



## The asthma-anxiety connection



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### ARTICLE INFO

#### Article history:

Received 28 March 2016

Received in revised form

16 September 2016

Accepted 20 September 2016

Available online 21 September 2016

#### Keywords:

Asthma

Anxiety

Depression

Psychiatric disorders

DSM-IV

SCID

### ABSTRACT

**Background:** The literature reports a significant association between various mental disorders and asthma, in particular depression and/or anxiety, with some more robust data regarding anxiety disorders. However, the nature of this association remains largely unclear.

**Objectives:** (1) To test the hypothesis of a specific association of anxiety and depressive disorder (according to the DSM-IV) with asthma and (2) to test the bidirectional hypothesis of causality between asthma and psychiatric disorders.

**Methods:** Ninety-six adults were compared with 96 control subjects matched according to main socio-demographic variables (i.e., gender, age, marital status, cohabiting/non-cohabiting, and BMI). Subjects with asthma were divided according to GINA and ACT classifications. All subjects underwent Structured Clinical Interviews for DSM-IV Axis I (SCID-I) diagnosis.

**Results:** Significant association between asthma and lifetime anxiety disorders emerged (OR 3.03;  $p = 0.003$ ); no significant association with other psychiatric diagnosis emerged. Moreover, lifetime and current anxiety were associated with asthma severity levels ( $p < 0.01$  and  $p = 0.001$  based on age). Asthma preceded anxiety in 48% of cases; in 52% of cases, anxiety preceded asthma, without significant group differences. The risk of asthma, particularly of severe, uncontrolled forms ( $p < 0.01$ ), resulted higher in lifetime anxiety disorder patients ( $p = 0.003$  and  $p = 0.001$  based on age at onset). Current anxiety increased the risk of asthma, and that of an uncontrolled form ( $p < 0.05$ ). Asthma increased the risk of lifetime anxiety disorders ( $p = 0.002$  and  $p = 0.018$  using ages). Intermittent asthma increased the risk of lifetime and current anxiety disorders ( $p < 0.01$ ).

**Conclusions:** Anxiety disorders, in particular Lifetime Anxiety Disorders, represent the only psychiatric disorder significantly associated with asthma, with a possible bidirectional, anxiety-asthma relationship, each of which can be caused or result from the other.

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## 1. Introduction

Asthma is a major global health problem affecting over 300 million people of all ages worldwide and represents a significant socio-economic burden [1–3]. Its prevalence continues to increase in many areas of the world. Asthma and psychological factors have been associated for centuries: Moses Maimonides, in his “Treatise

on Asthma,” defined asthma as “difficulty of breathing or a pain in the chest,” suggesting behavioural changes as one of the measures to cure it [4]. The literature reports a significantly greater prevalence of mental disorders in people with asthma, with a particular emphasis on those with depression and/or anxiety [5–7]. This association has important implications for these patients deriving from the presence of psychiatric comorbidity including symptom severity [8,9] and reduced asthma control [10,11]; lower quality of life [12]; low therapy adherence [6]; higher incidence of smoking, inactivity, and obesity [13]; and increased use of healthcare services and, therefore, an increase in financial burden [10,14]. However, the evidence about the association between asthma and mental

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disorders is not unequivocal, largely due to significant methodologic differences between studies (e.g., differences in study design, sampling, methods of psychiatric evaluation), only appearing sound where the asthma-anxiety association is concerned [15]. Thus, whether a specific association does exist between anxiety disorders and/or depression and asthma remains a question to be answered. Moreover, the evidence for an association between asthma and affective disorders raises an ongoing debate on the true nature of this relationship: whether asthma is associated with a higher risk of affective disorders, and/or whether affective disorders increase the risk of developing asthma [16]. Our study was performed based on a reliable methodology for the evaluation of psychiatric diagnosis to test the hypotheses that: (a) anxiety and/or depressive disorders are the psychiatric conditions specifically associated with asthma and (b) a bidirectional link exists between these disorders and asthma.

## 2. Methods

To test the abovementioned hypotheses, a case-control study was conducted on a clinical sample of asthma patients referred to a public health centre, who were compared to a group of individuals without asthma and matched according to the main social and demographic variables and body mass index (BMI).

