., 2015).

2.3. Behavioural measures

The Hospital Anxiety and Depression Scale (HADS) was administered at baseline. The HADS is a reliable, practical and valid tool for identifying and quantifying anxiety (HADS-A) and depression (HADS-D). The questionnaire contains 7 anxiety and 7 depression questions, each scoring 0–3 points. It has been used in hospital, primary care and in the general population. The internal consistency of the HADS has been well demonstrated and optimal balance between sensitivity and specificity for HADS as a screening tool is achieved using a cut-off of 8 + for both HAD anxiety and depression subscales (Cooper et al., 2007).

2.4. Measures of inflammatory markers

Blood samples were collected and a large set of inflammatory markers measured. For the purpose of this study, the following were analysed: Eotaxin 3 (CCL26), Interleukin-17A (IL-17A), IL-13, periostin, macrophage inflammatory protein 1 beta (MIP1b, CCL4), IL-6, interferon (IFN)- γ , IFN- γ -inducible protein 10 (IP10, CXCL10), monocyte chemoattractant protein 1 (MCP1, CCL2), chemokine (C-C motif) ligand 18 (CCL18), chemokine (C-C motif) ligand 22 (CCL22), chemokine (C-C motif) ligand 17 (CCL17), tumour necrosis factor (TNF)- α , IL-8, and Eotaxin (CCL11) were analysed using the SomaScan v3 platform (SomaLogic, Boulder, Colo).

2.5. Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS version 22). All variables were tested for normality

using the Kolmogorov–Smirnov test before analysis. ANOVA was used for multiple group comparisons of normally distributed variables. The Kruskal–Wallis test was used for multiple-group comparisons of non-normally distributed variables, and the Chi-square test was used for categorical variables. Spearman correlational analysis was conducted to test associations among measures of anxiety, depression and serum levels of inflammatory markers.

3. Results

3.1. Demographic features

The demographic characteristics of participants are shown in Table 1. There were significant differences between group in terms of age, sex, marital status and ethnicity ($p < 0.05$). However, there were no differences in terms of education level ($p > 0.05$).

3.2. Psychometric measures of anxiety and depression

The average anxiety scores, depression scores, and HADS total scores among each of the four cohorts were shown in Table 2a,b. There was a significant group effect on anxiety score ($H = 37.66, p < 0.001$), with the SAs group showing the highest anxiety level. There was a significant group effect on depression score ($H = 45.71, p < 0.001$). There was also a significant group effect on total scores ($H = 46.18, p < 0.001$) (see Table 2a). Post-hoc analysis found that anxiety, depression and total scores of HADS of SAn and SAs groups were significantly higher than that of MMA and HC groups ($p < 0.01$), however, there were no significant differences between SAn and SAs groups or between the MMA and HC groups. The effect of oral corticosteroid use was also examined in both the SAn and SAs groups. There were 102 SAn who took oral corticosteroid (OCS) whereas 96 SAs patients did not use OCS. Within the SAn cohort, there were 38 patients took OCS whereas 27 patients did not. Data analysis did not reveal any significant treatment effects on anxiety or depression ($p > 0.05$), see Table 2b.

Table 1
Group demographic characteristics.

	SAn (n = 198)	SAs/ex (n = 65)	MMA (n = 61)	HC (n = 20)	H	p
Age (years)	51.21 ± 14.11	54.45 ± 11.12	40.70 ± 15.01	38.70 ± 13.85	39.99	0.000**
					χ^2	p
Sex					11.20	0.011*
Male	71	29	33	13		
Female	127	36	28	7		
Education					6.19	0.403
University and above	83	25	28	13		
Secondary school	108	39	32	7		
Others	7	1	1	0		
Marital					14.26	0.027*
Married	109	38	25	4		
No-relationship	33	8	15	7		
Others	56	19	21	9		
Ethnicity White_caucasian					10.51	0.015*
Others	176	64	59	20		
	22	1	2	0		

SAn: nonsmoking patients with severe asthma; SAs/ex: smoking patients with severe asthma; MMA: nonsmoking patients with mild-to-moderate asthma; HC: healthy nonsmokers.

