



Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article



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

Ruihua Hou^{a,*}, Gang Ye^b, Xiaojing Cheng^c, Dominick E. Shaw^d, Per S. Bakke^e, Massimo Caruso^f, Barbro Dahlen^g, Sven-Erik Dahlen^g, Stephen J. Fowler^h, Ildikó Horváthⁱ, Peter Howarth^a, Norbert Krug^j, Paolo Montuschi^k, Marek Sanak^l, Thomas Sandström^m, Charles Auffrayⁿ, Bertrand De Meulderⁿ, Ana R. Sousa^o, Ian M. Adcock^p, Kian Fan Chung^p, Peter J. Sterk^q, Paul J. Skipp^r, James Schofield^{r,s}, Ratko Djukanović^{a,s}, on behalf of the U-BIOPRED Study Group

^a Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, UK

^b Suzhou Guangji Hospital, Suzhou, Jiangsu, China

^c Shandong Mental Health Centre, Shandong, China

^d Respiratory Research Unit, University of Nottingham, Nottingham, UK

^e Department of Clinical Science, University of Bergen, Bergen, Norway

^f Dept of Clinical and Experimental Medicine Hospital University, University of Catania, Catania, Italy

^g The Centre for Allergy Research, The Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

^h Faculty of Biology, Medicine and Health, School of Biological Sciences, Division of Infection, Immunity & Respiratory Medicine, The University of Manchester and Manchester Academic Health Science Centre and NIHR Manchester Biomedical Research Unit and Manchester University NHS Foundation Trust, UK

ⁱ Dept of Pulmonology, Semmelweis University, Budapest, Hungary

^j Fraunhofer Institute for Toxicology and Experimental Medicine Hannover, Hannover, Germany

^k Pharmacology, Faculty of Medicine, Catholic University of the Sacred Heart, Rome, Italy

^l Department of Internal Medicine, Jagiellonian University Medical College, Krakow, Poland

^m Department of Medicine, Department of Public Health and Clinical Medicine Respiratory Medicine Unit, Umea University, Sweden

ⁿ European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL-INSERM, Université de Lyon, France

^o Respiratory Therapeutic Unit, GlaxoSmithKline, Stockley Park, UK

^p National Heart and Lung Institute, Imperial College London, UK

^q Amsterdam UMC, University of Amsterdam, Holland, Netherlands

^r Biological Sciences, University of Southampton, Southampton, UK

^s NIHR Southampton Respiratory Biomedical Research Centre, UK

ARTICLE INFO

Keywords:

Asthma
Depression
Anxiety
Inflammation
U-BIOPRED

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 (SA_n), 65 smoking patients with severe asthma (SA_s), 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 SA_n and SA_s 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

* Corresponding author at: Clinical and Experimental Sciences, University of Southampton Faculty of Medicine, Academic Centre, College Keep, 4-12 Terminus Terrace, Southampton SO14 3DT, UK.

E-mail address: r.hou@soton.ac.uk (R. Hou).

<https://doi.org/10.1016/j.bbi.2023.04.011>

Received 22 October 2022; Received in revised form 13 April 2023; Accepted 23 April 2023

Available online 3 May 2023

0889-1591/© 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

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://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.

Acknowledgements

This article is presented on behalf of the U-BIOPRED Study Group with input from the U-BIOPRED Patient Input Platform, Ethics Board, and Safety Management Board. We thank all the members of each

recruiting center for their dedicated effort, devotion, promptness, and care in the recruitment and assessment of the participants in this study. Members of the U-BIOPRED Study Group are as follows: H. Ahmed, European Institute for Systems Biology and Medicine, University of Lyon; D. Allen, North West Severe Asthma Network; Pennine Acute Hospital NHS Trust; P. Badorrek, Fraunhofer ITEM; S. Ballereau, European Institute for Systems Biology and Medicine, University of Lyon; F. Baribaud, Janssen R&D; M. K. Batuwitige, Imperial College, London; A. Bedding, Roche Diagnostics GmbH, Mannheim; A. F. Behndig, Umea University; A. Berglind, Karolinska University Hospital and Karolinska Institutet; A. Berton, Boehringer Ingelheim Pharma GmbH & Co. KG; J. Bigler, Amgen; M.J. Boedigheimer, Amgen; K. Bønnelykke, University of Copenhagen and Danish Pediatric Asthma Center, Gentofte Hospital, University of Copenhagen; P. Brinkman, Academic Medical Centre, University of Amsterdam; A. Bush, Department of Paediatrics and National Heart and Lung Institute, Imperial College, and Department of Respiratory Paediatrics, Royal Brompton Hospital, London; D. Campagna, University of Catania; C. Casaulta, University Children's Hospital Bern; A. Chaiboonchoe, European Institute for Systems Biology and Medicine, University of Lyon; T. Davison, Janssen R&D; B. De Meulder, European Institute for Systems Biology and Medicine, University of Lyon; I. Delin, Institute of Environmental Medicine, Karolinska Institutet, Stockholm; P. Dennison, NIHR Southampton Respiratory Biomedical Research Unit and University of Southampton; P. Dodson, AstraZeneca, Mølndal; L. El Hadjam, European Institute for Systems Biology and Medicine, University of Lyon; D. Erzen, Boehringer Ingelheim Pharma GmbH & Co. KG; C. Faulenbach, Fraunhofer ITEM; K. Fichtner, Boehringer Ingelheim Pharma GmbH & Co. KG; N. Fitch, BioSci Consulting, Belgium; E. Formaggio, PhD, Project manager, Verona; M. Gahlemann, Boehringer Ingelheim (Schweiz) GmbH; G. Galffy, Semmelweis University, Budapest; D. Garissi, Global Head Clinical Research Division, CROMSOURCE; T. Garret, BioSci Consulting, Belgium; J. Gent, Royal Brompton and Harefield NHS Foundation Trust; E. Guillmant-Farry, Royal Brompton Hospital, London; E. Henriksson, Karolinska Institutet; U. Hoda, Imperial College; J. M. Hohlfeld, Fraunhofer ITEM; X. Hu, Amgen; A. James, Karolinska Institutet; K. Johnson, Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, University Hospital of South Manchester, NHS Foundation Trust, Manchester; N. Jullian, European Institute for Systems Biology and Medicine, University of Lyon; G. Kerry, Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, University Hospital of South Manchester, NHS Foundation Trust, Manchester; M. Klüglic, Boehringer Ingelheim Pharma GmbH & Co. KG; R. Knowles, Arachos Pharma, Stevenage; J.R. Konradsen, Karolinska University Hospital and Karolinska Institutet; K. Kretsos, UCB, Slough, UK; L. Krueger, University Children's Hospital Bern; A.-S. Lantz, Karolinska University Hospital and Karolinska Institutet; C. Larmine, GSK, London; P. Latzin, University Children's Hospital Bern; D. Lefaudeux, European Institute for Systems Biology and Medicine, University of Lyon; N. Lemonnier, European Institute for Systems Biology and Medicine, University of Lyon; L. A. Lowe, Centre for respiratory medicine and allergy, Institute of Inflammation and Repair, University Hospital of South Manchester, NHS Foundation Trust, Manchester; R. Lutter, Academic Medical Centre, University of Amsterdam; A. Manta, Roche Diagnostics GmbH, Mannheim; A. Mazein, European Institute for Systems Biology and Medicine, University of Lyon; L. McEvoy, University Hospital, Department of Pulmonary Medicine, Bern; A. Menzies-Gow, Royal Brompton and Harefield NHS Foundation Trust; N. Mores, Università Cattolica del Sacro Cuore C.S. Murray, Centre for Respiratory Medicine and Allergy, University of Manchester, Manchester Academic Health Science Centre, University Hospital of South Manchester NHS Foundation Trust, Manchester; K. Nething, Boehringer Ingelheim Pharma GmbH & Co. KG; U. Nihlen, Department of Respiratory Medicine and Allergology, Skane University Hospital, Lund, and AstraZeneca R&D, Mølndal; R. Niven, North West Severe Asthma Network, University Hospital South Manchester NHS Trust; B. Nordlund, Astrid Lindgren Children's Hospital,

