



The asthma-anxiety connection



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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 (± 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:

intermittent asthma, mild persistent asthma, moderate persistent asthma, severe persistent asthma). Psychiatric dichotomous variables (present/not present) were grouped into seven categories of disorders: lifetime anxiety, current anxiety, lifetime mood, current mood, lifetime personality; others lifetime; others current (where “others” stands for any mental disorder other than those cited among those considered by SCID). To further strengthen the evidence of any association between asthma and mental disorders, ages of onset of asthma and mental disorders were considered. A description of such onset ages is provided by usual Kaplan-Meier estimations of survival functions, where survival is intended with respect to the onset of asthma and/or mental disorder. Finally, the classical Cox proportional hazard regression (CPHR) model has been used to assess significance of the risk factors in the increment of the hazard rate (or decrement of survival) of asthma and mental disorder. As the CPHR model is semi-parametric, the results are free from any specific hazard rate assumption. In the CPHR model and in the logistic regression, response and explanatory variables have been given, but these methods do not allow assessment if asthma (mental disorder) is the natural response to mental disorder (asthma). All data were analysed using statistical R software (R Core Team, 2014) [51].

4. Results

4.1. Sample characteristics

The socio-demographic characteristics and the weight status of the samples are reported in Table 1. Subjects examined (both cases and controls) are prevalently women (75%), with a mean age between 40 and 41 years, mostly with a good level of education (>60% with a high school or university degree), married (approx. 60%) and employed (approx. 65%). Approximately one-third of the sample is comprised of overweight or obese subjects. No significant differences were observed between cases and controls with regard to distribution according to gender, age, marital status, education,

work status, and BMI classes.

4.2. Association between mental disorders and asthma: non-parametric analysis

Data on the association between asthma variables and psychiatric conditions (current and lifetime diagnosis) (Table 2) showed a significant association between asthma and lifetime anxiety disorders (OR, 3.03; $p = 0.003$), but not between asthma and current anxiety disorders. Moreover, no other psychiatric diagnosis was found to be associated with asthma. With regard to ACT, the only significant association shown was between ACT and the presence of a lifetime anxiety disorder (Table 3) ($p = 0.007$). However, the proportion of controlled and partially or totally uncontrolled asthma case subjects suffering from lifetime anxiety disorders is practically comparable, and the difference observed was substantial between cases (both controlled and partially controlled/uncontrolled) and controls. No other significant association with ACT emerged regarding current anxiety disorder or any other psychiatric diagnoses, whether lifetime or current. With regard to GINA, when the distribution of cases according to severity of asthma at the time of diagnosis was evaluated by the presence of a mental disorder, a close association between the presence of a lifetime anxiety disorder and asthma severity levels ($p = 0.0006$) was found. This reflects the overall difference in distribution of anxiety between cases and controls, with an increased level of prevalence of lifetime anxiety disorders in patients with “intermittent” and “moderate and severe persistent” asthma (Table 4). A similar association was observed regarding current anxiety disorders ($p = 0.008$), more represented among subjects with both intermittent and moderate/severe persistent asthma (Table 4). Even in this case, no other significant association emerged with regard to other psychiatric diagnoses.

4.3. Association between asthma (response variable) and anxiety (explanatory variable)

Logistic regression, in which asthmatic state was considered as the dependent variable and the diagnosis of current and lifetime anxiety as the explicative variables (Table 5), with socio-

Table 1
Characteristics for cases and controls.

	Cases (N = 96)	Controls (N = 96)
Age		
Median – yrs.	40.50	41.00
Range – yrs.	(19.00–67.00)	(18.00–65.00)
Gender – no. (%)		
Males	24 (25)	24 (25)
Females	72 (75)	72 (75)
Education – no. (%)		
Primary school	8 (8)	8 (8)
Secondary school	24 (25)	24 (25)
High school	35 (36)	35 (36)
University not completed	3 (3)	3 (3)
University degree	26 (27)	26 (27)
General marital status – no. (%)		
Married/living with a cohabiting partner	56 (58)	56 (58)
Not living with a cohabiting partner	40 (42)	40 (42)
Professional status – no. (%)		
Employed	60 (63)	66 (69)
Unemployed	9 (9)	3 (3)
Student	7 (7)	6 (6)
Pensioner	6 (6)	3 (3)
Housewife	12 (13)	16 (17)
Occasional jobs	2 (2)	2 (2)
BMI category – no. (%)		
Normal weight	62 (65)	62 (65)
Overweight	18 (19)	18 (19)
Obesity type 1	13 (13)	13 (13)
Obesity type 2	1 (1)	1 (1)
Obesity type 3	2 (2)	2 (2)

Table 2
Prevalence rates of Psychiatric Disorders in Cases and Controls. [Fisher test's odds ratio and p-value].

	Cases (N = 96)	Controls (N = 96)	Odds ratio (95% CI)	P-Value
Lifetime anxiety – no. (%)				
Yes	31 (32)	13 (14)	3.03 (1.41–6.84)	0.003
No	65 (68)	83 (86)		
Current anxiety – no. (%)				
Yes	20 (21)	11 (11)	2.03 (0.86–5.01)	0.11
No	76 (79)	85 (89)		
Lifetime mood disorders – no. (%)				
Yes	17 (18)	12 (12)	1.50 (0.63–3.69)	0.42
No	79 (82)	84 (88)		
Current mood disorders – no. (%)				
Yes	5 (5)	5 (5)	1 (0.22–4.50)	1
No	91 (95)	91 (95)		
Personality disorders – no. (%)				
Yes	17 (18)	11 (11)	1.66 (0.68–4.18)	0.30
No	79 (82)	85 (89)		
Other lifetime disorders – no. (%)				
Yes	10 (10)	4 (4)	2.66 (0.73–12.07)	0.16
No	86 (90)	92 (96)		
Other current disorders – no. (%)				
Yes	9 (9)	2 (2)	4.83 (0.96–47.13)	0.05
No	87 (91)	94 (98)		

Table 3

Prevalence rates of Psychiatric Disorders in Controls and in controlled and partially controlled/uncontrolled asthma according to ACT. [Fisher test's p-value.].

	Controls (N = 96)	Controlled asthma (N = 63)	Partially controlled and uncontrolled asthma (N = 33)	P-Value
Lifetime anxiety – no. (%)				
Yes	13 (14)	21 (33)	10 (30)	0.007
No	83 (86)	42 (67)	23 (70)	
Current anxiety – no. (%)				
Yes	11 (11)	13 (21)	7 (21)	0.197
No	85 (89)	50 (79)	26 (79)	
Lifetime mood disorders – no. (%)				
Yes	12 (12)	8 (13)	9 (27)	0.115
No	84 (88)	55 (87)	24 (73)	
Current mood disorders – no. (%)				
Yes	5 (5)	2 (3)	3 (9)	0.461
No	91 (95)	61 (97)	30 (91)	
Personality disorders – no. (%)				
Yes	11 (11)	10 (16)	7 (21)	0.347
No	85 (89)	53 (84)	26 (79)	
Other lifetime disorders – no. (%)				
Yes	4 (4)	5 (8)	5 (15)	0.099
No	92 (96)	58 (92)	28 (85)	
Other current disorders – no. (%)				
Yes	2 (2)	5 (8)	4 (12)	0.039
No	94 (98)	58 (92)	29 (88)	

Table 4

Prevalence rates of psychiatric disorders in Controls and different GINA severity levels. [Fisher test's p-value.].