* $p < 0.05$.

** $p < 0.01$.

Table 2a
Comparisons of anxiety and depression across 4 cohorts.

	SAn (n = 198)	SAs (n = 65)	MMA (n = 61)	HC (n = 20)	H	p
HADS_D	5.49 ± 4.06	5.86 ± 4.76	2.56 ± 2.99	1.90 ± 2.49	45.71	<0.001**
HADS_A	7.09 ± 4.54	7.71 ± 4.56	3.98 ± 3.24	3.65 ± 3.82	37.66	<0.001**
HADS_Total	12.58 ± 7.96	13.57 ± 8.64	6.54 ± 5.35	5.55 ± 5.95	46.18	<0.001**

SAn: nonsmoking patients with severe asthma; SAs/ex: smoking patients with severe asthma; MMA: nonsmoking patients with mild-to-moderate asthma; HC: healthy nonsmokers; HADS: Hospital Anxiety and Depression Scale; H: Kruskal–Wallis test statistic; ** $p < 0.01$. OCS: oral corticosteroid; OCS+: use of OCS; OCS-: without use of OCS.

Table 2b
Treatment effect of oral corticosteroid use in Severe asthma cohorts.

	SAn OCS+ (n = 102)	SAn OCS- (n = 96)	p	Sas OCS+ (n = 38)	SAs OCS- (n = 27)	p
HADS_D	5.69 ± 4.01	5.28 ± 4.13	0.47	5.58 ± 4.51	6.26 ± 5.16	0.58
HADS_A	7.15 ± 4.67	7.02 ± 4.41	0.85	6.89 ± 4.35	8.85 ± 4.69	0.09
HADS_Total	12.84 ± 8.05	12.30 ± 7.91	0.63	12.47 ± 8.26	15.11 ± 9.08	0.24

SAn: nonsmoking patients with severe asthma; SAs/ex: smoking patients with severe asthma; MMA: nonsmoking patients with mild-to-moderate asthma; HC: healthy nonsmokers; HADS: Hospital Anxiety and Depression Scale; H: Kruskal–Wallis test statistic; ** $p < 0.01$. OCS: oral corticosteroid; OCS+: use of OCS; OCS-: without use of OCS.

3.3. Measures of inflammatory markers

There was a significant group effect on serum IL-6, MCP1, CCL18, CCL17, IL-8, and Eotaxin (see Table 3). Post-hoc analysis using

Table 3
Comparisons of Inflammatory Markers.

	SAn	SAs	MMA	HC	H	p
Eotaxin3	17.6 (3.08,75.30)	17.90 (3.08,94.3)	17.10 (3.08,42.80)	18.80 (7.96,26.)	1.03	0.794
IL17A	0.36 (0.03,1.72)	0.31 (0.14,1.83)	0.31 (0.11,2.18)	0.35 (0.14,0.70)	5.36	0.147
IL13	0.64 (0.01,10.40)	0.58 (0.01,3.95)	0.59 (0.11,2.29)	0.41 (0.15,0.96)	4.62	0.202
Periostin	50.19 (27.76,142.60)	43.81 (24.99,78.30)	47.79 (26.84,72.24)	47.66 (31.74,80.15)	6.53	0.088
MIP1b	54.65 (20.20,289.00)	53.80 (22.30,290.00)	50.80 (21.00,252.00)	39.50 (22.60 , 98.40)	6.31	0.097
IL6	0.94 (0.16,14.60)	1.04 (0.16,5.41)	0.53 (0.16,9.72)	0.49 (0.16,1.37)	33.31	<0.001**
IP10	310.00 (57.58,2010.00)	304.00 (109.00,954.00)	270.00 (119.00,890.00)	275.50 (157.00,1010.00)	2.83	0.418
MCP1	109.00 (41.00,293.00)	113.00 (47.20,240.00)	92.60 (47.00,200.00)	95.40 (58.60,327.00)	12.84	0.005**
CCL18	173.17 (30.58,804.58)	190.26 (76.43,754.63)	121.48 (38.66,383.73)	118.29 (12.91,317.38)	32.85	<0.001**
CCL22	821.50 (165.00,2600.00)	925.00 (244.00,2250.00)	859.00 (224.00,2180.00)	721.50 (487.00,1260.00)	3.50	0.320
CCL17	85.05 (9.74,844.00)	79.60 (15.90,897.00)	59.50 (8.98,808.00)	40.60 (11.30,289.00)	17.59	0.001**
IFN-γ	6.58 (1.31,87.60)	5.05 (1.31,34.60)	5.08 (1.31,80.70)	5.65 (2.76,20.30)	7.29	0.063
TNFα	1.83 (0.62,8.74)	1.96 (0.78,4.02)	1.65 (0.94,4.09)	1.74 (1.06,3.01)	3.80	0.284
IL8	3.41 (1.12,183.00)	3.96 (1.69,9.15)	2.99 (1.40,11.70)	2.37 (0.84,8.97)	17.24	0.001**
Eotaxin	107.00 (14.75,855.00)	117.00 (51.60,370.00)	88.80 (31.50,308.00)	94.35 (32.80,163.00)	12.18	0.007**