Karolinska University Hospital, Stockholm, and the Department of Women's and Children's Health, Karolinska Institutet, Stockholm; S. Nsubuga, Royal Brompton Hospital, London; J. Pellet, European Institute for Systems Biology and Medicine, University of Lyon; C. Pison, European Institute for Systems Biology and Medicine, University of Lyon; G. Pratico, CROMSOURCE, Verona; M. Puig Valls, CROMSOURCE, Barcelona; K. Riemann, Boehringer Ingelheim Pharma GmbH & Co. KG; J.P. Rocha, Royal Brompton and Harefield NHS Foundation Trust; C. Rossios, Imperial College; G. Santini, Universita Cattolica del Sacro Cuore; M. Saqi, European Institute for Systems Biology and Medicine, University of Lyon; S. Scott, North West Severe Asthma Network; Countess of Chester NHS Trust; N. Sehgal, North West Severe Asthma Network and Pennine Acute Hospital NHS Trust; A. Selby, NIHR Southampton Respiratory Biomedical Research Unit, Clinical and Experimental Sciences and Human Development and Health, Southampton; P. Söderman, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, and the Department of Women's and Children's Health, Stockholm; A. Sogbesan, Royal Brompton and Harefield NHS Foundation Trust; F. Spycher, University Hospital, Department of Pulmonary Medicine, Bern; S. Stephan, Centre for respiratory medicine and allergy, Institute of Inflammation and repair, University Hospital of South Manchester, NHS Foundation Trust, Manchester; J. Stokholm, University of Copenhagen and Danish Pediatric Asthma Center, Gentofte Hospital, University of Copenhagen; M. Sunther, Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, University Hospital of South Manchester, NHS Foundation Trust, Manchester; M. Szentkereszty, Semmelweis University, Budapest; L. Tamasi, Semmelweis University, Budapest; K. Tariq, NIHR Southampton Respiratory Biomedical Research Unit and University of Southampton; S. Valente, Universita Cattolica del Sacro Cuore; W. M. van Aalderen, Academic Medical Centre, University of Amsterdam; C. M. van Drunen, Academic Medical Centre, University of Amsterdam; J. Van Eyll, UCB, Slough; A. Vyas, North West Severe Asthma Network and the Lancashire Teaching Hospitals NHS Trust; W. Yu, Amgen; W. Zetterquist, Department of Woman and Child Health, Karolinska Institutet, Department of Woman and Child Health, Karolinska Institutet, Stockholm; Z. Zolkipli, NIHR Southampton Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton; the Clinical and Experimental Sciences and Human Development in Health Academic Unit, University of Southampton Faculty of Medicine, Southampton, UK; and the David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight; and A. H. Zwinderman, Academic Medical Centre, University of Amsterdam. The U-BIO-PRED consortium wishes to acknowledge the help and expertise of the following individuals and groups without whom the study would not have been possible: Investigators and contributors Nora Adriaens, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; Antonios Aliprantis, Merck Research Laboratories, Boston, Massachusetts; Kjell Alving, Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden; Per Bakke, Department of Clinical Science, University of Bergen, Bergen, Norway; David Balgoma, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Clair Barber, NIHR Southampton Respiratory Biomedical Research Unit and Clinical and Experimental Sciences, Southampton, United Kingdom; Frederic Baribaud, Janssen R&D; Stewart Bates, Respiratory Therapeutic Unit, GSK, London, United Kingdom; An Bautmans, MSD, Brussels, Belgium; Jorge Beleta, Almirall S.A., Barcelona, Spain; Grazyna Bochenek, II Department of Internal Medicine, Jagiellonian University Medical College, Krakow, Poland; Joost Brandsma, University of Southampton, Southampton, United Kingdom; Armin Braun, Fraunhofer Institute for Toxicology and Experimental Medicine, Hannover, Germany; Dominic Burg, Centre for Proteomic Research, Institute for Life Sciences, University of Southampton, Southampton, United Kingdom; Leon Carayannopoulos, previously at MSD; Jo ~ ao Pedro Carvalho da Purificac, ~ao Rocha, Royal Brompton and Harefield NHS Foundation Trust, London, United Kingdom; Romanas Chaleckis, Centre of Allergy