	Controls (N = 96)	Intermittent (N = 28)	Mild persistent (N = 44)	Moderate and severe persistent (N = 24)	P-Value
Lifetime anxiety – no. (%)					
Yes	13 (14)	14 (50)	9 (20)	8 (33)	0.0006
No	83 (86)	14 (50)	35 (80)	16 (67)	
Current anxiety – no. (%)					
Yes	11 (11)	10 (36)	4 (9)	6 (25)	0.008
No	85 (89)	18 (64)	40 (91)	18 (75)	
Lifetime mood – no. (%) disorders					
Yes	12 (12)	3 (11)	8 (18)	6 (25)	0.377
No	84 (88)	25 (89)	36 (82)	18 (75)	
Current mood – no. (%) disorders					
Yes	5 (5)	0 (0)	3 (7)	2 (8)	0.501
No	91 (95)	28 (100)	41 (93)	22 (92)	
Personality disorders – no. (%)					
Yes	11 (11)	5 (18)	8 (18)	4 (17)	0.593
No	85 (89)	23 (82)	36 (82)	20 (83)	
Other lifetime disorders – no. (%)					
Yes	4 (4)	3 (11)	4 (9)	3 (12)	0.251
No	92 (96)	25 (89)	40 (91)	21 (88)	
Other current disorders – no. (%)					
Yes	2 (2)	3 (11)	4 (9)	2 (8)	0.083
No	94 (98)	25 (89)	40 (91)	22 (92)	

Table 5

Association of Anxiety as independent variable and Asthma as dependent variable. Results of Regression Analysis. [Regression coefficients, standard errors and p-values for the logistic regressions.].

Dependent variable	Independent variable	Beta coefficient	Std. error	P-value
Asthma	Lifetime anxiety	–1.114	0.370	0.003
ACT	Lifetime anxiety	0.870	0.317	0.006
GINA	Lifetime anxiety	1.112	0.317	<0.001
Asthma	Current anxiety	0.077	0.796	0.047
ACT	Current anxiety	1.279	0.565	0.024
GINA	Current anxiety	0.999	0.526	0.058

demographic and BMI variables considered as possible confounding factors, showed a significantly higher risk of suffering from asthma in patients with a lifetime anxiety disorder ($p = 0.003$). Using the level of control of the asthma (ACT) as the dependent variable, the ordinal logistic regression results show that suffering from a lifetime anxiety disorder increases the risk of

being affected by uncontrolled asthma ($p = 0.006$). Considering the “severity of asthma” (GINA) as the dependent variable, ordinal logistic regression demonstrates how a lifetime anxiety disorder tends to increase significantly the risk of suffering a more severe form of asthma ($p < 0.001$). Moreover, current anxiety increases the risk of asthma ($p = 0.047$) and of being affected by an

uncontrolled form of asthma ($p = 0.024$).

4.4. Association between anxiety (response variable) and asthma (explanatory variable)

Considering the psychiatric condition as the dependent variable and the asthma state as the explicative variable (Table 6), regression analysis showed in age-matched conditions, how the risk of having a lifetime anxiety disorder was increased by the presence of asthma ($p = 0.002$). Furthermore, having controlled asthma increased the risk of developing a lifetime anxiety disorder, but only in female subjects ($p = 0.001$). Considering the severity of asthma evaluated through GINA, data show that intermittent asthma increases significantly the risk of being affected by both a lifetime ($p < 0.001$) and current ($p = 0.004$) anxiety disorder.

4.5. Bidirectional relationship between asthma and anxiety according to age at onset

In the subgroup of subjects with asthma affected by lifetime anxiety disorders, the age at onset of the psychiatric disorder was compared with the age at onset of asthma. Age at onset of the anxiety disorder was obtained through the SCID-I structured clinical interview, whereas for asthma, it corresponded to the age at diagnosis. Of a total of 31 affected subjects, both with asthma and an anxiety disorder, onset of asthma preceded the anxiety disorder in 48% of cases; in the remaining 52%, anxiety preceded the onset of asthma, without any significant differences between the two groups.

Using age at onset, anxiety was also found to be a risk factor for asthma, conditionally on all available information from the socio-demographic variables (see Table 7). In particular, lifetime anxiety is a risk factor ($p = 0.001$) for asthma, increasing this risk 3.7 times (95% C.I.: 1.6–8.4). The Kaplan-Meier estimation of survival curve for asthma onset of these subjects is significantly higher than in those affected by lifetime anxiety (see Fig. 1-left).

Similarly, considering age at onset, asthma was found to also be a risk factor for anxiety conditionally on all available information from the socio-demographic variables (see Table 8). In particular, asthma is a risk factor ($p = 0.018$) for anxiety, with a 2.1 times increase of the risk of the disorder (95% C.I.: 1.1–3.9). The Kaplan-Meier estimation of survival curve of these subjects based on age

at onset of anxiety is significantly higher than in those affected by asthma (see Fig. 1-right).

5. Discussion

A significant association between mental disorders and asthma, in particular depression and/or anxiety, is reported in the literature [5–7,52]. These data emerge from both population and clinical studies, although substantial methodological problems may limit the relevance of results. Indeed, population studies, whose strength is generally found in the large cohorts of individuals studied, suffer from relevant design limitations, such as the clinically uncontrolled, mainly self-reported, diagnosis of asthma [13,53–61]. Moreover, many of these studies based psychiatric diagnoses on self-evaluation questionnaires [13,54,57,62], clinical evaluation scales that do not allow a categorical psychiatric diagnosis [63], or structured clinical interviews administered by lay (i.e., nonclinical) interviewers [11,12,58,61]. Other population studies, irrespective of the psychiatric evaluation methods employed, concern only anxiety and/or depressive disorders [13,54,57,61,63,64]. In summary, in the literature, we found only a single population study using structured clinical interviews for psychiatric disorder and a medical diagnosis for asthma [65]. Alternatively, studies of clinical populations, which have the strength of a controlled diagnosis of asthma, are often burdened by some limitations such as the use of self-evaluation instruments for psychiatric diagnosis [66–68] or on clinical evaluation scales that do not allow a categorical psychiatric diagnosis [69,70]; other studies are focused on anxiety and/or depressive disorders only [69–75], and some have not used control groups [11,16,65,69,70,72,76–88]. Finally, some clinical studies involved only special populations such as paediatric [89] and/or adolescents patients [90].

To our knowledge, this is the first clinical study to present data on the association of current and lifetime Axis I mental disorders according to DSM-IV, evaluated through the use of a semi-structured clinical interview conducted by clinicians, in a population of asthma patients with a clinically controlled diagnosis and compared to a healthy control group matched for socio-demographic variables and weight status (BMI) in order to avoid the possible confounding effect due to the co-presence of obesity [61]. In this regard, it should be underlined that several studies demonstrated the association between specific psychiatric syndromes or states such as eating disorders [35–37], depression [38], below-threshold depressive and anxiety syndromes [39,40],

Table 6
Association of Asthma as independent variable and Anxiety as dependent variable. Results of Regression Analysis. [Regression coefficients, standard errors and p-values for the logistic regressions.].

Dependent variable	Independent variable	Beta coefficient	Std. error	P-value
Lifetime anxiety	Age	0.042	0.015	0.005
	Asthma	1.152	0.378	0.002
Current anxiety	Age	0.034	0.017	0.042
	Asthma	0.717	0.412	0.082
Lifetime anxiety	ACT controlled	1.379	0.424	0.001
	ACT partially controlled or uncontrolled	0.795	0.497	0.109
	Sex male	−0.748	0.482	0.121
Current anxiety	Age	0.043	0.015	0.006
	Age	0.034	0.016	0.042
Lifetime anxiety	GINA intermittent	1.969	0.501	<0.001
	GINA mild persistent	0.563	0.490	0.250
	GINA moderate or severe	1.070	0.538	0.047
	Age	0.044	0.016	0.005
	GINA intermittent	1.508	0.518	0.004
Current anxiety	GINA mild persistent	−0.226	0.620	0.715
	GINA moderate or severe	0.857	0.577	0.138
	Age	0.034	0.017	0.049

Table 7

Explanatory variables of Asthma according to its age of onset: Regression Analysis. [Regression coefficients, standard errors and p-values for the Cox proportional hazard model. Also exponential of coefficients along with their 95% Confidence Intervals are shown. Effects must be interpreted with respect to their alias (the category not shown).].

