



Depression is associated with poor control of symptoms in asthma and rhinitis: A population-based study

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ABSTRACT

Background: Although many studies have highlighted the link between asthma/rhinitis and depression, it is still unclear which characteristics of these diseases are associated with the risk of depression. We aimed to explore the relationship between depression and asthma or rhinitis in a representative sample of the Italian general population.

Methods: The data were collected in GEIRD, an Italian multicenter, population-based, multicase-control study. 2227 participants (age 21–86 years, female 50%) underwent standardized interviews, skin prick and lung function tests, and were divided into cases of current asthma (n = 528), rhinitis without asthma (n = 972), and controls (n = 727). Two specific questions from the Patient Health Questionnaire (PHQ-2) were asked to identify symptoms of depressed mood and anhedonia, which were used as a proxy of major depression disorder.

Results: The prevalence of depression was 16.7%, 11.9%, and 5.1% in subjects with asthma, rhinitis and controls, respectively. Both in asthma and rhinitis, subjects with depression had worse respiratory-health related quality of life and more frequent disease-related symptoms than their non-depressed counterparts. In asthma, depression was associated with poorer disease control. In rhinitis, depression was significantly associated with a disease-related limitations in daily activities and greater risk of symptom exacerbations and prescriptions of medicines for breathing. Cases of rhinitis with depression were less likely to be atopic.

Conclusions: Our results suggest that rhinitis exacerbations, particularly in non-atopic subjects, and low asthma control are strongly related to the presence of depressed mood in adults from the general population.

1. Background

Depression commonly co-exists with chronic diseases, including chronic respiratory diseases, where it represents a significant risk factor for morbidity and mortality [1–3].

Literature has well documented a cross-sectional association of depression with asthma and rhinitis [4–6], while it is still debated whether depression is related to the severity and control of these diseases

[7,8]. Anyway, depression reduces health-related quality of life (HR-QOL) and can complicate the management of respiratory diseases [9–11]. Systematic reviews also reported a robust link between psychosocial factors and several atopic disorders, both in clinical and population-based samples of individuals with asthma, eczema, dermatitis and allergic rhinitis [12–14]. Depression is associated with high systemic levels of inflammatory mediators, which may have pathogenic roles in asthma and allergic rhinitis. [15,16] On the other hand,

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corticosteroids used for the treatment of atopic disorders have shown to induce depressive symptoms on the long-term [17]. Moreover, the evidence for an association between asthma and depression raises an ongoing debate on the true nature of this relationship: whether the respiratory disease is causatively associated with a higher risk of depression, and/or whether depression increases the risk of developing asthma or deteriorating the asthmatic condition. Nevertheless, the increasing prevalence of chronic physical diseases and depression raises the question of how they affect the overall individual health status.

Although many studies have highlighted the link between asthma/rhinitis and depression, it is still unclear which characteristics of rhinitis or asthma are associated with the risk of depression. So far, the findings have been confusing and often contradictory [18]. Our study aimed to explore the relationship between depression and asthma/or rhinitis in a representative sample of the Italian general population, and to investigate the differences in pulmonary function, respiratory symptoms and respiratory health related quality of life in subjects suffering from asthma or rhinitis with and without depression.

2. Methods

2.1. Study design

GEIRD (Gene-Environment Interaction in Respiratory Disease) is a 2-stage multi-centre, multicase-control study on respiratory health. Cases and controls were identified through a two-stage screening process in pre-existing cohorts and in new random samples from the Italian general population [19].

In the first stage (2007–2010), a postal screening questionnaire on the occurrence of respiratory symptoms was administered to random subjects from the general population. Overall, 13,958 subjects from the centres of Verona, Pavia, Torino, Ancona, Sassari answered the questionnaire (response rate: 59%). In the second stage (2008–2016) all the responders with symptoms suggestive of asthma, chronic obstructive pulmonary disease (COPD) and a random sample of subjects without respiratory symptoms or with symptoms suggestive of rhinitis, were referred to clinical centres. Additionally, a sample of 439 subjects from Palermo were invited. Overall, 5885 subjects were invited to GEIRD stage-2. The participants in GEIRD stage-2 between 2007 and 2015 were 2642 subjects (participation rate: 45%).

In clinics, a structured medical interview, the GEIRD Clinical Questionnaire, was administered to all subjects. The GEIRD Clinical Questionnaire is a modification of the European Community Respiratory Health Survey (ECRHS) questionnaire (<http://www.ecrhs.org>) including detailed questions on respiratory symptoms, medical history, use of medication and health services, occupation, socio-economic status, home environment and lifestyle. Participants were further characterized with anthropometric measurements, skin prick and pulmonary function tests [20]. The full protocol and the descriptive characteristics of the GEIRD study are available on the web site <http://www.geird.org>.

