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The impact of clinical and psychological factors on asthma control: the experience of a single asthma center in Poland

Marek Przybylski, MD^a, Rafal Pilinski, MSc^b, Agnieszka Sliwka, PhD^b , Romuald Polczyk, PhD^c , Roman Nowobilski, PhD^b , Krzysztof Sladek, MD, PhD^a, and Grazyna Bochenek, MD, PhD^a

^aDepartment of Pulmonology, Szczekliki Department of Internal Medicine, Faculty of Medicine, Jagiellonian University Medical College, Krakow, Poland; ^bUnit of Rehabilitation in Internal Diseases, Faculty of Health Sciences, Jagiellonian University Medical College, Krakow, Poland; ^cInstitute of Psychology, Jagiellonian University, Krakow, Poland

ABSTRACT

Objective: The asthma control test (ACT) is commonly used to identify patients with uncontrolled asthma. The goal of this study was to determine whether clinical parameters such as asthma history and medications, exacerbation rate, comorbidities, lung function, and socioeconomic status are risk factors for uncontrolled asthma assessed with the ACT, and to evaluate the psychological status of controlled and uncontrolled asthmatics.

Methods: Adult asthmatics ($n = 104$) were recruited from a single asthma center, Poland. Asthma control was assessed with the ACT, using <20 as the cutoff point for uncontrolled asthma. Data on clinical factors were collected and spirometry was performed. Patients completed the Asthma Quality of Life Questionnaire, General Health Questionnaire, Acceptance of Illness Scale, Life Orientation Test-Revised, and Eysenck's Personality Inventory.

Results: Asthma was uncontrolled in 42.3% of patients. Asthma exacerbations in the preceding 12 months and high inhaled corticosteroid (ICS) doses were identified as independent risk factors for uncontrolled asthma. Uncontrolled asthmatics had a significantly worse psychological status than controlled asthmatics. The groups did not differ in terms of personality traits, but in the controlled asthma group numerous significant correlations between psychological factors and personality traits were observed. In the uncontrolled asthma group, however, the occurrence of correlations between personality traits and other psychological variables was rarer.

Conclusions: The study identified independent risk factors for uncontrolled asthma, namely, exacerbations in the recent 12 months and treatment with high-dose ICS. Uncontrolled asthmatics have a significantly worse psychological status than controlled asthmatics, irrespective of personality traits.

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Introduction

The asthma control test (ACT) produces a five-item numerical score, created to identify asthmatics with poor control of the disease (1). In the nearly 20 years since its inception, the ACT has shown its ability to determine the current level of asthma control and predict future exacerbations (2,3).

Identified factors linked to poor asthma control include older age, comorbidities, environmental exposures and aggravating factors, insufficient education about asthma, poor adherence to controller treatment and incorrect inhaler technique (4–7). Despite improvements in asthma management and expanding knowledge about factors affecting treatment outcomes, approximately 50% of patients fail to reach good

control (8). This, in turn, leads to exacerbations, lower quality of life and steep healthcare costs (5,9). Moreover, studies have revealed alarming signals concerning dangerous treatment regimens, including excessive use of oral corticosteroids (OCS) and short-acting β_2 -agonists (SABA), which have been linked to increased morbidity and mortality (10,11).

A high burden of asthma symptoms resulting from uncontrolled asthma can also be associated with psychological disorders, such as anxiety and depression (12,13). In addition, it has been observed that personality traits of asthmatic patients may influence adherence to treatment and control of asthma (14,15). However, the relationship between uncontrolled asthma and emotional status is hard to determine, as these factors may influence each other bilaterally (12).

Previous studies of the impact of various factors on the level of asthma control usually presented clinical and psychological data separately. A combined evaluation of these factors in the same patients would provide valuable insight into their impact on asthma control.

The aim of this study was to identify clinical risk factors for uncontrolled asthma assessed with the ACT, and to evaluate relationships between asthma control level and psychological status among patients with asthma treated in a single asthma center in Poland.

Methods

Patients

This cross-sectional study was conducted at the Outpatient Clinic of the Department of Pulmonology, Jagiellonian University Medical College, Krakow, Poland, which is a specialty asthma center. The study enrolled 104 consecutively recruited patients with asthma, ages 23–78 years. All of them had been diagnosed and treated for asthma for at least six months prior to enrollment. Diagnosis was based on asthma symptoms (dyspnea, wheezing, cough, chest tightness) and lung function tests results using criteria described in the Global Initiative for Asthma (GINA) (16). All patients were without any asthma exacerbations and any changes in asthma controller medications during the six weeks preceding enrollment into the study.

The study was approved by the Jagiellonian University Ethics Review Committee. All patients gave written informed consent to participate in the study.