Explanatory variable	Category	Coefficient	Std. error	P-value	Exp (coeff.)	95% conf. interval
Response: Age at first asthma episode						
Gender	Female	0.247	0.270	0.360	1.281	0.754 2.176
Education	Primary school	−0.533	0.471	0.258	0.587	0.233 1.477
	Secondary school	0.131	0.292	0.654	1.140	0.643 2.020
	University not completed	−0.155	0.659	0.815	0.857	0.236 3.117
	University degree	0.494	0.293	0.092	1.638	0.923 2.909
General marital status	Non-cohabiting	0.084	0.268	0.754	1.087	0.643 1.838
Professional status	Employed	0.280	0.383	0.464	1.324	0.625 2.804
	Unemployed	0.811	0.510	0.112	2.249	0.828 6.112
	Student	1.558	0.608	0.010	4.749	1.442 15.643
	Pensioner	0.147	0.580	0.800	1.159	0.371 3.615
BMI category	Occasional jobs	−0.124	0.848	0.884	0.883	0.167 4.659
	Overweight	−0.308	0.316	0.331	0.735	0.395 1.367
	Obesity type 1	−0.355	0.341	0.297	0.701	0.359 1.368
	Obesity type 2	0.396	1.085	0.715	1.486	0.177 12.466
	Obesity type 3	−0.504	0.811	0.534	0.604	0.123 2.958
Lifetime anxiety	Yes	1.319	0.413	0.001	3.741	1.665 8.405
Lifetime mood disorders	Yes	−0.008	0.360	0.981	0.992	0.490 2.007
Personality disorders	Yes	0.146	0.376	0.698	1.157	0.553 2.420
Other lifetime disorders	Yes	−1.939	1.168	0.097	0.144	0.015 1.419
Current anxiety	Yes	−0.957	0.459	0.037	0.384	0.156 0.945
Current mood disorders	Yes	−0.164	0.581	0.777	0.848	0.272 2.651
Other current disorders	Yes	2.204	1.201	0.067	9.057	0.861 95.293

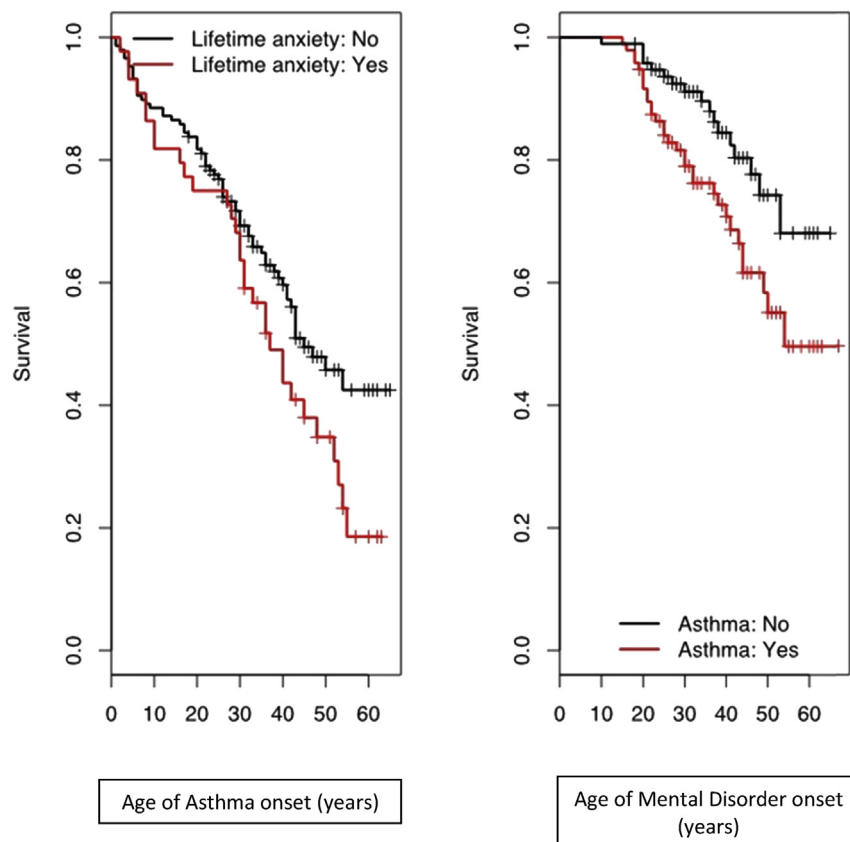


Fig. 1. Conditional Kaplan-Meier estimations of survivals functions for asthma (left) and mental disorder (right) with respect to significant risk factors: lifetime anxiety for asthma and asthma for mental disorder.

symptoms of anxiety [41], personality traits and disorders [42–44], and obesity. In particular, consensus exists on the relationship between obesity and depression, with important implications in terms of prevention, early diagnosis, and treatment. A condition of obesity/overweight has been found to increase the risk of

depression, and depression has been found to be predictive of future development of obesity, with an increased risk of 58% [45]. Similarly, other studies have found a relationship between obesity and anxiety disorders [46]. Moreover, obesity has been associated with both respiratory difficulty and asthma in various ways

Table 8
Explanatory variables of Anxiety according to its age of onset: Regression Analysis. [Regression coefficients, standard errors and p-values for the Cox proportional hazard model. Also exponential of coefficients along with their 95% Confidence Intervals are shown. Effects must be interpreted with respect to their alias (the category not shown).].

Explanatory variable	Category	Coefficient	Std. error	p-value	Exp (coeff.)	95% conf. interval
Response: Age at first psychiatric episode						
Asthma	Case	0.751	0.319	0.018	2.119	1.135 3.953
Gender	Female	−0.548	0.438	0.210	0.578	0.245 1.363
Education	Primary school	−0.643	0.634	0.310	0.526	0.152 1.821
	Secondary school	0.366	0.377	0.332	1.442	0.689 3.021
	University not completed	1.157	1.075	0.282	3.179	0.387 26.120
	University degree	−0.227	0.441	0.606	0.797	0.336 1.891
General marital status	Non-cohabiting	0.055	0.345	0.872	1.057	0.538 2.078
Professional status	Employed	−0.100	0.448	0.824	0.905	0.376 2.177
	Unemployed	0.498	0.594	0.402	1.646	0.514 5.271
	Student	−17.897	4601.208	0.997	0.000	0.000 ∞
	Pensioner	0.297	0.686	0.666	1.345	0.351 5.162
	Occasional jobs	1.121	0.852	0.189	3.068	0.577 16.308
BMI category	Overweight	−0.354	0.449	0.431	0.702	0.291 1.694
	Obesity type 1	−0.284	0.436	0.515	0.752	0.320 1.770
	Obesity type 2	0.661	1.109	0.551	1.936	0.220 17.033
	Obesity type 3	0.527	0.790	0.504	1.694	0.360 7.963

[91–93]. The common assumption is that weight increase occurs because asthma patients avoid physical exercise, as it could trigger their symptoms. Furthermore, obesity could increase the risk of gastro-oesophageal reflux, which in turn could trigger an asthma attack. Greater respiratory difficulty in asthma patients could be caused by “organic” rather than by functional damage, as obesity can reduce residual pulmonary function capacity by up to ≥ 500 mL. The association between airway hyper-responsiveness (AHR), pathognomonic to asthma, and changes in BMI, has been claimed as an explanation of the link between obesity and asthma, although this association remains controversial [94–99]. Finally, two meta-analyses [100,101] showed that being overweight or obese increases the odds of incident asthma in a dose-dependent manner; however, weight loss interventions show low-quality evidence of the beneficial effects of losing weight on asthma-related outcomes [101].