All procedures of the research project were approved by an Institutional Ethics Committee in each centre (Verona, Sassari, Turin, Pavia, Ancona and Palermo). All participants were fully informed about all aspects of the study and gave written informed consent.

2.2. Clinical measurements

Forced expiratory volume in 1s (FEV₁) and forced vital capacity (FVC) were measured using a Biomedin spirometer according the American Thoracic Society reproducibility criteria [21]. Lung function values, expressed as percentage of predicted values, and the lower limit of normal (LLN) for FEV₁/FVC ratio were calculated according to Quanjer [22]. Post bronchodilator (BD) lung function using 400 µg salbutamol was also measured in subjects with FEV₁/FVC < LLN. The subjects with FEV₁/FVC ≥ LLN underwent methacholine challenge

tests, according to a standardized protocol [23].

Atopy was assessed by skin prick tests (SPT). Individuals with at least one positive SPT were considered to be atopic. The allergens selected in all centres were *Cupressus arizonica*, *Graminaceae mix*, *Dermatophagoides pteronyssinus*, *Artemisia vulgaris*, *Dermatophagoides farina*, *Ambrosia artemisiifolia*, *Alternaria tenuis*, *Parietaria Judaica*, *Dog dander*, *Corylus avellana*, *Cat hair*, *Olea europea*, *Betula verrucosa*, *Cladosporium herbarum* (ALK diagnostics, Denmark) [24].

2.3. Identification of cases and controls in clinics

The 2642 participants were classified as follows, based on the symptoms reported and the results of the clinical tests:

- cases of **asthma** (n = 528): 1) self-reported asthma, plus one among 1.1) having had an asthma attack in the last 12 months, 1.2) current use of medications for asthma; or 2) asthma-like symptoms or use of asthma medicines in the last 12 months, plus one among 2.1) positive methacholine challenge test (PD20 < 1 mg), 2.2) pre-bronchodilator FEV₁/FVC < LLN with a positive reversibility test (i.e. FEV₁ > 12% and > 200 mL);
- cases of **rhinitis** (n = 972): subjects without asthma, with one among lifetime nasal allergies, including “hay fever”; lifetime problem with sneezing, or a runny or a blocked nose (without cold/flu); recurrent nasal/eye symptoms in the presence of dust, pollens or animals;
- **controls** (n = 727): subjects without asthma or rhinitis, who did not report other respiratory symptoms or diseases, and had both pre-bronchodilator FEV₁/FVC ≥ LLN and FEV₁ > 70% predicted.

Subjects with both rhinitis and asthma have been categorized within the asthma group, according to a hierarchical order of these diseases. Subjects with respiratory symptoms that did not match any of the definitions above and those with missing information on key variables (n = 415) were excluded from the analysis.

2.4. Definition of depression and other variables

Depression was assessed using the following two questions from the Patient Health Questionnaire (PHQ-2), which were asked during the clinical interview: “In the last month did you get down, have you been depressed or without hope?“, “In the last month have you often felt low interest or pleasure in doing things?“. The positive answers to both these questions, which identify symptoms of depressed mood and anhedonia, were used as proxy indicator of depression, and were reported to have 97% sensitivity and 67% specificity in adults [25].

The general and respiratory health-related quality of life (QoL) were assessed using the SF-36 and the Rhinasthma questionnaires, respectively [26,27].

Asthma control was evaluated by means of the Asthma Control Test (ACT). The score ranges from 0 to 25, with 25 indicating optimal asthma control, 20–24 well controlled asthma, and < 20 suggesting a condition of uncontrolled asthma [28,29].

Information on the following variables was collected during the clinical interview and was taken into account for the analyses: age, sex, body mass index (< 25, 25–30, > 30 kg/m²), school education as a proxy of the socioeconomic status (“low” if completed full-time education before the age of 16), smoking habits (lifetime nonsmoker, ex-smoker, current smoker), current alcohol consumption (lifetime non-consumer, ex-consumer, moderate intake (≤ 15 g/day), high intake (> 15 g/day), limitation in daily activities (yes if answered “moderately” or “very high” to the question: “How much did hay fever or nasal problems limit your abilities in each of these fields in the last 12 months?”).

2.5. Statistical analysis

The associations between respiratory diseases and the indicator of MDD were estimated through relative risk ratios (RRR) by multinomial logistic regression models, setting the case/control indicator as the dependent variable. The potential interactions of depression with sex and atopy in the associations with respiratory diseases were evaluated using likelihood ratio tests and stratified analyses.