### 2.1. Study subjects

All consecutive adult asthma patients referred to the outpatient unit of the Allergy Centre of the University Hospital in Cagliari, Italy, in a 24-month period, were invited to participate in the study. Subjects affected by asthma who met the following criteria were enrolled: age 18–65 years and diagnosis of asthma. Patients affected by other severe somatic comorbidities (e.g., cardiac diseases, pulmonary diseases other than asthma, autoimmune diseases, past and current malignancies, neuromuscular disorders, and any other condition potentially influencing the respiratory function) and pregnant patients were excluded. Of the 134 patients that consented to participate, 96 were eligible (24 men, 72 women). Non-eligibility reasons after signing the informed consent form were mainly: (i) decided to not undergo the psychiatric interview; (ii) discovered further documentation of another disease or condition listed in the exclusion criteria; and (iii) pregnancy (1 case). Demographic, social, and clinical data were collected. Concurrently, during a 24-month period, an equal convenience sample comprising caretakers or relatives of patients or by members of the university hospital administrative staff was selected and used as a control group. All subjects were paired with the asthma patients according to sex, age ( $\pm 4$  years), marital status, cohabit status (cohabiting/non-cohabiting), education, and BMI (normal weight; overweight; and mild, moderate, or severe obesity). Control subjects affected by the same exclusion criteria were excluded. The Ethics Committee of the University of Cagliari approved the study.

### 2.2. Diagnosis of asthma

Diagnosis of asthma was based on previous positivity to broncho-provocation tests (methacholine, mannitol) or on broncho-reversibility test. Diagnosis was made by a physician from our outpatient clinic or by an external Allergy or Respiratory Medicine Specialist.

Severity of asthma at the time of diagnosis, according to previous GINA guidelines [17], was used to stratify patients. However, since GINA classification by severity levels applies to untreated patients, we also adopted the parameter of “asthma control” (AC),

which better reflects the real clinical status of the patient in clinical practice. AC is multidimensional in nature, being characterized by symptoms, changes in pulmonary function, and effects on quality of life and functional ability [18]. The ACT (Asthma Control Test) [19,20], the well-known five-item survey to assess asthma control, was employed. The parameters considered in the questionnaire are daytime and nocturnal asthma symptoms, the use of rescue medications, and the effect of asthma on daily functioning. Each item includes five response options corresponding to a 5-point Likert-type rating scale, and the sum of the responses to the five items provides a score ranging from 5 (poor control of asthma) to 25 (complete control of asthma) [20]. The questionnaire was completed by patients under the supervision of the interviewer.

### 2.3. Psychiatric assessment

Following specific informed consent, all patients and controls underwent global psychiatric evaluation regarding the presence or absence of Axis I and II disorders according to the DSM-IV criteria using the Structured Clinical Interview for DSM-IV diagnosis of Axis I (SCID-I, Research version) [21] and the Structured Clinical Interview for DSM-IV diagnosis of Axis II disorders (SCID-II) [22]. Interviews were conducted by resident psychiatrists who were trained in the use of the instruments by a senior specialist (FP, BC); inter-rater reliability evaluated using Cohen's kappa [23] before the start of the study was no lower than 0.80 [5]. For the purpose of this study, we will discuss only results obtained through the SCID-I.

### 2.4. Confounding factors

The two groups were paired not only for gender and age, but also for other well-known potential confounding variables relevant for psychiatric disorders, such as marital status [24], cohabitation [25], education [26–28], and weight status, given that obesity and weight excess are associated with psychiatric disorders [29–46], such as eating disorders [35–37], depression [38,45], below-threshold depressive and anxiety syndromes [39,40], anxiety [41,46], and personality traits and disorders [42–44].

## 3. Statistical analysis

Non-parametric analysis was first used to examine the association between asthma variables and psychiatric variables (current and lifetime diagnosis). For the purpose of our research, no specific direction in the relationship between asthma and psychiatric disorders is assumed. Statistical analysis included the calculation of the significance of the association between the asthma of a patient and his/her psychiatric status in a regression analysis setting in which there is a response variable and a set of explanatory factors. Some classic non-parametric tests such as Fisher's exact test for count data (in its generalized version: generalized Fisher's test) [47,48] and the permutation test [49] were employed when one variable was continuous and the other was categorical. Moreover, given that the main response variable, that is the condition of asthma, is a polytomous order variable, polytomous logistic regression [50] of the asthma variable over other variables representing the psychiatric status was employed. The odds ratios between cases and controls were also evaluated along with the goodness of fit of the model. Specifically, three different variables that describe the condition of asthma were considered: asthma (dichotomous: yes/no); ACT (ordinal variable with three levels: controlled asthma, partially controlled asthma, uncontrolled asthma); GINA severity levels (ordinal variable with four levels:

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