Research, Karolinska Institutet, Stockholm, Sweden; Arnaldo D'Amico, University of Rome 'Tor Vergata,' Rome Italy; Jorge De Alba, Almirall S. A., Barcelona, Spain; Inge De Lepeleire, MSD, Brussels, Belgium; Tamara Dekker, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; Annemiek Dijkhuis, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; Aleksandra Draper, BioSci Consulting, Maasmechelen, Belgium; Jessica Edwards, Asthma UK, London, United Kingdom; Rosalia Emma, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy; Magnus Ericsson, Karolinska University Hospital, Stockholm, Sweden; Breda Flood, European Federation of Allergy and Airways Diseases Patient's Associations, Brussels, Belgium; Hector Gallart, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Cristina Gomez, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Kerry Gove, NIHR Southampton Respiratory Biomedical Research Unit and Clinical and Experimental Sciences, Southampton, United Kingdom; Neil Gozzard, UCB, Slough, United Kingdom; John Haughney, International Primary Care Respiratory Group, Aberdeen, Scotland; Lorraine Hewitt, NIHR Southampton Respiratory Biomedical Research Unit, Southampton, United Kingdom; Jens Hohlfeld, Fraunhofer Institute for Toxicology and Experimental Medicine, Hannover, Germany; Cecile Holweg, Respiratory and Allergy Diseases, Genentech, San Francisco, California; Richard Hu, Amgen, Thousand Oaks, California; Sile Hu, National Heart and Lung Institute, Imperial College, London, United Kingdom; Juliette Kamphuis, Longfords, Amersfoort, The Netherlands; Erika J. Kennington, Asthma UK, London, United Kingdom; Dyson Kerry, CromSource, Stirling, United Kingdom; Hugo Knobel, Philips Research Laboratories, Eindhoven, The Netherlands; Johan Kolmert, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Maxim Kots, Chiesi Pharmaceuticals, SPA, Parma, Italy; Scott Kuo, National Heart and Lung Institute, Imperial College, London, United Kingdom; Maciej Kupczyk, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Bart Lambrecht, University of Gent, Gent, Belgium; Saeeda Lone-Latif, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; Matthew J. Loza, Janssen R&D; Lisa Marouzet, NIHR Southampton Respiratory Biomedical Research Unit, Southampton, United Kingdom; Jane Martin, NIHR Southampton Respiratory Biomedical Research Unit, Southampton, United Kingdom; Sarah Masefield, European Lung Foundation, Sheffield, United Kingdom; Caroline Mathon, Centre of Allergy Research, Karolinska Institutet, Stockholm, Sweden; Sally Meah, National Heart and Lung Institute, Imperial College, London, United Kingdom; Andrea Meiser, Data Science Institute, Imperial College, London, United Kingdom; Leanne Metcalf, previously at Asthma UK, London, United Kingdom; Maria Mikus, Science for Life Laboratory and the Royal Institute of Technology, Stockholm, Sweden; Montse Miralpeix, Almirall, Barcelona, Spain; Philip Monk, Synairgen Research, Southampton, United Kingdom; Shama Naz, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Ben Nicholas, University of Southampton, Southampton, United Kingdom; Peter Nilsson, Science for Life Laboratory and the Royal Institute of Technology, Stockholm, Sweden; Jørgen Ostling, AstraZeneca, M € €olndal, Sweden; Antonio Pacino, Lega Italiano Anti Fumo, Catania, Italy; Susanna Palkonen, European Federation of Allergy and Airways Diseases Patient's Associations, Brussels, Belgium; Stelios Pavlidis, National Heart and Lung Institute, Imperial College, London, United Kingdom; Giorgio Pennazza, University of Rome 'Tor Vergata,' Rome Italy; Anne Petren, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Sandy Pink, NIHR Southampton Respiratory Biomedical Research Unit, Southampton, United Kingdom; Anthony Postle, University of Southampton, United Kingdom; Pippa Powell, European Lung Foundation, Sheffield, United Kingdom; Malayka RahmanAmin, previously at Asthma UK, London, United Kingdom; Navin Rao, Janssen R&D; Lara Ravanetti, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; Emma Ray, NIHR Southampton Respiratory Biomedical Research Unit, Southampton, United Kingdom; Stacey