Data collection

Study subjects were recruited during routine visits in the outpatient clinic. Every patient who met the criteria mentioned above was asked to participate in the study. After obtaining the patient's written consent, detailed medical history based on a patient interview and data from medical records were collected by a physician—the study team member. Collected data included demographic and socioeconomic characteristics, asthma history, comorbidities, as well as current treatment with OCS and inhaled corticosteroids (ICSs). Comorbidities such as allergic rhinitis, chronic rhinosinusitis, gastro-esophageal reflux (GERD), and anxiety/depression were identified based on medical records provided by the patient. Obesity was defined as a body mass index of 30 kg/m² or higher and was calculated from self-reported weight. In addition, rescue medication use, estimated as a number of packs of a SABA during the previous 12 months; and

number of asthma exacerbations over the same time period, measured as a number of emergency department (ED) visits and hospitalizations were analyzed. All the above data were recorded in a paper form by the study team member. During the same outpatient visit, each patient completed the paper versions of the questionnaires used in the study and then underwent spirometry.

Assessment of asthma control, quality of life and psychological status

The Asthma Control Test (ACT) assesses the control status of asthma over the previous four weeks. The Polish translation of the ACT is available from the official questionnaire's website (www.asthmacontroltest.com) (1). According to the GINA Guidelines and ACT design, patients are divided into those with well controlled (20–25 points), not well controlled (16–19 points) and very poorly controlled (≤ 15 points) asthma (16). As the objective of our study was to identify the risk factors for uncontrolled asthma, we used a binary split into two groups: with controlled and uncontrolled asthma, with a cutoff point for uncontrolled asthma of less than 20 points.

Quality of life was evaluated with the Asthma Quality of Life Questionnaire (AQLQ) in the official Polish translation, consisting of 32 items referring to four sub-domains of everyday functioning of the patient: symptoms, activity limitation, emotional function, and environmental stimuli. For this questionnaire, scores range from 1 to 7 points. A score < 5 points is considered abnormal, although no strict cutoff point for low quality of life has been established (17).

The General Health Questionnaire—28 item version (GHQ-28)—was used for identifying non-psychotic and minor psychiatric disorders. Four domains, namely somatic symptoms, anxiety and insomnia, social dysfunction and severe depression, each consisting of seven items, were assessed, with Likert scoring from 0 to 3 points. A total score equal or greater than 22 points is indicative of the presence of psychopathology (18).

Personality traits were determined using Choynowski's Polish adaptation of the Eysenck Personality Inventory (EPI) (19). The questionnaire consists of 64 items assessing neuroticism (emotional stability or lability), extraversion (direction of energy and orientation outwards or inwards), and the tendency to answer the questions in a socially desirable manner (the "lie scale").

Assessment of individual tendency toward generalized optimism versus pessimism was performed using Life Orientation Test-Revised (LOT-R), a 10-item brief measure, whereby high scores imply patient's optimism (20). A score of 0–13 points indicates low optimism, 14–18 points indicates moderate optimism, and 19–24 points indicates high optimism.

Acceptance of asthma by the patient was evaluated using the Acceptance of Illness Scale (AIS), which consists of eight statements about negative consequences of health state, each rated on a 5-point Likert scale (21). The score is a sum of all points, and ranges from 8 to 40. Low scores (8–18) indicate the lack of acceptance and poor adaptation to the disease, moderate scores (19–29) imply modest acceptance, while high scores (30–40) indicate acceptance of the disease.

The psychological questionnaires including GHQ-28, EPI, LOT-R and AIS were obtained and evaluated by one of the study team members, a qualified psychologist with permission to purchase and assess these questionnaires.

Lung function measurement

Spirometry (MasterScreen, Jaeger, Wurzburg, Germany) was performed in the spirometry laboratory by a technician qualified in lung function tests. The test was done at baseline and after administration of four puffs of salbutamol (400 µg). The reversibility test was automatically calculated.

Statistical analysis

Differences between the two subgroups of patients were explored: one with controlled asthma, and the other with uncontrolled asthma, as determined by the ACT. Continuous variables were presented as mean and SD, while categorical variables were presented as proportions (percentage). Significance analysis for continuous variables was performed with the Student *t* test in case of normal distribution or with the Mann-Whitney *U* test if the distribution was abnormal. Categorical variables were analyzed using the chi-square test and Fisher's exact test. For dichotomous variables, Pearson's *r* correlation was used. For all analyzed parameters, the odds ratios (ORs) and 95% confidence intervals (CIs) for uncontrolled asthma were calculated. Then, backward stepwise multiple regression analysis was applied (Wald method). At the beginning, intercorrelations among all variables were computed to identify pairs of variables substantially intercorrelated. Only predictors statistically significant

Table 1. Basic demographic and clinical characteristics of the study subjects.