Our study demonstrates that the proportion of subjects diagnosed with a current or lifetime mental disorder was generally higher among those affected by asthma, compared to the healthy control subjects. However, the only common disorder for which a significantly higher prevalence among those with asthma was observed was lifetime anxiety disorder (32% vs. 14% of controls), with a three-fold greater risk. Moreover, non-parametric analysis showed how poor control of asthma is associated with a higher prevalence of lifetime anxiety disorders, whereas intermittent asthma, and, to a lesser degree, persistent and moderate/severe levels of asthma, are associated with a higher risk of lifetime anxiety disorders, and in a less evident manner, to current anxiety disorders. These results appear to confirm the particular association of asthma with anxiety disorders, but not depressive disorders, for which data in the literature are somewhat contradictory [15]. Our data are generally consistent with those of the only population study [102] that evaluated the association between mental disorders and asthma, using a structured clinical interview to assess psychiatric diagnosis and a clinical evaluation for the diagnosis of asthma. This study, involving a large sample of adult subjects, demonstrates how severe asthma is associated with a significantly higher risk of anxiety disorders, whereas current non-severe asthma is associated only to an increased risk of mood disorders, and non-severe lifetime asthma is associated to an increased risk of anxiety and somatoform disorders (22). Overall, our investigation substantially confirms the close relationship between asthma, particularly when uncontrolled or poorly controlled and of a moderate/severe degree, and anxiety disorders. Indeed, the

association between anxiety (and/or various depressive disorders) and poorly controlled asthma has been repeatedly confirmed in several clinical studies, irrespective of methodologies employed [11,13,16,69,72,76,80,87]. Data on the association between higher levels of asthma severity (evaluated through GINA or other methods) and a more elevated probability of psychiatric disorders appear to be more heterogeneous, with positive results reported in some studies [61,72,77,79,84,86], negative results in others [16,75,78,81,85,87,88], whilst other studies show positive results, but only limited to subjective self-evaluation of anxiety and/or depression [83,84].

Confirmation of a significant association between asthmatic disorders and anxiety takes us back to the problem regarding the specificity of the link between asthma and anxiety disorders and of the nature of such an association [103]. In particular, it remains unclear whether the subsequent onset of anxiety manifestations is favoured by asthma or whether the latter favours the subsequent development of anxiety. In our study, data are in favour of a bidirectional hypothesis of causality, given that asthma precedes anxiety onset with almost the same frequency that the anxiety disorder precedes asthma onset; moreover, the latter is associated with an increased risk of lifetime anxiety disorders, but even being affected by an anxiety disorder, especially lifetime, is associated to an increased risk of suffering from asthma. Our data appear to substantially confirm what emerged from prospective longitudinal studies, namely that both clinically significant anxiety and/or depression constitute significant risk factors for developing asthma [104–107], and asthma may be the cause of subsequent affective disorders [108,109]. However, a recent study reports that a history of respiratory disease does not appear to confer an increased risk of depression or anxiety [110]. Above all, our study is in line with findings from longitudinal studies which are in favour of a bidirectional hypothesis: the large prospective population study including all people aged 15 years or above with a clinical diagnosis of asthma and of anxiety disorder according to ICD-9 codes by Lee et al. [64] and the longitudinal cohort study by Hasler et al. [111], both demonstrating the validity of the hypothesis of a bidirectional association between the two conditions. In addition, the large meta-analysis based on prospective studies investigating the relationship between psycho-social factors (stressful life events, anxiety and/or depression, scarce social support) and atopic disorders in children and adults [112] confirms the same findings. Hypothetical explanations for such a bidirectional relationship lead us to two substantial possibilities:

both of the diseases can constitute a causative factor for the other through direct or indirect mechanisms, or both disorders can be explained based on mutual etiopathogenetic mechanisms. Asthma can lead to the development of anxiety disorders in relation to different putative mechanisms: the perception of threat due to a potentially lethal disease, the development of conditioning to anxiety induced by recurrent dyspnoea [113], and above all because of the unpredictability and occasionally uncontrollability of the respiratory manifestations, the progressive de-railing of respiratory receptors. The anxiogenic role of some anti-asthmatic drug types must also be considered, in particular of adrenergic agonists [111,114]. Anxiety disorders, in turn, especially in the event of early onset, could be causatively correlated to asthma through behavioural mechanisms (i.e., increased cigarette smoking [115]) or through biological mechanisms (i.e., hyperventilation, that can act as a “trigger” with respect to asthmatic attacks, determining bronchoconstriction) [106,111]. Furthermore, the mutual role of adverse childhood events as a risk factor not only for anxiety disorders, but also for the development of asthma [55,106], must be considered.

Finally, the mechanisms of the effects of inflammation on the brain have become an area of intensive study, and evidence suggests that the high comorbidity between these disorders can be explained by the inflammation due to the mutual pathogenic mechanisms, linked to the complex psycho-neuro-immunological pathways involving mainly pro-inflammatory cytokines and imbalance towards the Th2 T-cell response [116–119].

6. Conclusions

The data obtained appear to be of a certain interest, considering several strong points of the study such as: clinical diagnosis of asthma; psychiatric diagnoses based on semi-structured interviews conducted by non-lay-interviewers (psychiatrists or residents in psychiatry) and the use of controls paired not only for the main socio-demographic variables confounding factors, but also for BMI.

In this study, lifetime anxiety disorders represent the diagnosis most significantly and unequivocally associated with asthma, especially if inadequately controlled. Regression analysis showed that having a lifetime anxiety disorder bears an almost four-fold higher risk of having asthma, in particular uncontrolled and more severe asthma. Similarly, having asthma bears a more than two-fold higher risk of having an anxiety disorder, confirming the possibility of a bidirectional relationship between anxiety and asthma, either of which can be the cause or consequence of the other, even though some underlying mutual etiopathogenetic mechanisms that explain the frequency of their association cannot be excluded. In either case, evidence of a close link between the two conditions confirms the need for a multi-disciplinary approach, not only with regard to research, but also in the daily clinical practice for the evaluation and treatment of the asthmatic patient, given the importance of anxiety as a comorbidity for the course of asthma, its prognosis, and response to therapy.

Author contributions

Study conception and design: SDG, AC, BC, FP.
 Statistical analysis of Data: SP, SC.
 Analysis and interpretation of data: all authors.
 Drafting the work: SDG, AC, BC, FP.
 Critical Revision for important intellectual content: all authors.
 Final approval of the version to be published: all authors.
 Agreement on accuracy and integrity of the work: all authors.

Conflict of interest statement

All the authors and collaborators declare no conflicts of interest involving the work under consideration for publication.