Differences between subjects with and without depression in the lung function, presence of atopy, occurrence of symptoms of asthma and rhinitis, in the scores of asthma control and quality of life were evaluated separately in subjects with asthma and in subjects with rhinitis alone, using linear, quantile, or binomial regression models, as appropriate according to the distribution of the outcome.

Sex, age, smoking habits, alcohol consumption, body mass index, and education were included for adjustment in the models as potential confounders. Centre was considered a clustering factor and cluster-robust standard errors were used.

Statistical analyses were performed with STATA 15.0 (Stata Corp. College Station, TX, USA).

3. Results

In total, 2227 subjects participated to the clinical stage of GEIRD and were assigned to the following cases-control groups: asthma ($n = 528$), rhinitis ($n = 972$), controls without respiratory symptoms ($n = 727$). Of note, in the asthma group were included both subjects with asthma alone ($n = 86$) and subjects with both asthma and rhinitis ($n = 442$). Additional 415 participants with other respiratory conditions or missing data were excluded from the present analyses. The characteristics of cases and controls are summarized in Table 1.

The prevalence of depression was 16.7%, 11.9%, and 5.1% in subjects with asthma, rhinitis, and controls, respectively. Within groups, the prevalence of depression was generally higher in females compared to men, and it was significantly higher in subject with non-atopic rhinitis compared to atopic rhinitis (17.1% vs. 7.7%, $p < 0.001$) [Fig. E1, reported in the supplementary material]. After controlling for potential confounders, the relative risk ratio (RRR) of depression was 5.02

(95%CI:3.17–7.97) and 3.11 (95%CI:2.30–4.21) folds greater in subjects with asthma and rhinitis, respectively, compared to control [Fig. 1]. There was a significant interaction between depression and atopic status ($p = 0.03$), but not with sex, in the association with respiratory diseases. After stratifying for atopic status (Table E1), depression was significantly associated with asthma both in atopic (RRR, 95%CI: 3.09, 1.50–6.33) and non-atopic subjects (RRR, 95%CI: 5.25, 2.49–11.1), as well as rhinitis in non-atopic subjects (RRR, 95%CI: 4.32, 3.18–5.87), but not in the atopic ones (RRR, 95%CI: 1.51, 0.69–3.33).

The characteristics of subjects with and without depression, respectively, among subjects with asthma and those with rhinitis are shown in Table 2 and Table 3, respectively.

Both in asthma and rhinitis, there were no significant differences in the age at onset of the disease and in lung function between subjects with and without depression.

Among subjects with asthma, those with depression had poorer asthma control than those without depression (37% with poor asthma control vs 21%).

Among subjects with rhinitis, those with depression were significantly less atopic than their counterpart (41% vs. 63%).

Both in asthma and rhinitis, subjects with depression had lower quality of life (QoL) than those without depression, not only when considering the mental component (SF-36 MCS) but also when considering the physical component (SF-36 PCS). Subjects with depression also reported significantly worse respiratory health-related QoL because of their respiratory diseases.

Especially in the rhinitis group, subjects with depression reported a greater impairment of their daily activities caused by their nasal symptoms. Subjects with rhinitis and depression were more likely to suffer from nasal symptoms for more than 6 months per year than those without depression. Moreover, in both asthma and rhinitis groups, subjects with depression had higher occurrence of respiratory symptoms out of the pollen season than those without depression [Fig. 2].

Among subjects with rhinitis, subjects with depression had over 4-fold greater risk of having exacerbations of respiratory symptoms and being forced to consult a doctor because of these attacks than those without depression. Moreover, subjects with rhinitis and depression were over twice more likely of receiving prescription of medicines for exacerbation than those without depression.

4. Discussion

In our Italian sample of adults from the general population, the prevalence of depression was 17%, 12%, and 5% in those with asthma, rhinitis, and controls without respiratory symptoms. Independently potential lifestyle and socio-economic confounders, adults with rhinitis or asthma had about 3 to 5-folds greater risk of being depressed than those without.

The results from this study are consistent with previous reports regarding the presence of mood disorders as common comorbidities among asthmatic patients and patients with rhinitis [30]. Published research found that 9–25% of patients with rhinitis report a previous physician diagnosis of depression [31,32]. Moreover, many authors, who used validated screening instruments, were able to identify an additional 8–15% of these patients with previously undiagnosed depression [3,33]. Different studies on asthmatic subjects have consistently shown high rates of depressive disorders, although there was great variability in the reported rates, from 1% to 45% [9,34,35]. Unfortunately, most of them have been conducted on clinic or convenience samples, while few studies on the adult general population sample [4,36], limiting conclusions that may be drawn about the generalizability of the results. For this reason we think that our results give an important contribution to previous findings by producing prevalence estimates for depression among adults of the general population with asthma and rhinitis.