Parameter	Data
Subjects, n (%)	104 (100.0)
Female, n (%)	69 (66.3)
Age (y), mean (SD)	53.2 (14.4)
Smoking, n (%)	8 (7.7)
Asthma duration (y), mean (SD)	14.6 (15.2)
Early onset of asthma (<12 y old), n (%)	14 (13.5)
Baseline FEV1 % predicted, mean (SD)	81.4 (21.0)
ΔFEV1 ≥ 12%, n (%)	26 (25.0)
FEV1/FVC after bronchodilator, mean (SD)	71.9 (11.0)
Fixed obstruction: FEV1/FVC after bronchodilator <70%, n (%)	39 (37.5)
OCS (mg/day) ^a , mean (SD)	10.5 (8.6)
ICS (µg/day) ^b , mean (SD)	892.2 (1034.8)
SABA use (inhalers/year) ^c , mean (SD)	4.5 (7.9)
ED visits ^d , mean (SD)	2.4 (4.0)
Hospitalizations ^d , mean (SD)	0.5 (1.4)
Atopy confirmed by SPT ^e , n (%)	65 (62.5)
Education in inhaler use, n (%)	83 (79.8)
Adherence to treatment, n (%)	40 (38.5)
ACT score, mean (SD)	19.0 (4.7)
Subjects with ACT score <20, n (%)	44 (42.3)

ED, emergency department; FEV1, forced expiratory volume in the first second; ICS, inhaled glucocorticosteroids; OCS, oral glucocorticosteroids; SABA, short-acting β_2 mimetic; SPT, skin prick tests.

^aMaintenance dose, methylprednisolone equivalent.

^bMaintenance dose, fluticasone equivalent.

^cNumber of inhalers of SABA used in the previous 12 months.

^dDue to asthma exacerbation in the previous 12 months.

^ePositive for at least 1 aeroallergen.

in the univariate analyses were included, with adjustment for age and sex. For psychological parameters, as a cause-effect relationship between variables was difficult to establish, intercorrelations among all variables were computed for controlled and uncontrolled asthma groups separately. It was found that the subscales of the AQLQ were correlated at the $r=0.80$ level or higher. As such high intercorrelations among predictors are problematic due to multicollinearity problems, they were dropped from the analyses, and the AQLQ score was used instead.

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 21.0; IBM Corp., Armonk, NY).

Results

The demographic and clinical characteristics of the studied group are presented in Table 1.

Based upon the ACT score, patients were divided into the controlled or uncontrolled asthma groups (Table 2). The Cronbach alpha for the ACT in the studied group equaled 0.86, indicating good internal consistency. In comparison to controlled asthmatics, uncontrolled asthmatics had more severe airflow obstruction expressed by the lower baseline FEV1% predicted and a lower FEV1/FVC ratio after bronchodilator use. Also, they used significantly higher doses

Table 2. Comparison of basic parameters in the patient groups stratified by asthma control level and odds ratios for clinical factors potentially associated with uncontrolled asthma by the ACT.

Parameter	Controlled (n = 60)	Uncontrolled (n = 44)	p	OR	95% CI
Female, n (%)	37 (62.7)	32 (72.7)	0.238	0.60	0.26–1.4
Age (y), mean (SD)	51.1 (15.4)	55.7 (11.5)	0.1	1.02	1.0–1.05
Smoking, n (%)	6 (10)	2 (4.5)	0.302	0.43	0.08–2.23
Asthma duration (y), mean (SD)	13.0 (15.2)	16.8 (15.1)	0.203	1.02	0.99–1.04
Early onset of asthma (<12 y old), n (%)	9 (15.0)	5 (11.4)	0.591	0.73	0.23–2.34
Baseline FEV ₁ % predicted, mean (SD)	86.3 (18.9)	74.7 (22.1)	0.005	0.97	0.95–0.99
ΔFEV ₁ ≥ 12%, n (%)	17 (29.3)	9 (24.3)	0.644	0.78	0.30–1.98
FEV ₁ /FVC % after bronchodilator, mean (SD)	73.8 (9.5)	69.3 (12.5)	0.039	0.96	0.93–0.99
Fixed obstruction: FEV ₁ /FVC after bronchodilator <70%, n (%)	17 (28.3)	22 (50.0)	0.024	2.53	1.12–5.72
OCS (mg/day) ^a , mean (SD)	0.87 (2.2)	4.77 (8.6)	0.001	1.17	1.04–1.31
ICS (μg/day) ^b , mean (SD)	592.3 (482.7)	1301.1 (1395.9)	<0.001	1.001	1.001–1.002
SABA use (inhalers/year) ^c , mean (SD)	2.5 (5.2)	7.1 (9.9)	0.003	1.12	1.02–1.23
ED visits ^e , mean (SD)	1.17 (1.8)	4.1 (5.3)	<0.001	1.42	1.16–1.74
Hospitalizations ^d , mean (SD)	0.2 (0.5)	0.9 (1.9)	0.006	2.01	1.12–3.61
Atopy confirmed by SPT ^e , n (%)	38 (63.3)	27 (61.4)	0.841	0.92	0.41–2.05
Adherence to treatment, n (%)	23 (38.3)	17 (38.6)	0.907	1.04	0.76–1.43
Education in inhaler use, n (%)	50 (83.3)	33 (75.0)	0.296	0.60	0.23–1.57

Uncontrolled asthma by the ACT: score < 20. ED, emergency department; GERD, gastro-esophageal reflux disease; ICS, inhaled glucocorticosteroid; OCS, oral glucocorticosteroid; SPT, skin prick tests.