SAn: nonsmoking patients with severe asthma; SAs/ex: smoking patients with severe asthma; MMA: nonsmoking patients with mild-to-moderate asthma; HC: healthy nonsmokers; IL17A: interleukin 17A; IL13: interleukin 13; MIP1b: macrophage inflammatory protein 1 beta; IL6: interleukin 6; IP10: IFN-γ-inducible protein 10; MCP1: monocyte chemoattractant protein 1; CCL18: chemokine (C C motif) ligand 18; CCL22: chemokine (C C motif) ligand 22; CCL17: chemokine (C C motif) ligand 17; IFN-γ: interferon gamma; TNFα: tumour necrosis factor alpha; IL8: interleukin 8; H: Kruskal–Wallis test statistic.

** p < 0.01.

Bonferroni tests indicated that IL6 and CCL18 levels in the SAn and SAs groups were significantly higher than in the MMA and HC groups ($p < 0.05$), MCP1 levels in the SAn and SAs groups were significantly higher than in the MMA group ($p < 0.05$), CCL17 levels in the SAn and SAs groups were significantly higher than in the HC group ($p < 0.05$) and the CCL17 level in SAn patients was significantly higher than in the MMA group ($p < 0.05$). The IL8 level in the SAn and SAs groups were significantly higher than in the HC group ($p < 0.05$) and IL8 levels in SAs/ex subjects was significantly higher than in the MMA group ($p < 0.05$). The Eotaxin levels in the MMA group was significantly higher than in the HC group ($p < 0.05$).

3.4. Correlations among anxiety, depression and inflammatory markers

There were significant positive correlations between serum IL-6 levels and the depression score ($r = 0.165, p < 0.01$) and total score ($r = 0.126, p < 0.05$), the MCP1 level and the depression score ($r = 0.152, p < 0.01$), CCL18 levels and the depression score ($r = 0.136, p < 0.05$) and total score ($r = 0.122, p < 0.05$), CCL17 levels and the depression score ($r = 0.108, p < 0.05$), anxiety score ($r = 0.115, p < 0.05$) and the total score ($r = 0.116, p < 0.05$) (Table 4). After controlling for gender, age and ethnicity, there was only a positive correlation between serum IL6 levels and the depression score ($r = 0.131, p < 0.05$). After controlling for anxiety, this association remained significant ($r = 0.144, p < 0.05$). Correlation analysis was also conducted between inflammatory markers for air flow obstruction and HADS scores. There was a small negative correlation between eosinophil count and HADS, and also a small negative correlation between FeNO and HADS in sever smoking asthma patients, see Table 5.

Table 4
Correlations between inflammatory markers and HADS in asthma patients.