An interesting finding of our study was that subjects with rhinitis

Table 1
Characteristics of the subjects by case/control group.

	Control	Asthma	Rhinitis alone	
	N = 727	N = 528	N = 972	p-value
Sex (females)	48.8%	50.2%	51.0%	.669
Age (years)	50.4 ± 13.0	46.4 ± 12.6	49.1 ± 13.4	< .001
Depression	5.1%	16.7%	11.9%	< .001
FEV1 (% of predicted)	103.1 ± 12.3	92.5 ± 15.7	100.4 ± 13.2	< .001
FEV1/FVC (%)	82.8 ± 6.1	76.2 ± 8.8	80.9 ± 6.7	< .001
Atopy	26.1%	76.7%	60.8%	< .001
Smoking status				.001
Never smoker	52.7%	46.4%	49.3%	
Ex smoker	31.8%	28.6%	30.5%	
Current smoker	15.4%	25.0%	20.2%	
Alcohol consumption				.336
none	60.4%	58.6%	60.7%	
Past consumer	1.1%	1.9%	1.9%	
Moderate intake (< 15 g/day)	28.2%	25.8%	25.0%	
High intake (≥ 15 g/day)	10.3%	13.6%	12.5%	
Low schooling	19.7%	19.0%	17.6%	.534
BMI				.029
< 25 kg/m2	51.4%	53.5%	56.9%	
25–30 kg/m2	34.0%	31.0%	32.4%	
> 30 kg/m2	14.6%	15.5%	10.7%	

Data are expressed in percentage or mean ± standard deviation.

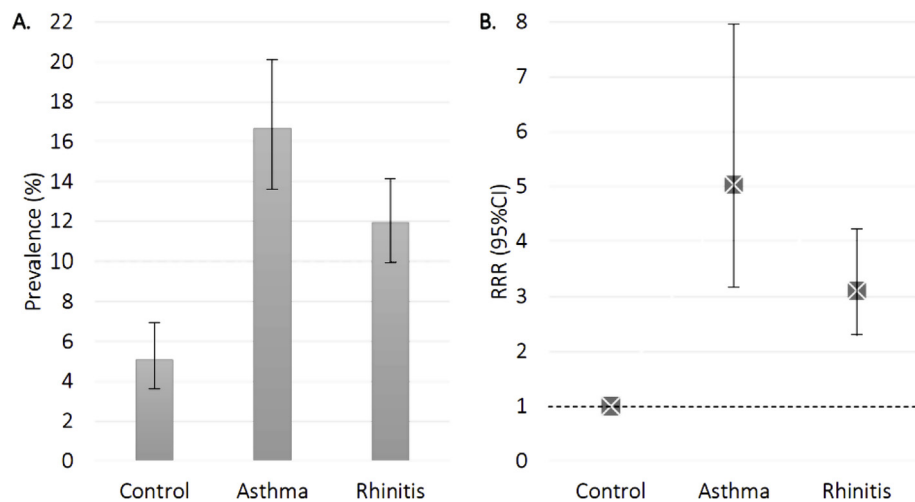


Fig. 1. A) Prevalence of depression across case-control groups. B) Associations of asthma and rhinitis with risk of depression. Relative risk ratios (95%CI) are adjusted for sex, age, smoking habits, alcohol consumption, schooling, body mass index and atopy.

Table 2

Clinical characteristics **in subjects with asthma**, according to the presence/absence of depression.