^aMaintenance dose, methylprednisolone equivalent.

^bMaintenance dose, fluticasone equivalent.

^cNumber of inhalers of short-acting rescue medication used in the previous 12 months.

^dDue to asthma exacerbation in the previous 12 months.

^ePositive for at least 1 aeroallergen.

Table 3. Comparison of comorbidities and socioeconomic factors in the patient groups stratified by asthma control level and odds ratios for factors potentially associated with uncontrolled asthma by the ACT.

Parameter	Controlled (n = 60)	Uncontrolled (n = 44)	p	OR	95% CI
Comorbidities					
Allergic rhinitis, n (%)	32 (53.3)	21 (47.7)	0.572	0.80	0.37–1.74
Chronic rhinosinusitis, n (%)	28 (46.7)	19 (43.2)	0.724	0.87	0.40–1.90
GERD, n (%)	16 (26.7)	21 (47.7)	0.027	2.51	1.10–5.72
Anxiety/depression, n (%)	4 (6.7)	11 (25.0)	0.009	4.67	1.37–15.85
Obesity (BMI ≥ 30kg/m ²), n (%)	17 (28.3)	20 (45.5)	0.072	2.11	0.93–4.77
Socioeconomic factors					
Place of residence (city), n, (%)	46 (76.7)	35 (79.6)	0.727	0.18	0.46–3.05
No. of cohabitants, mean, (SD)	2.3 (1.8)	1.8 (1.2)	0.099	0.80	0.61–1.04
Education					
Primary	1 (1.7)	0 (0.0)	0.183		
Vocational	8 (13.3)	12 (27.3)			
Secondary	18 (30.0)	15 (34.1)			
Higher	33 (55.0)	17 (38.6)			
Occupation					
Physical worker	12 (20.0)	10 (22.7)	0.095		
Office worker	26 (43.3)	12 (27.3)			
Unemployed	4 (6.7)	2 (4.6)			
Retired	16 (26.7)	12 (27.3)			
Disabled	2 (3.3)	8 (18.2)			

Uncontrolled asthma by the ACT: score < 20. GERD, gastro-esophageal reflux disease; BMI, body mass index.

of OCS and ICS, and required significantly more SABA. ED visits and hospitalizations due to asthma exacerbations in the previous 12 months were also significantly more frequent in this group. The groups did not differ significantly in terms of adherence to prescribed medications (Table 2). GERD and anxiety/depression disorder were significantly more common among uncontrolled asthmatics (Table 3). No significant differences in socioeconomic factors were noted (Table 3).

The univariate regression analysis revealed that for every 1% increase in FEV₁, the risk of uncontrolled

asthma decreased by 3%. The presence of fixed airway obstruction, expressed by FEV₁/FVC ratio below 70% increased the risk of uncontrolled asthma 2.5-fold. The use of higher doses of OCS and ICS increased the odds of uncontrolled asthma by 17% per each milligram of methylprednisolone, and by 10% per each 100 micrograms of fluticasone, respectively. Every additional inhaler with SABA spent per year, increased the likelihood of being in the uncontrolled asthma group by 12%. Asthma-related ED visits and hospitalizations in the previous year increased the odds of uncontrolled asthma 1.4-fold and 2.0-fold,

Table 4. Multivariate logistic regression analysis for factors associated with uncontrolled asthma by the ACT.

Parameter	OR	95% CI	<i>p</i> ^a
ICS dose ($\mu\text{g/day}$) ^b , mean (SD)	1.001	1.00–1.002	0.047
ED visits in the previous 12 months, mean (SD)	1.48	1.10–1.98	0.01

ICS, inhaled glucocorticosteroids; ED, emergency department.

^aAdjusted for age and sex.^bMaintenance dose, fluticasone equivalent.**Table 5.** Comparison of quality of life and psychological parameters in the patient groups stratified by asthma control level.