Reinke, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Leanne Reynolds, previously at Asthma UK, London, United Kingdom; John Riley, Respiratory Therapeutic Unit, GSK, London, United Kingdom; Martine Robberechts, MSD, Brussels, Belgium; Amanda Roberts, Asthma UK, London, United Kingdom; Kirsty Russell, National Heart and Lung Institute, Imperial College, London, United Kingdom; Michael Rutgers, Longfonds, Amersfoort, The Netherlands; Marco Santoninco, University of Rome 'Tor Vergata,' Rome Italy; Corinna Schoelch, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; James P. R. Schofield, Centre for Proteomic Research, Institute for Life Sciences, University of Southampton, Southampton, United Kingdom; Marcus Sjödin, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Paul J. Skipp, Centre for Proteomic Research, Institute for Life Sciences, University of Southampton, Southampton, United Kingdom; Barbara Smids, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; Caroline Smith, NIHR Southampton Respiratory Biomedical Research Unit, Southampton, United Kingdom; Jessica Smith, Asthma UK, London, United Kingdom; Katherine M. Smith, University of Nottingham, United Kingdom; Doroteya Staykova, University of Southampton, Southampton, United Kingdom; Kai Sun, Data Science Institute, Imperial College, London, United Kingdom; John-Olof Thörnengren, Karolinska University Hospital, Stockholm, Sweden; Bob Thornton, MSD; Jonathan Thorsen, COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark; Marianne van de Pol, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; Marleen van Geest, AstraZeneca, Mölndal, Sweden; Jenny Versnel, previously at Asthma UK, London, United Kingdom; Anton Vink, Philips Research Laboratories, Eindhoven, The Netherlands; Frans Wald, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; Samantha Walker, Asthma UK, London, United Kingdom; Jonathan Ward, Histochemistry Research Unit, Faculty of Medicine, University of Southampton, Southampton, United Kingdom; Zsoka Weiszhart, Semmelweis University, Budapest, Hungary; Kristiane Wetzler, Boehringer Ingelheim Pharma GmbH, Biberach, Germany; Craig E. Wheelock, Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; Coen Wiegman, National Heart and Lung Institute, Imperial College, London, United Kingdom; Si'an Williams, International Primary Care Respiratory Group, Aberdeen, Scotland; Susan J. Wilson, Histochemistry Research Unit, Faculty of Medicine, University of Southampton, Southampton, United Kingdom; Ashley Woodcock, Centre for Respiratory Medicine and Allergy, Institute of Inflammation and Repair, University of Manchester and University Hospital of South Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom; Xian Yang, Data Science Institute, Imperial College, London, United Kingdom; and Elizabeth Yeyasingham, UK Clinical Operations, GSK, Stockley Park, United Kingdom. Partner organizations Novartis Pharma AG; University of Southampton, Southampton, United Kingdom; Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; Imperial College London, London, United Kingdom; University of Catania, Catania, Italy; University of Rome 'Tor Vergata,' Rome, Italy; Hvidovre Hospital, Hvidovre, Denmark; Jagiellonian University Medical College, Krakow, Poland; University Hospital, Inselspital, Bern, Switzerland; Semmelweis University, Budapest, Hungary; University of Manchester, Manchester, United Kingdom; Université d'Aix-Marseille, Marseille, France; Fraunhofer Institute, Hannover, Germany; University Hospital, Umea, Sweden; Ghent University, Ghent, Belgium; Ctr. Nat. Recherche Scientifique, Villejuif, France; Università Cattolica del Sacro Cuore, Rome, Italy; University Hospital, Copenhagen, Denmark; Karolinska Institutet, Stockholm, Sweden; Nottingham University Hospital, Nottingham, United Kingdom; University of Bergen, Bergen, Norway; Netherlands Asthma Foundation, Leusden, The Netherlands; European Lung Foundation, Sheffield, United Kingdom; Asthma UK, London, United Kingdom; European Federation of Allergy and Airways Diseases Patients' Associations, Brussels, Belgium; Lega Italiano Anti Fumo,

Catania, Italy; International Primary Care Respiratory Group, Aberdeen, Scotland; Philips Research Laboratories, Eindhoven, The Netherlands; Synairgen Research, Southampton, United Kingdom; Aerocrine AB, Stockholm, Sweden; BioSci Consulting, Maasmechelen, Belgium; Almirall; AstraZeneca; Boehringer Ingelheim; Chiesi; GlaxoSmithKline; Roche; UCB; Janssen Biologics BV; Amgen NV; and Merck Sharp & Dohme Corp. Third Parties to the project, contributing to the clinical trial Academic Medical Centre (AMC), Amsterdam (in the U-BIOPRED consortium the legal entity is AMC Medical Research BV [AMR]; AMR is a subsidiary of both AMC and the University of Amsterdam; AMC contribute across the U-BIOPRED project); University Hospital Southampton NHS Trust (third party of the University of Southampton and contributor to the U-BIOPRED clinical trial); South Manchester Healthcare Trust (third party to the University of Manchester, South Manchester Healthcare Trust, contributor to the U-BIOPRED clinical trial and to the U-BIOPRED Biobank); Protisvalor Mediterranean SAS (third party to University of the Mediterranean; contributor to the U-BIOPRED clinical trial); Karolinska University Hospital (third party Karolinska Institutet [KI]) contributor to the U-BIOPRED clinical trial); Nottingham University Hospital (third party to University of Nottingham, contributor to the U-BIOPRED clinical trial); and NIHR-Wellcome Trust Clinical Research Facility. Members of the ethics board Jan-Bas Prins, biomedical research, LUMC, The Netherlands; Martina Gahlemann, clinical care, BI, Germany; Luigi Visintin, legal affairs, LIAF, Italy; Hazel Evans, paediatric care, Southampton, United Kingdom; Martine Puhl, patient representation (co-chair), NAF, The Netherlands; Lina Buzermaniene, patient representation, EFA, Lithuania; Val Hudson, patient representation, Asthma UK; Laura Bond, patient representation, Asthma UK; Pim de Boer, patient representation and pathobiology, IND; Guy Widdershoven, research ethics, VUMC, the Netherlands; and Ralf Sigmund, research methodology and biostatistics, BI, Germany. Patient input platform Amanda Roberts, United Kingdom; David Supple (chair), United Kingdom; Dominique Hamerlijnck, The Netherlands; Jenny Negus, United Kingdom; Julitte Kamphuis, The Netherlands; Lehanne Sergison, United Kingdom; Luigi Visintin, Italy; Pim de Boer (cochair), The Netherlands; and Susanne Onstein, The Netherlands. Members of the safety monitoring board William MacNee, clinical care; Renato Bernardini, clinical pharmacology; Louis Bont, paediatric care and infectious diseases; Per-Ake Wecksell, patient representation; Pim de Boer, patient representation and pathobiology (chair); Martina Gahlemann, patient safety advice and clinical care (cochair); and Ralf Sigmund, bioinformatician. This work was partially funded by the Engineering and Physical Sciences Research Council, United Kingdom (EP/N014189: Joining the Dots, From Data to Insight). Instrumentation in the Centre for Proteomic Research is supported by the BBSRC (BM/M012387/1) and the Wessex Medical Trust. We thank Ayasdi for use of, and support with, the Ayasdi TDA software.