	HADS_D p	HADS_A p	HADS_Total p
IL6	0.165**	0.077	0.126*
MCP1	0.152**	0.039	0.097
CCL18	0.136*	0.098	0.122*
CCL17	0.108*	0.115*	0.116*

Spearman test was used; HADS: Hospital Anxiety and Depression Scale; IL6: interleukin 6; MCP1: monocyte chemoattractant protein 1; CCL18: chemokine (C C motif) ligand 18; CCL17: chemokine (C C motif) ligand 17.

* p < 0.05.

** p < 0.01.

4. Discussion

Findings from our study support severe asthma associated with higher levels of anxiety and depression, and inflammatory responses may underlie this comorbid condition. The study was able to analyse a large European dataset collected involving three cohorts of asthma patients and examine how asthma severity was linked to psychological distress utilising measurements of multiple inflammatory markers and taking into consideration of confounding factors in the study design and data analysis.

Asthma is often regarded as a chronic disease with psychosomatic elements (Mrazek, 2003), as psychological disturbances such as anxiety or depression are strongly associated with asthma (Oga et al., 2007). Previous studies have found elevated levels of anxiety (Ritz et al., 2005; Goodwin, 2003) and depression (Zielinski and Brown, 2003) in patients with asthma, but the association with asthma severity is controversial

Table 5
Correlations between eosinophils and FeNO and HADS.

		HADS_D	HADS_A	HADS_Total
HC	Blood eosinophils	-0.18	-0.13	-0.16
	FeNO	-0.11	-0.24	-0.19
MMA	Blood eosinophils	-0.25	-0.28	-0.30
	FeNO	-0.10	-0.20	-0.17
SAs	Blood eosinophils	-0.22	-0.19	-0.22
	FeNO	-0.12	-0.13	-0.14
SAs	Blood eosinophils	-0.01*	-0.05	-0.03*
	FeNO	-0.04*	-0.05	-0.04*

HADS: Hospital Anxiety and Depression Scale; HADS-A: HADS anxiety; HADS-D: HADS depression; FeNO: fractional exhaled nitric oxide.

* $p < 0.05$.

(Amelink et al., 2014). Findings from our study found that severe asthma patients are associated with higher levels of anxiety and depression in comparison to mild and moderate asthma patients, which is in line with findings from studies conducted by Goodwin et al. (2003b) and Mancuso et al., (2008). In addition, the current study did not find any treatment effect on these associations in severe asthma patient cohort. However, mild asthma was also found to be significantly associated with anxiety by Gada et al., (2014), whereas others did not find such differences (Yellowlees et al., 1988; ten Brinke et al., 2001; Lavoie et al., 2010).

Of note, we did not find any effect of smoking on the levels of anxiety or depression in severe asthma patients. This is not in line with previous studies as Gada et al. (2014) found smoking to be significantly associated with anxiety and Choi et al. (2014) found current smoking status significantly associated with depression in elderly asthma patients. Studies in adolescents with asthma have shown that those who smoked were more than twice as likely to have major depression and one or more anxiety disorders compared with non-smokers (Bush et al., 2007). A possible explanation for this is that our study examined smoking status within severe asthma patients while other studies did not take the severity of asthma into consideration. Secondly, previous work has examined asthma in specific populations such as adolescents and the elderly. Overall, the current study points to a significant effect of asthma severity on anxiety and depression rather than smoking status.

The cause and effect relationship between asthma and psychological stress is unclear. One model, proposed by Chen and Miller (2007), depicts the immunological mechanisms by which psychological stress can exacerbate clinical symptoms in patients with asthma by altering the magnitude of the airway inflammatory response caused by irritants, allergens and infections. Other more recent evidence has demonstrated activation in the ventrolateral periaqueductal grey matter associated with respiratory threat, and prefrontal activity linked to stress-related inflammation (Faull et al., 2016; Rosenkranz et al., 2016). The presence of inflammatory responses and the crucial role of cytokines in anxiety (Hou and Baldwin, 2012) and depression (Liu et al., 2019) have also been addressed in numerous studies.