	Controlled (<i>n</i> = 60)	Uncontrolled (<i>n</i> = 44)	<i>t</i>	<i>df</i>	<i>p</i> ^a
AQLQ score, mean (SD)	5.0 (1.1)	3.7 (0.8)	6.18	102	<0.001
GHQ A, mean (SD)	13.7 (3.8)	16.8 (4.6)	−3.66	102	<0.001
GHQ B, mean (SD)	12.8 (4.0)	14.3 (3.1)	−2.01	102	0.008
GHQ C, mean (SD)	14.2 (2.7)	16.6 (3.3)	−4.01	102	<0.001
GHQ D, mean (SD)	8.1 (2.1)	9.0 (4.0)	−1.49	102	0.068
GHQ-28 score, mean (SD)	48.9 (10.0)	56.6 (12.1)	−3.58	102	<0.001
AIS score, mean (SD)	33.3 (6.4)	25.6 (7.1)	5.77	102	<0.001
LOTR score, mean (SD)	16.1 (3.3)	15.5 (4.0)	0.8	102	0.618
EPI Extraversion score, mean (SD)	36.7 (4.9)	36.7 (5.1)	0.08	102	0.926
EPI Neuroticism score, mean (SD)	32.9 (5.8)	34.6 (6.1)	−1.43	102	0.181
EPI Lie scale score, mean (SD)	21.9 (2.8)	21.8 (2.7)	0.17	102	0.897

Uncontrolled asthma by ACT: score <20.

^a*p* Value from Mann-Whitney *U* test.

AIS, Acceptance of Illness Scale; AQLQ, Asthma Quality of Life Questionnaire; EPI, Eysenck Personality Inventory; GHQ, General Health Questionnaire; GHQ A subscale, somatic symptoms; GHQ B subscale, anxiety and insomnia; GHQ C subscale, social dysfunctioning; GHQ D subscale, severe depression; LOTR, Life Orientation Test-Revised.

Table 6. Inter correlations between quality of life in asthma and all studied psychological variables in the controlled asthma group.

	AQLQ Score	GHQ A Subscale	GHQ B Subscale	GHQ C Subscale	GHQ D Subscale	GHQ Score	AIS Score	LOTR Score	Extraversion	Neuroticism
GHQ A Subscale	−0.044**									
GHQ B Subscale	−0.43**	0.53**								
GHQ C Subscale	−0.23	0.61**	0.48**							
GHQ D Subscale	−0.32*	0.42**	0.57**	0.22						
GHQ Score	−0.47**	0.84**	0.85**	0.74**	0.66**					
AIS Score	0.74**	−0.42**	−0.26*	−0.22	−0.4**	−0.41**				
LOTR Score	0.32*	−0.22	−0.28*	−0.15	−0.24	−0.29*	0.23			
Extraversion	0.21	−0.18	−0.3*	−0.31*	−0.37**	−0.35**	0.27*	0.09		
Neuroticism	−0.38**	0.3*	0.57**	0.1	0.44**	0.46**	−0.18	−0.32*	0.0	
EPI Lie scale	0.02	−0.04	−0.12	−0.11	−0.17	−0.13	0.06	−0.22	−0.17	−0.10

Pearson correlation coefficients presented.

p* < 0.05; *p* < 0.01.

AIS, Acceptance of Illness Scale; AQLQ, Asthma Quality of Life Questionnaire; EPI, Eysenck Personality Inventory; GHQ, General Health Questionnaire; GHQ A subscale, somatic symptoms; GHQ B subscale, anxiety and insomnia; GHQ C subscale, social dysfunctioning; GHQ D subscale, severe depression; LOTR, Life Orientation Test-Revised.

respectively (Table 2). The presence of GERD and anxiety/depression was significantly associated with a higher risk of uncontrolled asthma 2.5-fold and 4.7-fold respectively (Table 3).

In a multivariate regression analysis adjusted for age and sex, intake of higher doses of ICS and asthma-related ED visits in the previous 12 months proved to be independent predictors associated with uncontrolled asthma (Table 4).

Patients with uncontrolled asthma experienced significantly lower quality of life and presented significantly lower acceptance of illness than controlled asthma patients (Table 5). Uncontrolled asthmatics scored significantly higher on GHQ-28 with all subscales, except for the severe depression subscale (Table

5). GHQ-28 score was high in both groups but significantly higher in the uncontrolled asthma group. No significant differences in personality traits or in the tendency to lie were found between both groups (Table 5).

Analysis of inter correlations between quality of life and psychological variables in the controlled asthma group revealed statistically significant negative correlations between AQLQ score and GHQ-28 score and all its subscales, except social dysfunction (Table 6). The AQLQ score correlated significantly positively with AIS and LOTR scores, but negatively with neuroticism. GHQ-28 score correlated positively with all its subscales. Negative significant correlation was found between AIS score and GHQ-28 score and all its

Table 7. Intercorrelations between quality of life in asthma and all studied psychological variables in the uncontrolled asthma group.

	AQLQ Score	GHQ A Subscale	GHQ B Subscale	GHQ C Subscale	GHQ D Subscale	GHQ Score	AIS Score	LOTTR Score	Extraversion	Neuroticism
GHQ A Subscale	−0.32*									
GHQ B Subscale	−0.36*	0.63**								
GHQ C Subscale	−0.18	0.57**	0.57**							
GHQ D Subscale	−0.33*	0.41**	0.43**	0.54**						
GHQ Score	−0.38*	0.84**	0.8**	0.82**	0.75**					
AIS Score	0.38*	−0.06	−0.16	−0.16	−0.44**	−0.26				
LOTTR Score	−0.13	0.1	0.02	0.08	0.12	0.11	0.0			
Extraversion	0.02	0.1	−0.1	0.14	−0.07	0.03	0.26	0.2		
Neuroticism	−0.13	0.06	−0.17	0.28	0.38**	0.27	−0.41**	−0.39**	−0.21	
EPI Lie scale	0.12	0.04	−0.11	−0.05	−0.22	−0.1	0.06	0.03	−0.16	−0.24

Pearson correlation coefficients presented.