References

- Ambrée, O., Klassen, I., Förster, I., Arolt, V., Scheu, S., Alferink, J., 2016. Reduced locomotor activity and exploratory behavior in CC chemokine receptor 4 deficient mice. *Behav Brain Res.* 314, 87–95. <https://doi.org/10.1016/j.bbr.2016.07.041>.
- M. Amelink S. Hashimoto P. Spinhoven H.R. Pasma P.J. Sterk H. Bel E., ten Brinke, Anneke., Anxiety, depression and personality traits in severe, prednisone-dependent asthma *Respir Med.* 2014 108,438–444 10.1016/j.rmed <https://doi.org/10.1016/j.rmed> <https://doi.org/10.1016/j.rmed>
- Barnes, J., Mondelli, V., Pariante, C.M., 2017. Genetic Contributions of Inflammation to Depression. *Neuropsychopharmacology* 42, 81–98. <https://doi.org/10.1038/npp.2016.169>.
- Berk, M., Williams, L.J., Jacka, F.N., O'Neil, A., Pasco, J.A., Moylan, S., Allen, N.B., Stuart, A.L., Hayley, A.C., Byrne, M.L., Maes, M., 2013. So depression is an inflammatory disease, but where does the inflammation come from? *BMC Med* 11 (1).
- Bush, T., Richardson, L., Katon, W., Russo, J., Lozano, P., McCauley, E., Oliver, M., 2007. Anxiety and Depressive Disorders Are Associated with Smoking in Adolescents with Asthma. *J Adolesc Health.* 40, 425–432. <https://doi.org/10.1016/j.jadohealth.2006.11.145>.
- Campbell, E.M., Charo, I.F., Kunkel, S.L., Strieter, R.M., Boring, L., Gosling, J., Lukacs, N. W., 1999. Monocyte chemoattractant protein-1 mediates cockroach allergen induced bronchial hyperreactivity in normal but not CCR2-/- mice: the role of mast cells. *J Immunol.* 163, 2160–2167.