	Non-depressed (n = 466)	Depressed (n = 88)	Association estimate (95%CI)	p-value
Lung function				
FEV1 (% of predicted)	92.6 ± 15.3	91.8 ± 17.7	+2.9 ^a (−4.1,10.0)	.355
FEV1/FVC (%)	76.1 ± 8.3	76.6 ± 11.1	+1.8 ^a (−0.3,3.9)	.085
Atopy	77.8%	71.1%	1.06 ^b (0.55,2.05)	.862
Asthma, age at onset	17 [6–33]	17 [6–35]	−2.4 ^c (−8.6,3.7)	.439
Rhinitis, age at onset	15 [8–24]	18 [12–30]	+1.8 ^c (−3.3,6.9)	.493
Asthma control				
ACT score	23 [20–25]	22 [18–24]	−2.0 ^c (−3.36,−0.63)	.004
Low asthma control (ACT score < 20)	20.6%	36.5%	1.57 ^b (0.86,2.84)	.140
Self-perceived quality of life				
SF-36, Physical Component Score	51.2 ± 7.7	46.7 ± 10.7	−2.4 ^a (−4.7,−0.2)	.040
SF-36, Mental Component Score	48.9 ± 8.6	35.5 ± 9.1	−12.2 ^a (−15.2,−9.1)	< .001
Respiratory health-related quality of life (RHRQL)				
Rhinasthma score	12 [6–25]	25 [12–40]	+8.6 ^c (2.5,14.6)	.006
Poor HRQL (Rhinasthma score > 20)	24.3%	45.8%	2.36 ^b (1.41,3.95)	.001
Nasal symptoms				
Had symptoms for > 6 months/year,	26.0%	34.9%	1.23 ^b (0.83,1.83)	.311
Persistent* nasal symptoms	46.0%	60.3%	1.91 ^b (0.98,3.72)	.058
Limitations in daily activities:				
Sport and recreational activities	20.7%	25.4%	1.25 ^b (0.51,3.04)	.629
Work or school attendance	12.6%	19.1%	1.58 ^b (0.94,2.67)	.086
Friendships	4.5%	7.9%	1.42 ^b (0.78,2.60)	.243
Sleeping at night	26.2%	38.1%	1.55 ^b (0.90,2.67)	.115
Other daily activities	9.7%	20.6%	2.05 ^b (1.05,4.02)	.035
Symptom exacerbations				
Prescription of medicines for breathing	57.9%	50.6%	0.68 ^b (0.47,0.97)	.036
Had worsening of respiratory symptoms in the last 12 months	18.2%	27.3%	1.26 ^b (0.58,2.74)	.562
Had episodes that forced to consult a doctor	11.6%	18.2%	1.12 ^b (0.75,1.67)	.573

Data expressed as mean ± standard deviation, median [25th–75th percentile], or percentage.

* more than 4 days a week for at least 4 weeks in the last 12 months.

Models for associations were adjusted for age, sex, smoking habits, alcohol consumption, school education, body mass index, centre. ^a: **beta** from multivariable linear regression model; ^b: **odds ratio** from multivariable binomial regression model; ^c: **beta** from multivariable quantile regression model.

alone who also suffered from depression were significantly less atopic than those without depression. Moreover, as a possible direct consequence of the previous point, subjects with rhinitis and depression were more likely to suffer from perennial nasal symptoms out of pollen season compared to the subjects without depression. This result was supported by the sub-analysis of the prevalence of depression between the group of subjects with non-atopic rhinitis (NAR) and the group with atopic rhinitis (AR), which showed that the prevalence of depression was higher in NAR subjects than the others. Additionally, in stratified analysis, depression was significantly associated to rhinitis only in non-atopic subjects.

This is new evidence, since in literature, only few studies analyzed

the association between non-atopic rhinitis and depression. Bedolla-Barajas and colleagues [37] found that both AR and NAR were identified as risk factors for depression, when compared to healthy subjects, with an increased risk among NAR (OR = 2.9 and 4.1, respectively, for AR and NAR, both $p < 0.001$). We can hypothesize that the cause of this association could be the chronic nature of the disease itself and not the atopic phenotype, as in many other chronic diseases.

Furthermore, unlike AR [38], NAR pathophysiology is not fully understood, probably in part because of the heterogeneity of conditions, some of which are associated with a particular trigger or cause (e.g. drug-induced, hormonal), although in the majority of patients with NAR, the cause is unknown [39]. It is possible that the state of

Table 3

Clinical characteristics in subjects with rhinitis alone, according to the presence/absence of depression.