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References

- [1] A. Custovic, S.L. Johnston, I. Pavord, M. Gaga, L. Fabbri, E.H. Bel, P. Le Souef, J. Lotvall, P. Demoly, C.A. Akdis, D. Ryan, M.J. Makela, F. Martinez, J.W. Holloway, S. Saglani, P. O'Byrne, A. Papi, S. Sergejeva, A. Magnan, S. Del Giacco, O. Kalayci, E. Hamelmann, N.G. Papadopoulos, EAACI position statement on asthma exacerbations and severe asthma, *Allergy* 68 (12) (2013) 1520–1531.
- [2] GINA, 2016-Pocket Guide for Asthma Management and Prevention, GINA Foundation, 2016.
- [3] C. Anandan, U. Nurmatov, O.C. van Schayck, A. Sheikh, Is the prevalence of asthma declining? Systematic review of epidemiological studies, *Allergy* 65 (2) (2010) 152–167.
- [4] F. Rosner, Moses Maimonides' treatise on asthma, *Thorax* 36 (4) (1981) 245–251.
- [5] W.J. Katon, L. Richardson, P. Lozano, E. McCauley, The relationship of asthma and anxiety disorders, *Psychosom. Med.* 66 (3) (2004) 349–355.
- [6] H. Baumeister, K. Balke, M. Harter, Psychiatric and somatic comorbidities are negatively associated with quality of life in physically ill patients, *J. Clin. Epidemiol.* 58 (11) (2005) 1090–1100.
- [7] R. Calam, L. Gregg, B. Simpson, J. Morris, A. Woodcock, A. Custovic, Childhood asthma, behavior problems, and family functioning, *J. Allergy Clin. Immunol.* 112 (3) (2003) 499–504.
- [8] D.E. Shaw, A.R. Sousa, S.J. Fowler, L.J. Fleming, G. Roberts, J. Corfield, I. Pandis, A.T. Bansal, E.H. Bel, C. Auffray, C.H. Compton, H. Bisgaard, E. Bucchioni, M. Caruso, P. Chanez, B. Dahlen, S.E. Dahlen, K. Dyson, U. Frey, T. Geiser, M. Gerhardsen de Verdier, D. Gibeon, Y.K. Guo, S. Hashimoto, G. Hedlin, E. Jeyasingham, P.P. Hekking, T. Higenbottam, I. Horvath, A.J. Knox, N. Krug, V.J. Erpenbeck, L.X. Larsson, N. Lazarinis, J.G. Matthews, R. Middelvel, P. Montuschi, J. Musial, D. Myles, L. Pahus, T. Sandstrom, W. Seibold, F. Singer, K. Strandberg, J. Vestbo, N. Vissing, C. von Garnier, I.M. Adcock, S. Wagers, A. Rowe, P. Howarth, A.H. Wagener, R. Djukanovic, P.J. Sterk, K.F. Chung, U.B.S. Group, Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort, *Eur. Respir. J. off. J. Eur. Soc. Clin. Respir. Physiol.* 46 (5) (2015) 1308–1321.
- [9] W. Katon, E.H. Lin, K. Kroenke, The association of depression and anxiety with medical symptom burden in patients with chronic medical illness, *General Hosp. psychiatry* 29 (2) (2007) 147–155.
- [10] L. Zhang, X. Zhang, J. Zheng, L. Wang, H.P. Zhang, L. Wang, G. Wang, Comorbid psychological dysfunction is associated with a higher risk of asthma exacerbations: a systematic review and meta-analysis, *J. Thorac. Dis.* 8 (6) (2016) 1257–1268.
- [11] F. Di Marco, P. Santus, S. Centanni, Anxiety and depression in asthma, *Curr. Opin. Pulm. Med.* 17 (1) (2011) 39–44.
- [12] H. Baumeister, N. Hutter, J. Bengel, M. Harter, Quality of life in medically ill persons with comorbid mental disorders: a systematic review and meta-analysis, *Psychother. Psychosom.* 80 (5) (2011) 275–286.
- [13] T.W. Strine, A.H. Mokdad, L.S. Balluz, J.T. Berry, O. Gonzalez, Impact of depression and anxiety on quality of life, health behaviors, and asthma control among adults in the United States with asthma, 2006, *J. asthma off. J. Assoc. Care Asthma* 45 (2) (2008) 123–133.
- [14] N. Hutter, A. Knecht, H. Baumeister, Health care costs in persons with asthma and comorbid mental disorders: a systematic review, *General Hosp. psychiatry* 33 (5) (2011) 443–453.
- [15] P.P. Roy-Byrne, K.W. Davidson, R.C. Kessler, G.J. Asmundson, R.D. Goodwin, L. Kubzansky, R.B. Lydiard, M.J. Massie, W. Katon, S.K. Laden, M.B. Stein, Anxiety disorders and comorbid medical illness, *General Hosp. psychiatry* 30 (3) (2008) 208–225.
- [16] K.L. Lavoie, A. Cartier, M. Labrecque, S.L. Bacon, C. Lemiere, J.L. Malo,