* $p < 0.05$; ** $p < 0.01$.

AIS, Acceptance of Illness Scale; AQLQ, Asthma Quality of Life Questionnaire; EPI, Eysenck Personality Inventory; GHQ, General Health Questionnaire; GHQ A subscale, somatic symptoms; GHQ B subscale, anxiety and insomnia; GHQ C subscale, social dysfunctioning; GHQ D subscale, severe depression; LOTTR, Life Orientation Test-Revised.

subscales, except social dysfunction. AIS score correlated positively with extraversion. LOTTR score was significantly negatively correlated with GHQ-28 score and its anxiety and insomnia subscale and with neuroticism. Moreover, extraversion was significantly negatively correlated with GHQ-28 and all its subscales, except somatic symptoms, while neuroticism was significantly positively correlated with GHQ-28 and all its subscales, except social dysfunction. No correlations were found between the lie scale and any psychological variables.

In the uncontrolled asthma group, the AQLQ score correlated significantly negatively with GHQ-28 score and all its subscales, except social dysfunction and positively with AIS score (Table 7). In addition, significant negative correlation was found between AIS score and the severe depression GHQ subscale. The GHQ-28 score correlated positively with all its subscales. There were few significant correlations between personality traits and the other analyzed variables. Only neuroticism correlated significantly positively with the severe depression GHQ subscale and negatively with AIS and LOTTR scores.

Discussion

The study revealed independent clinical risk factors for uncontrolled asthma, and relationships between asthma control level and both quality of life and psychological variables among asthmatics. To our knowledge, this is the first study that thoroughly explores correlations between quality of life, tendency for psychiatric disorders, acceptance of illness, and personality traits separately in controlled and uncontrolled asthmatics.

Asthma exacerbations are associated with poor control of the disease, and this association seems to be bidirectional. Data from prospective studies revealed

that a low ACT score predicted future asthma exacerbations (2,3), indicating that maintaining good asthma control is crucial to their prevention (16). Tomisa et al. revealed that exacerbations in the previous 12 months were among the strongest risk factors for poor asthma control, second only to poor inhaler technique (22). In another study, history of multiple ED visits in patients with asthma resulted in a lower ACT score (5). Similarly, in our study, ED visits due to exacerbations in the preceding 12 months turned out to be the strongest independent risk factor for uncontrolled asthma. It shows that, despite the ACT providing an estimate of asthma control over the previous four weeks, exacerbations in the last 12 months had an impact on current outcome.

Treatment with a high dose of ICS was identified as a second independent risk factor for uncontrolled asthma in our study. According to the recent GINA guideline, high ICS dose is needed by very few patients, and its long term use is associated with increased risk of local and systemic side-effects (16). Consequently, high ICS dose in combination with LABA is indicated only in Step 5 of asthma treatment or as another controller option in Step 4 (16). Increasing the ICS dose above small or moderate levels led to minimal gains in asthma control (23), but also increased the risk of treatment-associated side-effects, including adrenal suppression (24). Yet, in a real-world setting, increasing the dose of ICS remains one of the most common interventions in response to inadequately controlled asthma. A study by Bengtson et al. showed that patients with uncontrolled asthma remained uncontrolled and were experiencing asthma exacerbations despite therapy escalation (25). Likewise, in a long-term, 12-year follow-up study, Vahatalo et al. found that cumulative and average annual daily ICS doses were significantly higher in

uncontrolled asthmatics than in controlled ones (26). Also, an ICS daily dose $>2000\text{ }\mu\text{g}$ of a beclomethasone dipropionate equivalent, with a pre-bronchodilator FEV_1 of $<70\%$ on this dose of inhaled steroid, and a previous respiratory specialist referral turned out to be the strongest prognostic factors predicting therapy-resistant asthma (27). Therefore, our findings, which have shown that use of high, even above standard, ICS dose increased the chance of being in the uncontrolled asthma group, correspond with the above-mentioned studies. They suggest that in patients with poorly controlled asthma, the use of high ICS dose have limited benefits, and identifying potential modifiable risk factors can produce better outcomes than further step-up in controller treatment.