	Non-depressed (n = 850)	Depressed (n = 116)	Association estimate (95%CI)	p-value [†]
Lung function				
FEV1%	100.4 ± 13.0	100.1 ± 14.8	+0.5 ^a (−4.9,6.0)	.827
FEV1/FVC (%)	80.9 ± 6.6	80.6 ± 7.1	+0.6 ^a (−1.1,2.3)	.446
Atopy	63.3%	41.2%	0.53 ^b (0.33,0.86)	< .001
Rhinitis, age at onset	18 [10–30]	18 [4–28]	+0.1 ^c (−6.0,6.1)	.984
Self-perceived quality of life				
SF-36, Physical Component Score	52.9 ± 6.8	50.6 ± 8.8	−1.0 ^a (−2.4,0.4)	.122
SF-36, Mental Component Score	49.3 ± 8.3	37.4 ± 11.1	−12.1 ^a (−14.6,−9.5)	< .001
Respiratory health-related quality of life (RHRQL)				
Rhinasthma score	8 [2–13]	19 [12–28]	+9.6 ^c (5.5,13.7)	< .001
Poor RHRQL (Rhinasthma > 20)	12.1%	35.3%	4.14 ^b (1.74,9.82)	.001
Nasal symptoms				
Had symptoms for > 6 months/year,	21.0%	31.5%	1.77 ^b (1.03,3.04)	.039
Persistent* nasal symptoms	37.9%	48.0%	1.39 ^b (0.93,2.07)	.105
Limitations in daily activities:				
Sport and recreational activities	7.8%	17.8%	2.92 ^b (1.50,5.66)	.002
Work or school attendance	6.5%	11.0%	1.89 ^b (0.77,4.59)	.162
Friendships	2.4%	6.9%	3.04 ^b (0.95,9.75)	.062
Sleeping at night	13.3%	21.9%	1.77 ^b (1.18,2.65)	.006
Other daily activities	4.1%	9.6%	2.35 ^b (1.13,4.90)	.022
Symptom exacerbations				
Prescription of < !-Soft-enter Run-on- > medicines for breathing	9.3%	19.0%	2.71 ^b (2.09,3.51)	< .001
Had worsening of respiratory symptoms in the last 12 months	3.5%	13.9%	4.10 ^b (2.27,7.39)	< .001
Had episodes that forced to consult a doctor	2.0%	8.7%	4.85 ^b (2.34,10.0)	< .001

Data expressed as mean ± standard deviation, median [25th–75th percentile], or percentage.

* more than 4 days a week for at least 4 weeks in the last 12 months.

[†] Models for associations were adjusted for age, sex, smoking habits, alcohol consumption, school education, body mass index, centre. ^a: **beta** from multivariate linear regression model; ^b: **odds ratio** from multivariate binomial regression model; ^c: **beta** from multivariate quantile regression model.

uncertainty caused by the lack of knowledge of the true cause of rhinitis can induce a depressive condition.

Moreover, our subjects with rhinitis and depression reported many more exacerbations and visits to their physician for worsening symptoms (cough, phlegm, shortness of breath), than their counterparts. A possible explanation is that depression was associated with a worst symptom perception. In fact, a preferential access to negative content memories has been demonstrated in individuals with depression [40]. In addition, they received more prescription of medicines for exacerbation in comparison to those without depression, but we do not know if they were adherent with treatment. Many studies have found depression to be a significant determinant of medication adherence in several diseases such as asthma [41]. Additionally, patients with NAR may respond differently to treatments depending on their phenotype [42]. Thus can suggest a lack of rhinitis control in these patients with depression. On the other hand, we cannot exclude that the presence of

depressive condition could be related to a greater rhinitis severity.

It is therefore possible that the prolonged persistence of symptoms could have a negative impact on their lives. We found that subjects with depression suffered greater impairment of their daily activities, such as sport and recreational activities, as well as worse sleeping at night, because of their respiratory condition. Both in adults with asthma and in those with rhinitis, depression was associated with poorer general quality of life, considering either mental or physical domain, as well as poorer respiratory health related quality of life with respect to subjects without depression. Our findings are in line with those published by Moussavi and colleagues [43] who evaluated the effect of depression with other chronic diseases. They showed that comorbid state of depression significantly worsened the health status of people with chronic conditions (asthma, angina, arthritis, diabetes) in comparison to patients having chronic conditions without depression.

Our results also support a relation between worse asthma control

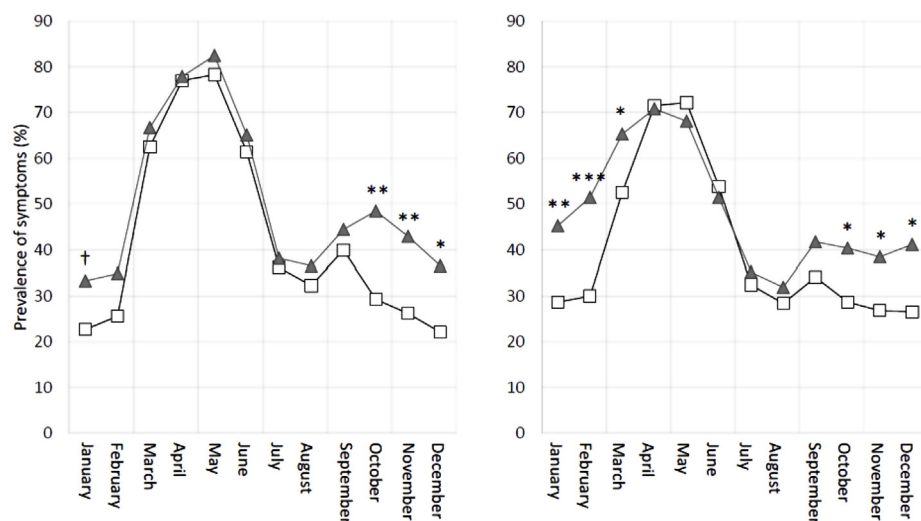


Fig. 2. Prevalence of nasal symptoms in the subjects with asthma and rhinitis (left) and in subjects with rhinitis only (right), according to the month of the year and status of depression. The subjects with and without depression are displayed in filled grey triangles and open black squares, respectively. †: $p < 0.10$; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