- G. Lacoste, S. Barone, P. Verrier, B. Ditto, Are psychiatric disorders associated with worse asthma control and quality of life in asthma patients? *Respir. Med.* 99 (10) (2005) 1249–1257.
- [17] E.D. Bateman, S.S. Hurd, P.J. Barnes, J. Bousquet, J.M. Drazen, M. FitzGerald, P. Gibson, K. Ohta, P. O'Byrne, S.E. Pedersen, E. Pizzichini, S.D. Sullivan, S.E. Wenzel, H.J. Zar, Global strategy for asthma management and prevention: GINA executive summary, *Eur. Respir. J. off. J. Eur. Soc. Clin. Respir. Physiol.* 31 (1) (2008) 143–178.
- [18] W.M. Vollmer, Assessment of asthma control and severity, *Ann. allergy, asthma & Immunol. off. Publ. Am. Coll. Allergy, Asthma, & Immunol.* 93 (5) (2004), 409–13; quiz 414–6, 492.
- [19] R.A. Nathan, C.A. Sorkness, M. Kosinski, M. Schatz, J.T. Li, P. Marcus, J.J. Murray, T.B. Pendergraft, Development of the asthma control test: a survey for assessing asthma control, *J. allergy Clin. Immunol.* 113 (1) (2004) 59–65.
- [20] M. Schatz, C.A. Sorkness, J.T. Li, P. Marcus, J.J. Murray, R.A. Nathan, M. Kosinski, T.B. Pendergraft, P. Jhingran, Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists, *J. allergy Clin. Immunol.* 117 (3) (2006) 549–556.
- [21] M.B.S. First, R.L. Spitzer, M. Gibbon, J.B.W. Williams, Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV), American Psychiatric Press, Inc., Washington, D.C., USA, 1996.
- [22] M.B.G. First, M. Gibbon, R.L. Spitzer, J.B.W. Williams, L.S. Benjamin, Structured Clinical Interview for DSM-IV Axis II Personality Disorders, (SCID-II), American Psychiatric Press, Inc., Washington, D.C., USA, 1997.
- [23] J. Cohen, Weighted kappa: nominal scale agreement with provision for scaled disagreement or partial credit, *Psychol. Bull.* 70 (4) (1968) 213–220.
- [24] S.E.J.R. Stack, Marital status and happiness: a 17-nation study, *J. Marriage Fam.* 60 (2) (1998) 527–536.
- [25] W.H. Horwitz AV, The relationship of cohabitation and mental health: a study of a young adult cohort, *J. Marriage Fam.* 60 (2) (1998) 505–514.
- [26] R.C. Kessler, K.A. McGonagle, S. Zhao, C.B. Nelson, M. Hughes, S. Eshleman, H.U. Wittchen, K.S. Kendler, Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the national comorbidity survey, *Arch. general psychiatry* 51 (1) (1994) 8–19.
- [27] K. Bhui, S. Stansfeld, J. Head, M. Haines, S. Hillier, S. Taylor, R. Viner, R. Booy, Cultural identity, acculturation, and mental health among adolescents in east London's multiethnic community, *J. Epidemiol. community health* 59 (4) (2005) 296–302.
- [28] L.H. Rogler, D.E. Cortes, R.G. Malgady, Acculturation and mental health status among Hispanics. Convergence and new directions for research, *Am. Psychol.* 46 (6) (1991) 585–597.
- [29] C.M. Lamertz, C. Jacobi, A. Yassouridis, K. Arnold, A.W. Henkel, Are obese adolescents and young adults at higher risk for mental disorders? A community survey, *Obes. Res.* 10 (11) (2002) 1152–1160.
- [30] U. John, C. Meyer, H.J. Rumpf, U. Hapke, Relationships of psychiatric disorders with overweight and obesity in an adult general population, *Obes. Res.* 13 (1) (2005) 101–109.
- [31] G.E. Simon, M. Von Korff, K. Saunders, D.L. Miglioretti, P.K. Crane, G. van Belle, R.C. Kessler, Association between obesity and psychiatric disorders in the US adult population, *Arch. general psychiatry* 63 (7) (2006) 824–830.
- [32] K.M. Scott, R. Bruffaerts, G.E. Simon, J. Alonso, M. Angermeyer, G. de Girolamo, K. Demyttenaere, I. Gasquet, J.M. Haro, E. Karam, R.C. Kessler, D. Levinson, M.E. Medina Mora, M.A. Oakley Browne, J. Ormel, J.P. Villa, H. Uda, M. Von Korff, Obesity and mental disorders in the general population: results from the world mental health surveys, *Int. J. Obes. (Lond)* 32 (1) (2008) 192–200.
- [33] R. Bruffaerts, K. Demyttenaere, G. Vilagut, M. Martinez, A. Bonnewyn, R. De Graaf, J.M. Haro, S. Bernert, M.C. Angermeyer, T. Brugha, C. Roick, J. Alonso, The relation between body mass index, mental health, and functional disability: a European population perspective, *Can. J. psychiatry. Revue Can. de psychiatrie* 53 (10) (2008) 679–688.
- [34] N.M. Petry, D. Barry, R.H. Pietrzak, J.A. Wagner, Overweight and obesity are associated with psychiatric disorders: results from the national epidemiologic survey on alcohol and related conditions, *Psychosom. Med.* 70 (3) (2008) 288–297.
- [35] C.E. Ramacciotti, E. Coli, C. Passaglia, M. Lacorte, E. Pea, L. Dell'Osso, Binge eating disorder: prevalence and psychopathological features in a clinical sample of obese people in Italy, *Psychiatry Res.* 94 (2) (2000) 131–138.
- [36] P. van Hanswijck de Jonge, E.F. Van Furth, J.H. Lacey, G. Waller, The prevalence of DSM-IV personality pathology among individuals with bulimia nervosa, binge eating disorder and obesity, *Psychol. Med.* 33 (7) (2003) 1311–1317.
- [37] J. de Man Lapidoth, A. Ghaderi, C. Norring, Eating disorders and disordered eating among patients seeking non-surgical weight-loss treatment in Sweden, *Eat. Behav.* 7 (1) (2006) 15–26.
- [38] A.J. Stunkard, K.C. Allison, Binge eating disorder: disorder or marker? *Int. J. Eat. Disord.* 34 (Suppl.) (2003) S107–S116.
- [39] A.C. Ahlberg, T. Ljung, R. Rosmond, B. McEwen, G. Holm, H.O. Akesson, P. Bjorntorp, Depression and anxiety symptoms in relation to anthropometry and metabolism in men, *Psychiatry Res.* 112 (2) (2002) 101–110.
- [40] A. Tuthill, H. Slawik, S. O'Rahilly, N. Finer, Psychiatric co-morbidities in patients attending specialist obesity services in the UK, *QJM Mon. J. Assoc. Physicians* 99 (5) (2006) 317–325.
- [41] A.J. Ruderman, Obesity, anxiety, and food consumption, *Addict. Behav.* 8 (3) (1983) 235–242.
- [42] R.A. Sansone, M.W. Wiederman, L.A. Sansone, The prevalence of borderline personality disorder among individuals with obesity: a critical review of the literature, *Eat. Behav.* 1 (1) (2000) 93–104.
- [43] M.S. Faith, J. Flint, C.G. Fairburn, G.M. Goodwin, D.B. Allison, Gender differences in the relationship between personality dimensions and relative body weight, *Obes. Res.* 9 (10) (2001) 647–650.
- [44] A. Ryden, M. Sullivan, J.S. Torgerson, J. Karlsson, A.K. Lindroos, C. Taft, Severe obesity and personality: a comparative controlled study of personality traits, *Int. J. Obes. Relat. Metabolic Disord. J. Int. Assoc. Study Obes.* 27 (12) (2003) 1534–1540.
- [45] F.S. Luppino, L.M. de Wit, P.F. Bouvy, T. Stijnen, P. Cuijpers, B.W. Penninx, F.G. Zitman, Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies, *Arch. general psychiatry* 67 (3) (2010) 220–229.
- [46] G. Garipey, D. Nitka, N. Schmitz, The association between obesity and anxiety disorders in the population: a systematic review and meta-analysis, *Int. J. Obes. (Lond)* 34 (3) (2010) 407–419.
- [47] C.R. Mehta, N.R. Patel, A network algorithm for performing fisher's exact test in $r \times c$ contingency tables, *J. Am. Stat. Assoc.* 78 (382) (1983) 427–434.
- [48] G.H. Freeman, J.H. Halton, Note on an exact treatment of contingency, goodness of fit and other problems of significance, *Biometrika* 38 (1–2) (1951) 141–149.
- [49] D.S. Moore, G.P. McCabe, W.M. Duckworth, S.L. Slovic, Bootstrap methods and permutation tests, in: D.S. Moore, G.P. McCabe, W.M. Duckworth, S.L. Slovic (Eds.), *The Practice of Business Statistics Companion*, W.H. Freeman, 2003.
- [50] A.J. Dobson, *An Introduction to Generalized Linear Models*, third ed., Chapman & Hall/CRC Press, Boca Raton, FL, USA, 2008.
- [51] R: A Language and Environment for Statistical Computing, R Core Team – R Foundation for Statistical Computing, 2014.
- [52] M. Thomas, A. Bruton, M. Moffat, J. Cleland, Asthma and psychological dysfunction, *Prim. care Respir. J. J. General Pract. Airw. Group* 20 (3) (2011) 250–256.
- [53] J. de Miguel Diez, V. Hernandez Barrera, L. Puente Maestu, P. Carrasco Garrido, T. Gomez Garcia, R. Jimenez Garcia, Psychiatric comorbidity in asthma patients. Associated factors, *J. asthma off. J. Assoc. Care Asthma* 48 (3) (2011) 253–258.
- [54] A. Ettinger, M. Reed, J. Cramer, Depression and comorbidity in community-based patients with epilepsy or asthma, *Neurology* 63 (6) (2004) 1008–1014.
- [55] R.D. Goodwin, D.M. Fergusson, L.J. Horwood, Asthma and depressive and anxiety disorders among young persons in the community, *Psychol. Med.* 34 (8) (2004) 1465–1474.
- [56] R.D. Goodwin, J. Pagura, B. Cox, J. Sareen, Asthma and mental disorders in Canada: impact on functional impairment and mental health service use, *J. Psychosom. Res.* 68 (2) (2010) 165–173.
- [57] A. Goral, J.D. Lipsitz, K. Muhsen, R. Gross, Depressive symptoms, risk factors and sleep in asthma: results from a national Israeli health survey, *General Hosp. psychiatry* 34 (1) (2012) 17–23.
- [58] K.M. Scott, M. Von Korff, J. Ormel, M.Y. Zhang, R. Bruffaerts, J. Alonso, R.C. Kessler, H. Tachimori, E. Karam, D. Levinson, E.J. Bromet, J. Posada-Villa, I. Gasquet, M.C. Angermeyer, G. Borges, G. de Girolamo, A. Herman, J.M. Haro, Mental disorders among adults with asthma: results from the World Mental Health Survey, *General Hosp. psychiatry* 29 (2) (2007) 123–133.
- [59] T.P. Ng, P.C. Chiam, E.H. Kua, Mental disorders and asthma in the elderly: a population-based study, *Int. J. Geriatric psychiatry* 22 (7) (2007) 668–674.
- [60] J.M. Feldman, E. Acosta Perez, G. Canino, E.L. McQuaid, R.D. Goodwin, A.N. Ortega, The role of caregiver major depression in the relationship between anxiety disorders and asthma attacks in island Puerto Rican youth and young adults, *J. Nerv. Ment. Dis.* 199 (5) (2011) 313–318.
- [61] E. Acosta-Perez, G. Canino, R. Ramirez, M. Prelip, M. Martin, A.N. Ortega, Do Puerto Rican youth with asthma and obesity have higher odds for mental health disorders? *Psychosomatics* 53 (2) (2012) 162–171.
- [62] K.O. Wong, B. Hunter Rowe, J. Douwes, A. Senthilselvan, Asthma and wheezing are associated with depression and anxiety in adults: an analysis from 54 countries, *Pulm. Med.* 2013 (2013) 929028.
- [63] B.M. Brumpton, L. Leivseth, P.R. Romundstad, A. Langhammer, Y. Chen, C.A. Camargo Jr., X.M. Mai, The joint association of anxiety, depression and obesity with incident asthma in adults: the HUNT study, *Int. J. Epidemiol.* 42 (5) (2013) 1455–1463.
- [64] Y.C. Lee, C.T. Lee, Y.R. Lai, V.C. Chen, R. Stewart, Association of asthma and anxiety: a nationwide population-based study in Taiwan, *J. Affect. Disord.* 189 (2016) 98–105.
- [65] R.D. Goodwin, M. Olsson, S. Shea, R.A. Lantigua, O. Carrasquillo, M.J. Gameroff, M.M. Weissman, Asthma and mental disorders in primary care, *General Hosp. psychiatry* 25 (6) (2003) 479–483.
- [66] E. Gada, D.A. Khan, L.F. DeFina, E.S. Brown, The relationship between asthma and self-reported anxiety in a predominantly healthy adult population, *Ann. allergy, asthma & Immunol. off. Publ. Am. Coll. Allergy, Asthma, & Immunol.* 112 (4) (2014) 329–332.
- [67] G.E. Erhabor, S.K. Mosaku, The association of anxiety with asthma among a sample of asthmatics in Ile-Ife Osun State Nigeria, *J. asthma off. J. Assoc. Care Asthma* 41 (7) (2004) 695–700.
- [68] G.E. Erhabor, F. Kuteyi, F. Obembe, Asthma: the psychosocial impact among a sample of south western Nigerians, *J. Natl. Med. Assoc.* 94 (11) (2002)