We observed a similar tendency regarding OCS. Uncontrolled asthmatics were treated with significantly higher doses of OCS than controlled asthmatics. The need for chronic OCS treatment to maintain asthma control was regarded as one of the major features of severe asthma. Previous studies revealed association between poor asthma control and frequent OCS use (22,28), however, it has been shown that the prevalence of truly severe asthma is much lower than difficult-to-treat asthma (29). Therefore, it seems reasonable to carefully assess the patient and modify potential factors impeding asthma control before diagnosis of severe asthma and introducing maintenance therapy with OCS. Moreover, such treatment is currently not preferred at Step 5 of the GINA recommendations due to side-effects (16). In the era of available biologics, these therapies should be considered for every patient with confirmed severe asthma due to the OCS-sparing effect they provide, along with significant improvement in asthma control (30,31).

Treatment of asthma with SABA alone is no longer recommended, even in the mildest forms of the disease (16). The use of three or more SABA inhalers during 12 months was identified as the best predictor of increased risk of an asthma related exacerbation (32). Shlomi et al. showed that use of at least two inhalers per year should alert the physician to the need for asthma control evaluation, and use of four SABA inhalers per year is indicative of poor asthma control (33). In our study, the mean values were alarmingly high, namely in the uncontrolled asthma group, SABA annual use exceeded seven inhalers, while in the controlled asthma group, it averaged 2.5 inhalers (Table 2). Therefore, even in the group of controlled asthmatics, as determined by ACT results, excessive SABA use should prompt physicians to

carefully analyze the treatment and further patients' education in this field. This shows that despite an overall good ACT result, it is worth looking beyond this single indicator. A similar concept comes from a study by Cajigal et al., which demonstrated that the total ACT score may not be more reliable than the single assessment of rescue medication use (ACT's Question 4) for predicting risk of severe asthma exacerbations (34).

Although a low FEV_1 is considered as one of the major risk factors for asthma exacerbation (16), the data on the influence of impaired lung function on asthma control are not consistent. On one hand, Bennet et al. did not reveal a significant link between asthma control level and the presence of fixed airway obstruction or occurrence of asthma exacerbation (35). In contrast, asthmatics with rapid decline of FEV_1 had significantly worse asthma control and higher exacerbation rates than asthmatics without this trait (36). Patients with low FEV_1 , together with an ACT score ≥ 20 points, were more prone to flare ups than those with an ACT score < 20 points (37). Our study demonstrated that a lower FEV_1 and, to a greater extent, fixed airway obstruction, significantly increased odds for uncontrolled asthma. Thus, spirometry seems to be a valuable additional parameter in multidimensional assessment of asthma patients.

Asthma control may also be affected by various comorbidities as well as social and psychological factors. It is increasingly apparent that extra-pulmonary comorbidities, recently described as a set of "treatable traits" in airway disease, significantly contribute to poor asthma control (38). Among the comorbidities analyzed in our study, the presence of GERD and anxiety/depression disorders increased the risk of poor asthma control. Liang et al. reported an independent association between GERD and uncontrolled asthma (39). In their study, GERD was identified in 21.4% of patients with well-controlled asthma and in more than 50% of those with uncontrolled asthma, which is in line with our findings. Additionally, GERD was associated with a higher frequency of asthma exacerbations (40). Anxiety/depression disorder was another comorbidity that significantly increased the risk of uncontrolled asthma in our study. Our results based on a self-reported doctor diagnosis are consistent with those based on psychological questionnaires, as discussed below.

Other studies reported that a low socioeconomic status and education level may have a detrimental effect on asthma control (41,42). However, we did not confirm such an association. This may be due to the

homogeneity of the study group (patients were treated in a single asthma center), and the above factors are also not as significant in Poland as in countries with diverse ethnic and economic background.

We did not observe any significant differences in adherence to treatment between controlled and uncontrolled asthmatics. This may be due to the fact that patients were asked only one question, namely, if they were following the doctor's recommendations regarding the use of asthma medications. It is possible that if a professional questionnaire was used, the results would be different.

In our study, patients with uncontrolled asthma had significantly lower AQLQ scores than patients with controlled disease, a result that aligns with findings from earlier studies (8,12,43). As the coexistence of uncontrolled asthma and poor quality of life is commonly observed, a study by Gonzalez et al. provided insight into the relation between these variables, namely low level of patient-rated asthma control proved to be the reason for low health-related quality of life (44). It seems evident that high incidence of asthma symptoms, limitation of activity, need for rescue medication use decrease patients' quality of life.

When GHQ-28 total scores increased above threshold value in both groups, the score was significantly higher in uncontrolled asthmatics. This group had significantly higher scores in somatization, anxiety and insomnia. They also scored higher on social dysfunction subscales and trended toward higher scores on severe depressive symptoms. These findings point to the occurrence of much more serious psychosocial issues in patients with uncontrolled asthma. Coban et al. demonstrated significantly higher scores of anxiety and depression connected with lower AQLQ score in uncontrolled asthmatics (12). In contrast, Lavoie et al. revealed that depression significantly impaired asthma control level, while anxiety disorders did not (45). The differences between the results might originate from different tools used to evaluate these psychopathologies. Some tools analyze depression in combination with anxiety, while in the GHQ-28 questionnaire, anxiety is evaluated together with insomnia. Similar to our study, Sundbom et al. found higher incidence of insomnia symptoms in uncontrolled asthmatics and vice versa: uncontrolled asthma proved to be a risk factor for insomnia (46). In turn, it was demonstrated, that patients with insomnia had a 2.4-fold increased risk for having uncontrolled asthma (47). There are also conflicting results regarding the somatization of symptoms. Asthmatics with panic disorder reported dyspnea despite optimal treatment of

asthma (48). Likewise, excessive asthma symptom reporting was not related to somatization and psychopathology (49).