Our study found elevated serum IL-6 level in severe asthma patients with depression and anxiety after controlling for gender, age, and ethnicity, which is in line with previous research. IL-6 is a multifunctional cytokine that plays a critical role in immune response and acute phase reactions (Kopf et al., 1994; Kiecolt-Glaser et al., 2003). A recent study found that there was a strong association between high systemic IL-6 levels and asthma severity (Peters et al., 2016), as well as a significant increase in serum sIL-6R levels in asthma patients compared to control subjects (Yokoyama et al., 1997). The role of IL-6 in asthma has also been supported by genetic evidence such as rs4129267 in the interleukin-6 receptor (IL6R) gene identified as a risk locus for asthma (Ferreira et al., 2011). Furthermore, IL6 SNP rs1800797 has been

associated with the risk of adult-onset asthma (Lajunen et al., 2016). Data from our U-BIOPRED also revealed that epithelial IL-6 trans-signaling defines a new asthma phenotype with increased airway inflammation (Jevnikar et al. 2019) and data also suggested that IL6R-high sub-population of severe asthma patients with high sputum neutrophilia could potentially benefit from interventions targeting IL-6 pathway (Turan et al. 2017). On the other hand, growing evidence suggests a strong association between IL6 and depressive symptoms (Liu et al., 2017; Liu et al., 2012; Valkanova et al., 2013) and genetic polymorphisms in the genes for IL-6 have been involved in both immune activation and depression (Barnes et al., 2017). IL-6 is a central mediator by which psychological and physical stressors contribute to the development of depression (Iwata et al., 2013). The clinical symptoms and the chronic course of asthma can be a serious stressor to patients, which may stimulate the pro-inflammatory cytokine network, including increased level of IL-6 (Berk et al., 2013), which leads to stress-related disorders, such as depression through activation of hypothalamic–pituitary–adrenal axis or influence of the neurotransmitter metabolism (Ting et al., 2020). At the same time, when the imbalance between Th1/Th2 of the immune system arose, it would generate further allergic responses (Jiang et al., 2014), forming a negative loop.

In this study the levels of the measured chemokines MCP1, CCL17, and CCL18 were positively correlated with depression. Chemokines and their receptors play an important role in the late inflammatory stage of asthma (Dhaouadi et al., 2013). MCP1 might play a significant role in allergic responses because of its ability to induce mast cell activation and leukotriene C4 release into the airways through its receptor CCR2, which directly induces airway hyper-responsiveness (Campbell et al., 1999). It is also expressed in highly regionalized neuronal areas in the brain, modulating neuronal activity and neuroendocrine functions commonly seen in patients with depression. Additionally, it is involved in the control of other cytokines associated with the development of depression (Pae, 2014). CCL17 is a chemokine produced by myeloid dendritic cells, endothelial cells, bronchial epithelial cells and several tumour cells (Kumai et al., 2015), and can recruit T cells, in particular Th2 cells, and to activate other antigen-presenting cells. It can trigger secondary inflammatory events, aggravating asthma pathogenesis (Jo et al., 2018). CCL18 is a chemokine preferentially expressed in the lung, secreted by APCs, induced by Th2-type cytokines (Nadai et al., 2006). It can exhibit both pro- and anti-inflammatory properties, the latter through its ability to generate adaptive regulatory T cells in healthy subjects, with a loss of function in allergic patients (Tsicopoulos et al., 2013). As chemokines, CCL17 and CCL18 can also affect synaptic transmission and plasticity, neurogenesis, and neuron-glia communication (Stuart and Baune, 2014; de Jong et al., 2008; Heinisch and Kirby, 2009; Pujol et al., 2005). The disruption of any of these functions, by activating an inflammatory response, could contribute to the pathogenesis of depression (Milenkovic et al., 2019). However, the negative correlation between FeNO and the depression score in severe and smoking asthma patients suggests that the airway obstruction alone may not be associated with depression in this cohort. Further research is needed to explore and confirm these findings.