- 987–993.
- [69] A.A. Vieira, I.L. Santoro, S. Dracoulakis, L.B. Caetano, A.L. Fernandes, Anxiety and depression in asthma patients: impact on asthma control, *J. Bras. Pneumol. Publicacao Of. Soc. Bras. Pneumol. Tisilogia* 37 (1) (2011) 13–18.
 - [70] S. Liu, R. Wu, L. Li, L. Liu, G. Li, X. Zhang, Y. Guo, Y. Wang, H. Zhang, G. Li, H. Li, The prevalence of anxiety and depression in Chinese asthma patients, *PloS one* 9 (7) (2014) e103014.
 - [71] A.O. Adewuya, O.O. Adeyeye, Anxiety and Depression among Nigerian patients with asthma; association with sociodemographic, clinical, and personality factors, *J. asthma off. J. Assoc. Care Asthma* (2016) [Epub ahead of print], doi:10.1080/02770903.2016.1208224.
 - [72] K.L. Lavoie, M. Boudreau, A. Plourde, T.S. Campbell, S.L. Bacon, Association between generalized anxiety disorder and asthma morbidity, *Psychosom. Med.* 73 (6) (2011) 504–513.
 - [73] M. Koltek, T.C. Wilkes, M. Atkinson, The prevalence of posttraumatic stress disorder in an adolescent inpatient unit, *Can. J. psychiatry. Revue Can. de psychiatrie* 43 (1) (1998) 64–68.
 - [74] E.M. Kean, K. Kelsay, F. Wamboldt, M.Z. Wamboldt, Posttraumatic stress in adolescents with asthma and their parents, *J. Am. Acad. Child Adolesc. Psychiatry* 45 (1) (2006) 78–86.
 - [75] V.A. Nejtek, E.S. Brown, D.A. Khan, J.J. Moore, J. Van Wagner, D.C. Perantie, Prevalence of mood disorders and relationship to asthma severity in patients at an inner-city asthma clinic, *Ann. allergy, asthma & Immunol. off. Publ. Am. Coll. Allergy, Asthma, & Immunol.* 87 (2) (2001) 129–133.
 - [76] H. Trzcińska, G. Przybylski, B. Kozłowski, S. Derdowski, Analysis of the relation between level of asthma control and depression and anxiety, *Med. Sci. Monit. Int. Med. J. Exp. Clin. Res.* 18 (3) (2012) CR190–4.
 - [77] A. Schneider, B. Lowe, F.J. Meyer, K. Biessecker, S. Joos, J. Szecsenyi, Depression and panic disorder as predictors of health outcomes for patients with asthma in primary care, *Respir. Med.* 102 (3) (2008) 359–366.
 - [78] A. ten Brinke, M.E. Ouwkerk, E.H. Bel, P. Spinhoven, Similar psychological characteristics in mild and severe asthma, *J. Psychosom. Res.* 50 (1) (2001) 7–10.
 - [79] M. Cordina, A.G. Fenech, J. Vassallo, J.M. Cacciottolo, Anxiety and the management of asthma in an adult outpatient population, *Ther. Adv. Respir. Dis.* 3 (5) (2009) 227–233.
 - [80] S. Cluley, G.M. Cochrane, Psychological disorder in asthma is associated with poor control and poor adherence to inhaled steroids, *Respir. Med.* 95 (1) (2001) 37–39.
 - [81] S. Centanni, F. Di Marco, F. Castagna, B. Boveri, F. Casanova, A. Piazzini, Psychological issues in the treatment of asthmatic patients, *Respir. Med.* 94 (8) (2000) 742–749.
 - [82] C.A. Mancuso, M.G. Peterson, M.E. Charlson, Effects of depressive symptoms on health-related quality of life in asthma patients, *J. general Intern. Med.* 15 (5) (2000) 301–310.
 - [83] L. Fernandes, J. Fonseca, S. Martins, L. Delgado, A.C. Pereira, M. Vaz, G. Branco, Association of anxiety with asthma: subjective and objective outcome measures, *Psychosomatics* 51 (1) (2010) 39–46.
 - [84] M.D. Eisner, P.P. Katz, G. Lactao, C. Iribarren, Impact of depressive symptoms on adult asthma outcomes, *Ann. allergy, asthma & Immunol. off. Publ. Am. Coll. Allergy, Asthma, & Immunol.* 94 (5) (2005) 566–574.
 - [85] J.M. Feldman, M.I. Siddique, E. Morales, B. Kaminski, S.E. Lu, P.M. Lehrer, Psychiatric disorders and asthma outcomes among high-risk inner-city patients, *Psychosom. Med.* 67 (6) (2005) 989–996.
 - [86] Z. Kaya, F. Erkan, M. Ozkan, S. Ozkan, N. Kocaman, B.A. Ertekin, N. Direk, Self-management plans for asthma control and predictors of patient compliance, *J. asthma off. J. Assoc. Care Asthma* 46 (3) (2009) 270–275.
 - [87] K.L. Lavoie, S.L. Bacon, S. Barone, A. Cartier, B. Ditto, M. Labrecque, What is worse for asthma control and quality of life: depressive disorders, anxiety disorders, or both? *Chest* 130 (4) (2006) 1039–1047.
 - [88] A.M. Valenca, R. Falcao, R.C. Freire, I. Nascimento, R. Nascentes, W.A. Zin, A.E. Nardi, The relationship between the severity of asthma and comorbidities with anxiety and depressive disorders, *Rev. Bras. Psiquiatr.* 28 (3) (2006) 206–208.
 - [89] R. Bussing, R.C. Burket, E.T. Kelleher, Prevalence of anxiety disorders in a clinic-based sample of pediatric asthma patients, *Psychosomatics* 37 (2) (1996) 108–115.
 - [90] C. Vila, C. Nollet-Clemencon, M. Vera, J.J. Robert, J. de Blic, R. Jouvant, M.C. Mouren-Simeoni, P. Scheinmann, Prevalence of DSM-IV disorders in children and adolescents with asthma versus diabetes, *Can. J. psychiatry. Revue Can. de psychiatrie* 44 (6) (1999) 562–569.
 - [91] R.P. Troiano, K.M. Flegal, R.J. Kuczmarski, S.M. Campbell, C.L. Johnson, Overweight prevalence and trends for children and adolescents. The national health and nutrition examination surveys, 1963 to 1991, *Arch. Pediatr. Adolesc. Med.* 149 (10) (1995) 1085–1091.
 - [92] K.M. Flegal, M.D. Carroll, R.J. Kuczmarski, C.L. Johnson, Overweight and obesity in the United States: prevalence and trends, 1960–1994, *Int. J. Obes. Relat. Metabolic Disord. J. Int. Assoc. Study Obes.* 22 (1) (1998) 39–47.
 - [93] S. Kautiainen, A. Rimpela, A. Vikat, S.M. Virtanen, Secular trends in overweight and obesity among Finnish adolescents in 1977–1999, *Int. J. Obes. Relat. Metabolic Disord. J. Int. Assoc. Study Obes.* 26 (4) (2002) 544–552.