- Chen, E., Miller, G.E., 2007. Stress and inflammation in exacerbations of asthma. *Brain Behav Immun.* 21, 993–999. <https://doi.org/10.1016/j.bbi.2007.03.009>.
- Choi, G.-S., Shin, Y.S., Kim, J.-H., Choi, S.Y., Lee, S.-K., Nam, Y.-H., Lee, Y.-M., Park, H.-S., 2014. Prevalence and Risk Factors for Depression in Korean Adult Patients with Asthma: Is There a Difference between Elderly and Non-Elderly Patients? *J Korean Med Sci* 29 (12), 1626.
- Cooper, C.L., Parry, G.D., Saul, C., Morice, A.H., Hutchcroft, B.J., Moore, J., Esmonde, L., 2007. Anxiety and panic fear in adults with asthma: prevalence in primary care. *BMC Fam Pract.* 8, 62. <https://doi.org/10.1186/1471-2296-8-62>.
- E.K. de Jong J. Vinet V.S. Stanulovic M. Meijer E. Wesseling K. Sjollem H.W. Boddeke K. Biber Expression, transport, and axonal sorting of neuronal CCL21 in large dense-core vesicles FASEB J. 2008 22,4136–4145 10.1096/fj.07-101907 <https://doi.org/10.1096/fj.07-101907>
- S.R. Del Giacco A. Cappali L. Gambula S. Cabras S. Perra P.E. Manconi B. Carpinello F. Pinna The asthma-anxiety connection *Respir Med.* 2016 120,44–53 10.1016/j.rmed.2016.09.014.
- Dhaouadi, T., Sfar, I., Aounallah-Skhiri, H., Jendoubi-Ayed, S., Bouacha, H., Ben Abdallah, T., Gorgi, Y., 2013. MCP-1, CCR2 and CCR5 polymorphisms in Tunisian patients with atopic asthma. *Iran J Allergy Asthma Immunol.* 12, 29–36. <https://doi.org/10.1186/1479-5876-9-S2-P10>.
- Edwards, M.R., Saglani, S., Schwarze, J., Skevaki, C., Smith, J.A., Ainsworth, B., Almond, M., Andreacos, E., Belvisi, M.G., Chung, K.F., Cookson, W., Cullinan, P., Hawrylowicz, C., Lommatzsch, M., Jackson, D., Lutter, R., Marsland, B., Moffatt, M., Thomas, M., Virchow, J.C., Xanthou, G., Edwards, J., Walker, S., Johnston, S.L., 2017. Addressing unmet needs in understanding asthma mechanisms: From the European Asthma Research and Innovation Partnership (EARIP) Work Package (WP) 2 collaborators. *Eur Respir J* 49 (5), 1602448.
- Faull, O.K., Jenkinson, M., Ezra, M., Pattinson, K.T., 2016. Conditioned respiratory threat in the subdivisions of the human periaqueductal gray. *Elife* 5. <https://doi.org/10.7554/eLife.12047>.
- Ferreira, M.A.R., Matheson, M.R., Duffy, D.L., Marks, G.B., Hui, J., Le Souëf, P., Danoy, P., Baltic, S., Nyholt, D.C., Jenkins, M., Hayden, C., Willemsen, G., Ang, W., Kuokkanen, M., Beilby, J., Cheah, F., de Geus, E.J.C., Ramasamy, A., Vedantam, S., Salomaa, V., Madden, P.A., Heath, A.C., Hopper, J.L., Visscher, P.M., Musk, B., Leeder, S.R., Jarvelin, M.-R., Pennell, C., Boomsma, D.I., Hirschhorn, J.N., Walters, H., Martin, N.G., James, A., Jones, G., Abramson, M.J., Robertson, C.F., Dharmage, S.C., Brown, M.A., Montgomery, G.W., Thompson, P.J., 2011. Identification of IL6R and chromosome 11q13.5 as risk loci for asthma. *Lancet* 378 (9795), 1006–1014.
- Gada, E., Khan, D.A., DeFina, L.F., Brown, E.S., 2014. The relationship between asthma and self-reported anxiety in a predominantly healthy adult population. *Ann Allergy Asthma Immunol.* 112, 329–332. <https://doi.org/10.1016/j.anaai.2013.08.027>.
- Goodwin, R.D., 2003. Asthma and anxiety disorder. *Adv Psychosom Med.* 24, 51–71. <https://doi.org/10.1159/000073780>.
- Goodwin, R.D., Olsson, M., Shea, S., Lantigua, R.A., Carrasquillo, O., Gameroff, M.J., Weissman, M.M., 2003a. Asthma and mental disorders in primary care. *Gen. Hosp. Psychiatry* 25 (6), 479–483.
- Goodwin, R.D., Pine, D.S., Hoven, C.W., 2003b. Asthma and Panic Attacks Among Youth in the Community. *J. Asthma* 40 (2), 139–145.
- Hasegawa, T., Koya, T., Sakagami, T., Muramatsu, Y., Muramatsu, K., Kagamu, H., Mashima, I., Arakawa, M., Gejyo, F., Miyaoka, H., Kamijima, K., Narita, I., Suzuki, E., 2012. Analysis of Depression in Asthmatic Patients Using the Japanese Version of Patient Health Questionnaire-9. *Allergol. Int.* 61 (3), 475–487.
- Heinisch, S., Kirby, L.G., 2009. Fractalkine/CX3CL1 enhances GABA synaptic activity at serotonin neurons in the rat dorsal raphe nucleus. *Neuroscience* 164 (3), 1210–1223.
- Hou, R., Baldwin, D.S., 2012. A neuroimmunological perspective on anxiety disorders. *Hum Psychopharmacol.* 27, 6–14. <https://doi.org/10.1002/hup.1259>.
- Iwata, M., Ota, K.T., Duman, R.S., 2013. The inflammasome: Pathways linking psychological stress, depression, and systemic illnesses. *Brain Behav. Immun.* 31, 105–114.
- Jevnikar, Z., Ostling, J., Ax, E., Calvén, J., Thörn, K., Israelsson, E., Öberg, L., Singhania, A., Lau, L.C.K., Wilson, S.J., Ward, J.A., Chauhan, A., Sousa, A.R., De Meulder, B., Loza, M.J., Baribaud, F., Sterk, P.J., Chung, K.F., Sun, K., Guo, Y., Adcock, I.M., Payne, D., Dahlen, B., Chanez, P., Shaw, D.E., Hohlfield, J.M., Sandström, T., Djukanovic, R., James, A., Hinks, T.S.C., Howarth, P.H., Vaarala, O., van Geest, M., Olsson, H., Adcock, I.M., Ahmed, H., Auffray, C., Bakke, P., Bansal, A., T., Baribaud, F., Bates, S., Bel, E.H., Bigler, J., Bisgaard, H., Boedigheimer, M.J., Bønnelykke, K., Brandsma, J., Brinkman, P., Bucchioni, E., Burg, D., Bush, A., Caruso, M., Chaiboonchoe, A., Chanez, P., Chung, F.K., Compton, C.H., Corfield, J., D'Amico, A., Dahlen, S.E., De Meulder, B., Djukanovic, R., Erpenbeck, V.J., Erzen, D., Fichtner, K., Fitch, N., Fleming, L.J., Formaggio, E., Fowler, S.J., Frey, U., Gahlemann, M., Geiser, T., Goss, V., Guo, Y., Hashimoto, S., Haughey, J., Hedlin, G., Hekking, P.W., Higenbottam, T., Hohlfield, J.M., Holweg, C., Horváth, I., James, A.J., Knowles, R., Knox, A.J., Krug, N., Lefaudeux, D., Loza, M.J., Manta, A., Matthews, J.G., Mazein, A., Meiser, A., Middeldel, R.J.M., Miralpeix, M., Montuschi, P., Mores, N., Murray, C.S., Musial, J., Myles, D., Pahu, L., Pandis, I., Pavlidis, S., Postle, A., Powel, P., Praticò, G., Rao, N., Riley, J., Roberts, A., Roberts, G., Rowe, A., Sandström, T., Schofield, J.P.R., Seibold, W., Selby, A., Shaw, D.E., Sigmund, R., Singer, F., Skipp, P.J., Sousa, A.R., Sterk, P.J., Sun, K., Thornton, B., van Aalderen, W.M., van Geest, M., Vestbo, J., Vissing, N.H., Wagener, A.H., Wagers, S.S., Weiszart, Z., Wheelock, C.E., Wilson, S.J., 2019. Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes study group. Epithelial IL-6 trans-signaling defines a new asthma phenotype with increased airway inflammation. *J Allergy Clin Immunol.* 143 (2), 577–590.