With respect to anxiety, we found that only CCL17 levels were positively correlated with anxiety levels. Recent evidence suggests that chemokines and their receptors are the key regulators of immune cell trafficking and activation which lead to pathophysiological changes that underly anxiety disorders (Stuart and Baune, 2014; Stuart et al., 2015). Evidence from animal models has shown that, compared to wild type mice, CCL17 deficient mice did not show an altered anxiety-related behaviour, while CCR4 knockout (CCR4^{-/-}) mice exhibited fewer anxiety related behaviour (Ambrée et al., 2016). In line with previous work, the current study further supports the association of CCL17 and anxiety in severe asthma patients.

However, the findings of the study must be interpreted considering some limitations. Firstly, we only analysed a single time-point (i.e. baseline data) in the U-BIOPRED study which does not allow a causal

judgement; secondly, subjective or historical data were assessed by questionnaires which might be prone to recall bias; thirdly, comparisons between asthma patients with and without anxiety/depression were not conducted due to the small numbers of subjects with this phenotype who were available for study and also that with the absence of a severe asthma group without anxiety/depression, it is not possible to determine the contribution of anxiety/depression to the greater inflammatory response found in severe asthma group; fourthly, due to limited access to records of life events, we were not able to examine any life events which could affect anxiety/depression and inflammatory markers. In addition, it would also be useful to evaluate lung functions and the frequency of exacerbations in future studies. Finally, the sample size of the four groups was relatively unbalanced which may minimise statistical power.

In conclusion, the findings of the current study suggest that severe asthma patients are associated with higher levels of anxiety and depression, and inflammatory responses may underlie this comorbid condition. In particular, IL6, MCP1, CCL18 and CCL17 are associated with comorbid depression whereas CCL17 is associated with anxiety in severe asthma. Future prospective studies are warranted to confirm the role of inflammation in the development of anxiety and depression in asthma, which could be used to stratify patients and develop targeted interventions to achieve improved outcomes.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Professor Hou sits on the ECNP Scientific Advisory Panel and currently holds a grant from Asthma Allergy Inflammation Research charity. Prof. Shaw receives consulting fees from Adherium, Nuvoair, Astra Zeneca and Chiesi. He also receives honoraria from Astra Zeneca and Chiesi and travel support from Chiesi and GSK. Professor Sven-Eric Dahlén declares consulting fees from Astra Zeneca, Cayman Chemicals, GSK, Novartis, Regeneron, Sanofi and Teva and honorarium from Sanofi. Dr Barbro Dahlén is in receipt of grants from GSK and Novartis and declares consulting fees from Novartis, Astra Zeneca and Sanofi. She is on the advisory board for Astra Zeneca and Sanofi. Prof. Fowler receives a grant from Boehringer Ingelheim and an honorarium from Chiesi. Prof. Sandstrom received payment for the Boehringer Ingelheim lecture (paid to his institution). Dr Auffrey and Dr De Meulder have both received support for the manuscript from the Innovative Medicines Initiative. Prof. Adcock has received grants from GSK, MRC and EPSRC. He also declares consulting fees from GSK, Sanofi, Chiesi and Kinaset. He has received honoraria from Astra Zeneca, Sanofi, Eurodrug, and Sunovion. He has also received payment for expert testimony from Chiesi and travel support from Astra Zeneca. Prof. Chung is in receipt of grants from MRC, EPSRC and GSK and honoraria from Astra Zeneca and Novartis. He is on the advisory board of Astra Zeneca, GSK, Roche and Novartis. Prof. Sterk received a grant from Innovative Medicines Initiative and has a non-substantial interest in SME Breathomix. Prof. Skipp has a grant from EU UBIPRED IMI FP and is a shareholder in TopMD Precision Medicine Ltd. Prof. Djukanovic receives consulting fees from Synairgen and honoraria from Regeneron, GSK and is on the advisory board for Synairgen. He also holds stock in Synairgen. Dr Ye, Dr Cheng, Dr Bakke, Dr Caruso, Dr Horváth, Prof. Howarth, Dr Krug, Dr Montuschi, Dr Sanak and Dr Schofield report no potential conflict of interest.

Data availability

Data will be made available on request.

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