 - [94] L.M. Schachter, C.M. Salome, J.K. Peat, A.J. Woolcock, Obesity is a risk for asthma and wheeze but not airway hyperresponsiveness, *Thorax* 56 (1) (2001) 4–8.
 - [95] C.A. Camargo Jr., S.T. Weiss, S. Zhang, W.C. Willett, F.E. Speizer, Prospective study of body mass index, weight change, and risk of adult-onset asthma in women, *Arch. Intern. Med.* 159 (21) (1999) 2582–2588.
 - [96] B. Stenius-Aarniala, T. Poussa, J. Kvarnstrom, E.L. Gronlund, M. Ylikahri, P. Mustajoki, Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study, *BMJ* 320 (7238) (2000) 827–832.
 - [97] S. Chinn, D. Jarvis, P. Burney, Relation of bronchial responsiveness to body mass index in the ECRHS. European Community Respiratory Health Survey, *Thorax* 57 (12) (2002) 1028–1033.
 - [98] D.D. Sin, R.L. Jones, S.F. Man, Obesity is a risk factor for dyspnea but not for airflow obstruction, *Arch. Intern. Med.* 162 (13) (2002) 1477–1481.
 - [99] D.R. Stukus, Obesity and asthma: the chicken or the egg? *J. allergy Clin. Immunol.* 135 (4) (2015 Apr) 894–895 doi: 10.1016/j.jaci.2014.11.002. [Epub 2014 Dec 18].
 - [100] D.A. Beutner, E.R. Sutherland, Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies, *Am. J. Respir. Crit. care Med.* 175 (7) (2007) 661–666.
 - [101] A. Moreira, M. Bonini, V. Garcia-Larsen, S. Bonini, S.R. Del Giacco, I. Agache, J. Fonseca, N.G. Papadopoulos, K.H. Carlsen, L. Delgado, T. Haahtela, Weight loss interventions in asthma: EAACI evidence-based clinical practice guideline (part I), *Allergy* 68 (4) (2013) 425–439.
 - [102] R.D. Goodwin, F. Jacobi, W. Thefeld, Mental disorders and asthma in the community, *Arch. general psychiatry* 60 (11) (2003) 1125–1130.
 - [103] R.D. Goodwin, Asthma and anxiety disorders, *Adv. Psychosom. Med.* 24 (2003) 51–71.
 - [104] P.F. Coogan, J. Yu, G.T. O'Connor, T.A. Brown, J.R. Palmer, L. Rosenberg, Depressive symptoms and the incidence of adult-onset asthma in African American women, *Ann. allergy, asthma & Immunol. off. Publ. Am. Coll. Allergy, Asthma, & Immunol.* 112 (4) (2014), 333–8 e1.
 - [105] B.S. W.D. Jonas, J.F. Lando, J.J. Feldman, Symptoms of anxiety and depression as risk factors for the development of Asthma, *J. Appl. Biobehav Res.* 4 (2) (1999) 91–110.
 - [106] K.M. Scott, M. Von Korff, J. Alonso, M.C. Angermeyer, C. Benjet, R. Bruffaerts, G. de Girolamo, J.M. Haro, R.C. Kessler, V. Kovess, Y. Ono, J. Ormel, J. Posada-Villa, Childhood adversity, early-onset depressive/anxiety disorders, and adult-onset asthma, *Psychosom. Med.* 70 (9) (2008) 1035–1043.
 - [107] J. Alonso, P. de Jonge, C.C. Lim, S. Aguilar-Gaxiola, R. Bruffaerts, J.M. Caldas-de-Almeida, Z. Liu, S. O'Neill, D.J. Stein, M.C. Viana, A.O. Al-Hamzawi, M.C. Angermeyer, G. Borges, M. Ciutan, G. de Girolamo, F. Fiestas, J.M. Haro, C. Hu, R.C. Kessler, J.P. Lepine, D. Levinson, Y. Nakamura, J. Posada-Villa, B.J. Wojtyniak, K.M. Scott, Association between mental disorders and subsequent adult onset asthma, *J. Psychiatric Res.* 59 (2014) 179–188.
 - [108] R.D. Goodwin, M. Robinson, P.D. Sly, I.W. McKeague, E.S. Susser, R.L. Zubrick, F.J. Stanley, E. Mattes, Severity and persistence of asthma and mental health: a birth cohort study, *Psychol. Med.* 43 (6) (2013) 1313–1322.
 - [109] M.A. Ramos Olazagasti, P.E. Shrout, H. Yoshikawa, H.R. Bird, G.J. Canino, The longitudinal relationship between parental reports of asthma and anxiety and depression symptoms among two groups of Puerto Rican youth, *J. Psychosom. Res.* 73 (4) (2012) 283–288.
 - [110] R.D. Goodwin, B. Scheckner, L. Pena, J.M. Feldman, F. Taha, J.D. Lipsitz, A 10-year prospective study of respiratory disease and depression and anxiety in adulthood, *Ann. allergy, asthma & Immunol. off. Publ. Am. Coll. Allergy, Asthma, & Immunol.* 113 (5) (2014) 565–570.
 - [111] G. Hasler, P.J. Gergen, D.G. Kleinbaum, V. Ajdacic, A. Gamma, D. Eich, W. Rossler, J. Angst, Asthma and panic in young adults: a 20-year prospective community study, *Am. J. Respir. Crit. care Med.* 171 (11) (2005) 1224–1230.
 - [112] Y. Chida, M. Hamer, A. Steptoe, A bidirectional relationship between psychosocial factors and atopic disorders: a systematic review and meta-analysis, *Psychosom. Med.* 70 (1) (2008) 102–116.
 - [113] M. Leander, E. Lampa, A. Rask-Andersen, K. Franklin, T. Gislason, A. Oudin, C. Svanes, K. Toren, C. Janson, Impact of anxiety and depression on respiratory symptoms, *Respir. Med.* 108 (11) (2014) 1594–1600.
 - [114] V.M. Deshmukh, B.G. Toelle, T. Usherwood, B. O'Grady, C.R. Jenkins, Anxiety, panic and adult asthma: a cognitive-behavioral perspective, *Respir. Med.* 101 (2) (2007) 194–202.
 - [115] K.M. Avallone, A.C. McLeish, Anxiety sensitivity as a mediator of the association between asthma and smoking, *J. asthma off. J. Assoc. Care Asthma* (2014) 1–7.
 - [116] A.H. Miller, E. Haroon, C.L. Raison, J.C. Felger, Cytokine targets in the brain: impact on neurotransmitters and neurocircuits, *Depress. anxiety* 30 (4) (2013) 297–306.
 - [117] R.J. Van Lieshout, G. Macqueen, Psychological factors in asthma, *Allergy Asthma Clin. Immunol.* 4 (1) (2008) 12–28.
 - [118] C.L. Raison, A.H. Miller, Do cytokines really sing the blues? *Cerebrum* 2013 (2013) 10.
 - [119] C.L. Raison, L. Capuron, A.H. Miller, Cytokines sing the blues: inflammation and the pathogenesis of depression, *Trends Immunol.* 27 (1) (2006) 24–31.