- Jiang, M., Qin, P., Yang, X.u., 2014. Comorbidity between depression and asthma via immune-inflammatory pathways: A meta-analysis. *J. Affect. Disord.* 166, 22–29.
- Jo, K.M., Lim, H.K., Sull, J.W., Choi, E., Lee, J.S., Cheong, M.A., Hong, M.H., Kim, Y., Kim, I.S., 2018. Thymus and activation-regulated chemokine (TARC)/CCL17 and IgE are associated with elderly asthmatics. *Immun Ageing.* 15, 13. <https://doi.org/10.1186/s12979-018-0118-7>.
- Katon, W.J., Richardson, L., Lozano, P., McCauley, E., 2004. The relationship of asthma and anxiety disorders. *Psychosom Med.* 66, 349–355. <https://doi.org/10.1097/01.psy.0000126202.89941.ea>.
- Kiecolt-Glaser, J.K., Preacher, K.J., MacCallum, R.C., Atkinson, C., Malarkey, W.B., Glaser, R., 2003. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proc Natl Acad Sci U S A.* 100, 9090–9095. <https://doi.org/10.1073/pnas.1531903100>.
- Köhler, C.A., Freitas, T.H., Stubbs, B., Maes, M., Solmi, M., Veronese, N., de Andrade, N. Q., Morris, G., Fernandes, B.S., Brunoni, A.R., Herrmann, N., Raison, C.L., Miller, B. J., Lancôt, K.L., Carvalho, A.F., 2018. Peripheral Alterations in Cytokine and Chemokine Levels After Antidepressant Drug Treatment for Major Depressive Disorder: Systematic Review and Meta-Analysis. *Mol Neurobiol.* 55, 4195–4206. <https://doi.org/10.1007/s12035-017-0632-1>.
- Kopf, M., Baumann, H., Freer, G., Freudenberg, M., Lamers, M., Kishimoto, T., Zinkernagel, R., Bluethmann, H., Köhler, G., 1994. Impaired immune and acute-phase responses in interleukin-6-deficient mice. *Nature* 368, 339–342. <https://doi.org/10.1038/368339a0>.
- Kumai, T., Nagato, T., Kobayashi, H., Komabayashi, Y., Ueda, S., Kishibe, K., Ohkuri, T., Takahara, M., Celis, E., Harabuchi, Y., 2015. CCL17 and CCL22/CCR4 signaling is a strong candidate for novel targeted therapy against nasal natural killer/T-cell lymphoma. *Cancer Immunol Immunother.* 64, 697–705. <https://doi.org/10.1007/s00262-015-1675-7>.
- Lajunen, T.K., Jaakkola, J.J., Jaakkola, M.S., 2016. Interleukin 6 SNP rs1800797 associates with the risk of adult-onset asthma. *Genes Immun.* 17, 193–198. <https://doi.org/10.1038/gene.2016.8>.
- Lavoie, K.L., Bouthillier, D., Bacon, S.L., Lemiere, C., Martin, J., Hamid, Q., Ludwig, M., Olivenstein, R., Ernst, P., 2010. Psychological distress and maladaptive coping styles in patients with severe vs moderate asthma. *Chest* 137, 1324–1331. <https://doi.org/10.1378/chest.09-1979>.
- Liu, C.S., Adibfar, A., Herrmann, N., Gallagher, D., Lancôt, K.L., 2017. Evidence for Inflammation-Associated Depression. *Curr Top Behav Neurosci.* 31, 3–30. https://doi.org/10.1007/7854_2016_2.
- Liu, Y., Ho, R.-M., Mak, A., 2012. Interleukin (IL)-6, tumour necrosis factor alpha (TNF- α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: A meta-analysis and meta-regression. *J. Affect. Disord.* 139 (3), 230–239.
- Liu, C.-H., Zhang, G.-Z., Li, B., Li, M., Woelfer, M., Walter, M., Wang, L., 2019. Role of inflammation in depression relapse. *J Neuroinflammation* 16 (1).
- Mancuso, C.A., Wenderoth, S., Westermann, H., Choi, T.N., Briggs, W.M., Charlson, M.E., 2008. Patient-reported and physician-reported depressive conditions in relation to asthma severity and control. *Chest* 133, 1142–1148. <https://doi.org/10.1378/chest.07-2243>.
- McCauley, E., Katon, W., Russo, J., Richardson, L., Lozano, P., 2007. Impact of anxiety and depression on functional impairment in adolescents with asthma. *Gen Hosp Psychiatry.* 29, 214–222. <https://doi.org/10.1016/j.genhosppsych.2007.02.003>.
- Milenkovic, V.M., Stanton, E.H., Nothdurfter, C., Rupprecht, R., Wetzel, C.H., 2019. The Role of Chemokines in the Pathophysiology of Major Depressive Disorder. *Int J Mol Sci.* 20 (2283) <https://doi.org/10.3390/ijms20092283>.
- Mrazek, D.A., 2003. Psychiatric symptoms in patients with asthma causality, comorbidity, or shared genetic etiology. *Child Adolesc Psychiatr Clin N Am.* 12, 459–471. [https://doi.org/10.1016/s1056-4993\(03\)00028-2](https://doi.org/10.1016/s1056-4993(03)00028-2).
- de Nadaï, P., Charbonnier, A.S., Chenivense, C., Sénéchal, S., Fournier, C., Gilet, J., Vornig, H., Chang, Y., Gosset, P., Wallaert, B., Tonnel, A.B., Lassalle, P., Tscicopoulos, A., 2006. Involvement of CCL18 in allergic asthma. *J Immunol.* 176, 6286–6293. <https://doi.org/10.4049/jimmunol.176.10.6286>.
- Oga, T., Nishimura, K., Tsukino, M., Sato, S., Hajiro, T., Mishima, M., 2007. Analysis of longitudinal changes in the psychological status of patients with asthma. *Respir Med.* 101, 2133–2138. <https://doi.org/10.1016/j.rmed.2007.05.009>.
- Pae, C.U., 2014. The potential role of monocyte chemoattractant protein-1 for major depressive disorder. *Psychiatry Investig.* 11, 217–222. <https://doi.org/10.4306/pi.2014.11.3.217>.
- Peters, M.C., McGrath, K.W., Hawkins, G.A., Hastie, A.T., Levy, B.D., Israel, E., Phillips, B.R., Mauger, D.T., Comhair, S.A., Erzurum, S.C., Johansson, M.W., Jarjour, N.N., Coverstone, A.M., Castro, M., Holguin, F., Wenzel, S.E., Woodruff, P. G., Bleeker, E.R., Fahy, J.V., 2016. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. *Lancet Respir. Med.* 4 (7), 574–584.
- Pujol, F., Kitabgi, P., Boudin, H., 2005. The chemokine SDF-1 differentially regulates axonal elongation and branching in hippocampal neurons. *J. Cell Sci.* 118, 1071–1080. <https://doi.org/10.1242/jcs.01694>.
- Richardson, L.P., Lozano, P., Russo, J., McCauley, E., Bush, T., Katon, W., 2006. Asthma symptom burden: relationship to asthma severity and anxiety and depression symptoms. *Pediatrics* 118, 1042–1051. <https://doi.org/10.1542/peds.2006-0249>.
- Ritz, T., Thöns, M., Fahrenkrug, S., Dahme, B., 2005. Airways, respiration, and respiratory sinus arrhythmia during picture viewing. *Psychophysiology.* 42, 568–578. <https://doi.org/10.1111/j.1469-8986.2005.00312.x>.
- J.D. Rosenblatt R.S. McIntyre Bipolar Disorder and Immune Dysfunction: Epidemiological Findings, Proposed Pathophysiology and Clinical Implications *Brain Sci.* 7 2017 144 10.3390/brainsci7110144.
- Rosenkranz, M.A., Davidson, R.J., 2009. Affective neural circuitry and mind-body influences in asthma. *Neuroimage* 47, 972–980. <https://doi.org/10.1016/j.neuroimage.2009.05.042>.