and depression status. In this analysis, depressive symptoms were associated with a greater perceived impairment of asthma, as assessed by ACT, but not observed with the measurement of pulmonary function impairment. There were no statistical significant differences on percent-predicted FEV₁/FVC ratio between subjects with and without depression. This discrepancy between subjective and objective markers of asthma control is consistent with the literature on psychiatric symptoms [44]. The control of asthma is actually considered the cornerstone goal in the management strategy because the control level helps to direct the therapeutic options. Our findings strongly support the idea that health care providers should consider the presence of depression among asthma patients who report poor asthma control but consistently display normal lung function. A recent study on patients with moderate to severe asthma presenting to a specialist clinic and evaluated with 2 follow-up visit in 6 months, showed that better control of depression (as measured by the Hospital Anxiety and Depression Scale questionnaires) was associated with better control of asthma [45].

The major strength of our study is the use of data recently collected from a large sample of more than 2000 subjects randomly drawn from the general population rather than from clinically selected groups. Moreover, for the first time, a comparison on the effect of depression in two chronic respiratory diseases, as asthma and rhinitis, has been evaluated in a large Italian population.

Other strengths include, besides the use of a representative population sample, the collection of high quality data, the standardized questionnaires and protocol procedures.

However, there are some limitations to be considered when interpreting our results. A limitation is the use of the PHQ-2 questionnaire as the only tool for measuring the presence of depression, because this questionnaire cannot be taken as a definitive diagnosis. Nevertheless, even if the diagnosis was performed without consulting mental health specialists, the percentage of depression prevalence among our samples with rhinitis and asthma is similar to that found in literature. Furthermore, the PHQ-2 questionnaire has a quite good sensitivity and specificity in identifying cases of depression [46], and was validated in other epidemiological studies to make a tentative diagnosis of depression in at-risk populations (e.g. patients with coronary heart disease or who had a stroke) [47,48].

Second, this study used a questionnaire based on patient self-reporting. In particular, the items for assessing asthma control and severity contained some subjective evaluations by the subject, so the reporting of respiratory symptoms may also be influenced by psychological status. Finally, because of the cross-sectional nature of our study, we were unable to determine a causal relation between asthma, rhinitis, depression, perceived lack of control, and impaired quality of life. We were also unable to examine the relationship between differing levels of asthma severity and psychological factors.

5. Conclusions

Our results suggest that rhinitis exacerbations, particularly in non-atopic subjects, and low asthma control are strongly related to the presence of depressed mood in adults from the general population.

To date, a few studies have shown that depression treatment positively affects other comorbid diseases [9]. In general, both the pharmacologic and psychotherapeutic techniques that are used in the psychiatric population have been shown to be efficacious when transferred to patients with medical illnesses [49]. While treating depression may increase adherence, improve breathing and respiratory function and lead to more effective asthma/rhinitis self-management, strong evidence suggests that treating depression markedly improves depression symptoms, general health and quality of life.

From a clinical perspective, a simple tool for detecting which patients with rhinitis or asthma are at higher risk for comorbid depression is important, as it creates an opportunity to identify patients who would benefit from depression treatment, in particular from psychotherapy

[50].

This research indicates that a multidimensional, integrative approach to health care should be considered when assessing patients with asthma and/or rhinitis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmed.2019.06.025>.

Conflicts of interest

The authors declare no conflict of interest.