We also noticed significant social dysfunction in our patients with uncontrolled asthma. This could result simply from the physical inability to perform exercise. However, as we have shown, this impairment exists also in the psychological sphere as it affects the patient's motivation to act and make important decisions.

Patients with controlled asthma had significantly better acceptance of illness than uncontrolled asthmatics, as shown by a high mean score in the former group and a range of moderate values in the latter one. This seems reasonable as fewer asthma symptoms would allow the patient to adapt better to the disease. It has also been demonstrated that asthmatic patients expressing high levels of confidence in doctors and acceptance of asthma have high asthma control levels (50). Development of acceptance of asthma is considered a dynamic process during which a patient's attitude changes from initial fear and rejection to acceptance and control over the disease (51). It is based on the integration of knowledge about asthma, self-awareness of the disease and mentoring from the physician. Therefore, achieving good asthma control undoubtedly depends on patient's attitude toward the disease, and the role of the physician.

Unlike previous studies, we did not find any differences in terms of personality traits between controlled and uncontrolled asthmatics. Witusik et al. determined that type D personality, characterized by negative emotionality and social inhibition, was associated with uncontrolled asthma (14). Axelsson et al. showed negative correlation between negative affectivity, impulsivity and asthma control (15). Similar to our results, however, Cheung et al. revealed that personality traits did not affect asthma control, but they did affect self-perception of asthma control and adherence to medications (52). These various findings suggest that there is no clear cut relationship between personality and asthma control.

Our further analysis of intercorrelations between psychological variables yielded important observations. In the controlled asthma group, psychopathology positively correlated with emotional instability, introversion and pessimism. In addition, neuroticism and pessimism significantly impaired quality of life. In contrast, these correlations were not observed in the uncontrolled asthma group, except for the positive correlation between emotional instability and tendency for severe depression. These results might suggest that poor asthma control could trigger psychopathology in

asthmatics. It could also be expected that improving asthma control will lead to improvement in psychological status. Since the correlation between asthma control and psychopathology might be bidirectional, this implies the probable improvement in asthma control following addressing the psychopathology in patients' therapy. Sastre et al. revealed that six months of optimal asthma treatment significantly reduced severity of psychological disorders in asthmatics (53). In controlled asthmatics, psychopathology seems to be closely related with patients' personality profile.

Our study has several limitations. First, the number of study subjects was limited in comparison to population studies. Perhaps this limitation was offset by our analysis, which was complex and multidimensional. The assessment of each patient required much time due to the number of questionnaires to be completed and the need for clinical evaluation and performing spirometry. Therefore, to make the assessment complete, fewer patients were recruited. Second, the small study population from one asthma center in Poland may not be representative of the general asthma population and the results cannot be generalized to the worldwide population of asthma patients. Third, the analysis was based upon cross-sectional observation of the population. Repeated assessment would provide closer insight into the relationships between changing asthma control level and psychological variables. Fourth, objective laboratory measures that might have affected the asthma status, such as blood or sputum eosinophilia or exhaled nitric oxide, were not included in the study. Fifth, we did not diagnose comorbidities in the study subjects, but data concerning them were extracted from medical records of the patients. Finally, the use of various questionnaires to assess psychological variables in our study, as well as others, may pose some problems when comparing the results of individual studies. For instance, our study used a specific version of Eysenck's Personality Inventory, namely a Polish adaptation by Choynowski, which has never been widely used outside that country. Furthermore, to avoid the use of more questionnaires, the evaluation of patients' adherence was simplified.

Conclusions

Exacerbations in the previous 12 months and a high ICS maintenance dose are independent clinical risk factors for uncontrolled asthma according to the ACT. Uncontrolled asthma is associated with worse quality of life, a greater tendency for psychopathology, and worse acceptance of the disease. The lack of a

relationship between personality traits and psychopathology among uncontrolled asthmatics may indicate the role of poor control as a factor affecting psychopathology in this group and vice versa. In contrast, in the controlled asthma group, personality and psychopathology are significantly related.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

ORCID

Agnieszka Sliwka  <http://orcid.org/0000-0002-1338-3819>

Romuald Polczyk  <http://orcid.org/0000-0002-0158-7742>

Roman Nowobilski  <http://orcid.org/0000-0002-3322-9018>

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