- Rosenkranz, M.A., Esnault, S., Christian, B.T., Crisafi, G., Gresham, L.K., Higgins, A.T., Moore, M.N., Moore, S.M., Weng, H.Y., Salk, R.H., Busse, W.W., Davidson, R.J., 2016. Mind-body interactions in the regulation of airway inflammation in asthma: A PET study of acute and chronic stress. *Brain Behav. Immun.* 58, 18–30.
- Shaw, D.E., Sousa, A.R., Fowler, S.J., Fleming, L.J., Roberts, G., Corfield, J., Pandis, I., Bansal, A.T., Bel, E.H., Auffray, C., Compton, C.H., Bisgaard, H., Bucchioni, E., Caruso, M., Chanez, P., Dahlén, B., Dahlen, S.-E., Dyson, K., Frey, U., Geiser, T., Gerhardsson de Verdier, M., Gibeon, D., Guo, Y.-k., Hashimoto, S., Hedlin, G., Jeyasingham, E., Hekking, P.-P., Higenbottam, T., Horváth, I., Knox, A.J., Krug, N., Erpenbeck, V.J., Larsson, L.X., Lazarinis, N., Matthews, J.G., Middelveld, R., Montuschi, P., Musial, J., Myles, D., Pahus, L., Sandström, T., Seibold, W., Singer, F., Strandberg, K., Vestbo, J., Vissing, N., von Garnier, C., Adcock, I.M., Wagers, S., Rowe, A., Howarth, P., Wagener, A.H., Djukanovic, R., Sterk, P.J., Chung, K.F., 2015. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J* 46 (5), 1308–1321.
- Stuart, M.J., Baune, B.T., 2014. Chemokines and chemokine receptors in mood disorders, schizophrenia, and cognitive impairment: a systematic review of biomarker studies. *Neurosci Biobehav Rev.* 42, 93–115. <https://doi.org/10.1016/j.neubiorev.2014.02.001>.
- Stuart, M.J., Singhal, G., Baune, B.T., 2015. Systematic Review of the Neurobiological Relevance of Chemokines to Psychiatric Disorders. *Front Cell Neurosci.* 9, 357. <https://doi.org/10.3389/fncel.2015.00357>.
- ten Brinke, A., Ouwerkerk, M.E., Bel, E.H., Spinhoven, P.h., 2001. Similar psychological characteristics in mild and severe asthma. *J. Psychosom. Res.* 50 (1), 7–10.
- ten Thoren, C., Petermann, F., 2000. Reviewing asthma and anxiety. *Respir Med.* 94, 409–415. <https://doi.org/10.1053/rmed.1999.0757>.
- Thomas, M., Bruton, A., Moffat, M., Cleland, J., 2011. Asthma and psychological dysfunction. *Prim Care Respir J.* 20, 250–256. <https://doi.org/10.4104/pccrj.2011.00058>.
- Ting, E.Y., Yang, A.C., Tsai, S.J., 2020 Mar. Role of Interleukin-6 in Depressive Disorder. *Int J Mol Sci.* 22 (21), 2194. <https://doi.org/10.3390/ijms21062194>. PMID: 32235786; PMCID: PMC7139933.
- Tsicopoulos, A., Chang, Y., Ait Yahia, S., de Nadai, P., Chenivresse, C., 2013. Role of CCL18 in asthma and lung immunity. *Clin Exp Allergy.* 43, 716–722. <https://doi.org/10.1111/cea.12065>.
- Turan, N., Bates, S., Edwards, M., Shaw, D.E., Chung, K.F., James, A., Loza, M.J., Van Oosterhout, A.J., 2017. A hypothesis driven approach investigating the interleukin-6 pathway in UBIOPRED severe asthma patients. *Eur. Respir. J.* 50, PA4941. <https://doi.org/10.1183/1393003.congress-2017.PA4941>.
- Valkanova, V., Ebmeier, K.P., Allan, C.L., 2013. CRP, IL-6 and depression: A systematic review and meta-analysis of longitudinal studies. *J. Affect. Disord.* 150 (3), 736–744.
- Weiser, E.B., 2007. The prevalence of anxiety disorders among adults with asthma: a meta-analytic review. *J. Clin. Psychol. Med. Settings* 14, 297–307. <https://doi.org/10.1007/s10880-007-9087-2>.
- Ye, G., Baldwin, D.S., Hou, R., 2021. Anxiety in Asthma: a systematic review and meta-analysis. *Psychol. Med.* 81, 105–110.
- Yellowlees, P.M., Haynes, S., Potts, N., Ruffin, R.E., 1988. Psychiatric morbidity in patients with life-threatening asthma: initial report of a controlled study. *Med J Aust.* 149 (5), 246–249.
- Yokoyama, A., Kohno, N., Sakai, K., Kondo, K., Hirasawa, Y., Hiwada, K., 1997. Circulating levels of soluble interleukin-6 receptor in patients with bronchial asthma. *Am J Respir Crit Care Med.* 156, 1688–1691. <https://doi.org/10.1164/ajrccm.156.5.9610070>.
- Zhu, M., Liang, Z., Wang, T., Chen, R., Wang, G., Ji, Y., 2016. Th1/Th2/Th17 cells imbalance in patients with asthma with and without psychological symptoms. *Allergy Asthma Proc.* 37, 148–156. <https://doi.org/10.2500/aap.2016.37.3928>.
- Zielinski, T.A., Brown, E.S., 2003. Depression in patients with asthma. In: Brown, E.S. (Ed.), *Advances in Psychosomatic Medicine Asthma: Social and Psychological Factors and Psychosomatic Syndromes*. KARGER, Basel, pp. 42–50.