Author contributions

AGC and GP conceived and designed the study. AG, AM, FA, EG, PM, SB, MF, AF, PP, LA, GV and AGC contributed to the data collection. GP performed statistical analysis. AG drafted the first version of the manuscript. All authors critically reviewed the paper for important intellectual content and approved the final version of the manuscript.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Figure E1. Prevalence of depression across case-control groups by (A) sex and (B) atopic status. SPT: skin prick test

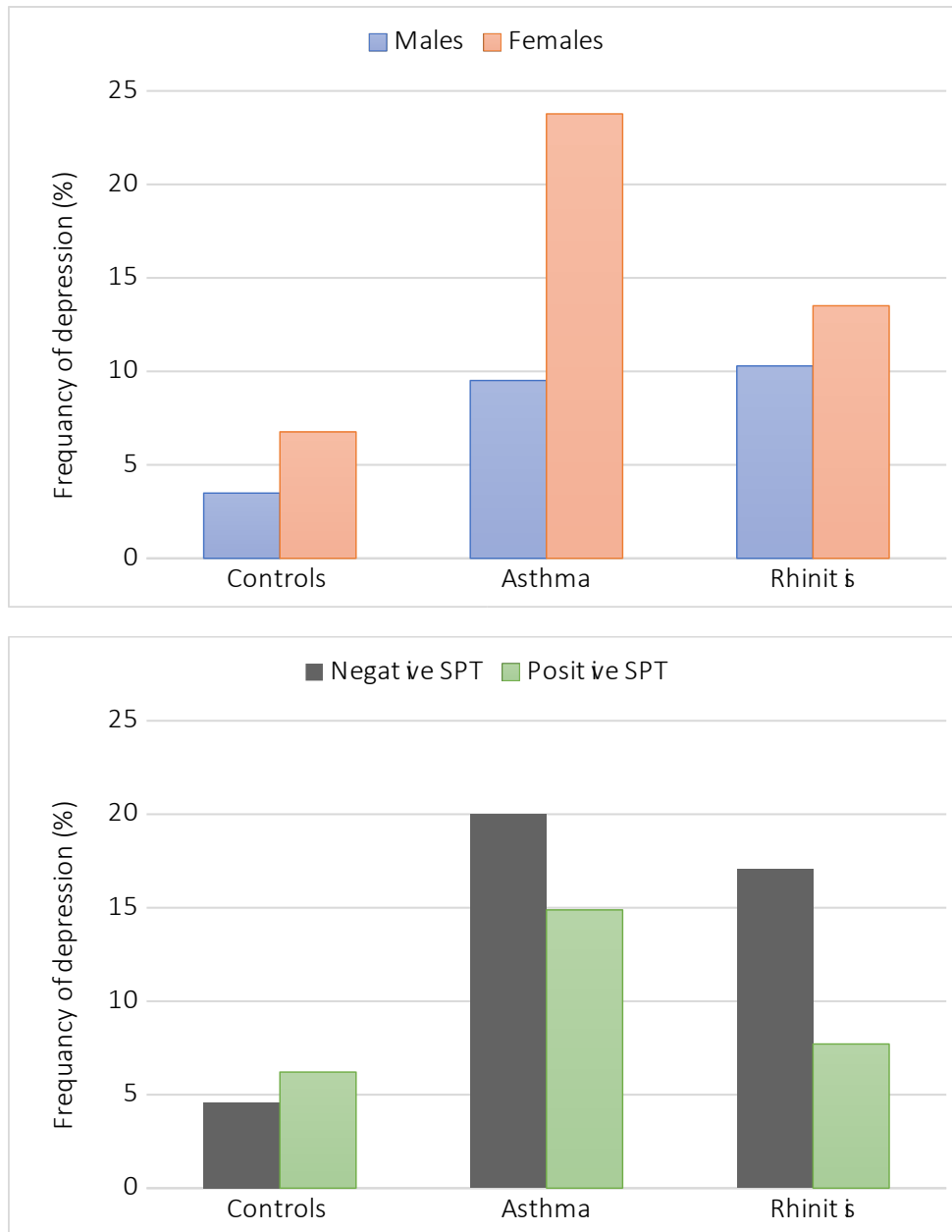


Table E1. Associations of asthma and rhinitis with risk of depression, stratified by sex and atopic status. Relative risk ratios (RRR, with 95%CI) are adjusted for age, smoking habits, alcohol consumption, schooling and body mass index plus, if applicable, sex and/or atopy.

	Control	Asthma	Rhinitis	
	RRR (95%CI)	RRR (95%CI)	RRR (95%CI)	p-value for interaction
Males	1	3.94 (1.67-9.33)**	3.74 (2.06-6.78)***	p=0.280
Females	1	5.59 (3.23-9.65)***	2.75 (2.02-3.76)***	
Negative SPT	1	5.25 (2.49-11.1)***	4.32 (3.18-5.87)***	p=0.029
Positive SPT	1	3.09 (1.50-6.33)**	1.51 (0.69-3.33)	
Overall	1	5.02 (3.17-7.97)***	3.11 (2.29-4.22)***	

SPT: skin prick test. **: p<0.01; ***: p<0.001