Chemical and Biological Hazards Prevention

Studies and Research Projects

REPORT **R-837**

Psychiatric Disorders among Patients under Investigation for Occupational Asthma

Prevalence and Impact on Employment Status and Health Service Use

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Kim L. Lavoie[1,2,3], Maryann Joseph[1,4], Hélène Favreau[1,2], Manon Labrecque[1], André Cartier[1], Catherine Lemière[1], Jean-Luc Malo[1], Denyse Gautrin[1], Blaine Ditto[4], Simon L. Bacon[1,3,5]

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PEER REVIEW

In compliance with IRSST policy, the research results published in this document have been peer-reviewed.

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SUMMARY

Background: Occupational asthma (OA) is a significant occupational health problem impacting the employment sector, health care resources, and the individual. From 10 to 30% of all adult-onset asthmatics mention that their asthma worsens at work, and is often difficult to diagnose and treat. The majority of patients referred for evaluation of OA (approximately 70%) do not receive a diagnosis of OA, and as many as 30% of them will fail to receive a final diagnosis of any medical (i.e., biological) disorder. However, these patients will remain symptomatic and unable to work. Though several differential diagnoses are considered (e.g., rhinitis, eosinophilic bronchitis, hyperventilation syndrome), psychiatric disorders (many of which present with somatic complaints that may mimic asthma such as panic disorder and hypochondriasis) are rarely, if ever, assessed. This suggests that a significant number of patients will not be diagnosed or offered appropriate treatment that may help them return to a normal level of functioning, including returning to the workforce. Failing to detect psychiatric morbidity in these patients may also have important implications for health service use. Left undetected and untreated, patients with psychiatric disorders are likely to continue being symptomatic, increasing their risk for health service use such as emergency department and physician visits, at a high cost to both them personally and the society.

Objectives: The primary objective of this study was to assess rates of psychiatric disorders (including mood and anxiety disorders, and hypochondriasis) and levels of psychological distress among patients under investigation for OA. The secondary objective of this study was to determine the impact of psychiatric morbidity on employment status, health service use and quality of life at 12-18 month follow-up.

Methods: A total of 219 consecutive patients (59% male, mean age 42 ± 11.1 years) underwent a sociodemographic and medical history interview on the day of their OA evaluation, which included spirometry and specific inhalation challenge testing. The Primary Care Evaluation of Mental Disorders (PRIME-MD) was used to assess mood and anxiety disorders, and patients completed the Whiteley Hypochondriasis Index (WI) to assess clinical levels of hypochondriasis. Patients also completed a battery of self-report questionnaires assessing levels of psychological distress including the Beck Depression (BDI-II) and Beck Anxiety (BAI) Inventories, and the Anxiety Sensitvity Index (ASI). Patients were re-contacted approximately 12-18 months later to assess employment status, health service use, and quality of life.

Results: Data were available for 196 patients, of which 152 (78%) met criteria for at least one diagnosable disorder. Final diagnostic results revealed that 26% (n=50) of patients had OA, 25% (n=48) had asthma or work-exacerbated asthma, 14% (n=28) had another inflammatory disorder, 13% (n=26) had a non-inflammatory disorder, and 22% (n=44) did not have a diagnosable disorder. A total of 34% (n=67) of the sample met criteria for a current psychiatric disorder; mood and anxiety disorders affected 29% (n=56) and 24% (n=47) of the sample respectively, and 6% (n=12) had scores on the WI suggestive of hypochondriasis. Levels of depression, anxiety and anxiety sensitivity were in the normal range and did not differ according to diagnostic group. Interestingly, while overall rates of psychiatric disorders were only marginally more common among patients without (45%) relative to those with (31%) a diagnosis ($F=3.12$, $p=0.079$), rates of hypochondriasis were significantly more common among patients without

(14%) relative to those with (4%) a diagnosis (F=5.71, p=0.018). Moreover, meeting criteria for hypochondriasis significantly increased the likelihood of not receiving a final diagnosis by nearly 4-fold (adjusted OR=3.92, 95% CI=[1.18;13.05], p=0.026). Follow-up results indicated that after adjustment for covariates (including diagnostic group), patients with versus without a psychiatric disorder at baseline had significantly worse 12-18 month outcomes, including being significantly less likely to be employed (working) (44% vs. 64%, F=7.02, p=0.009), and having higher rates of emergency visits over the course of the follow-up (35% vs. 19%, F=4.19, p=.042). There was no prospective association between the psychiatric status of the participants and their score on the Asthma Quality of Life Questionnaire, at follow-up, after adjustment for covariates.

Conclusions and clinical implications: Rates of mood or anxiety disorders were disproportionately high (2-4 times greater than rates observed in the general population) in patients presenting for evaluation of OA. Though overall rates of psychiatric disorders and levels of psychological distress were comparable among patients with and without eventual diagnoses of OA or other diagnosable disorders, hypochondriasis was more common among patients not receiving a diagnosable disorder, suggesting that it may underlie a significant proportion of 'un-diagnosable' cases of suspected OA. Follow-up results indicate that irrespective of the diagnostic group, patients with a psychiatric disorder at baseline have less favorable 12-18 month outcomes, including being less likely to be employed and having greater use of certain health services (emergency visits). Overall, the results of this study suggest that greater efforts should be made to assess (and treat) psychiatric disorders in this population.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

1.1 Asthma: an important medical problem in Canada

Asthma is a chronic disorder of the airways characterized by reversible and intermittent airway obstruction, airway inflammation, and hyper-reactivity of the airways in response to a variety of stimuli (e.g., pollen, dust, animal hair, smoke, and airborne pollutants). Symptoms of asthma include shortness of breath, wheezing, recurrent cough, tightness in the chest, and mucous congestion.[1] Asthma is one of the most prevalent chronic conditions affecting Canadians.[2] Despite important advances in diagnosis and treatment, the prevalence of asthma has increased among all age, sex and racial groups to affect approximately 6.2% of Canadians[2] and 7.2% of Americans[3,4] with a plateau in recent years. In absolute numbers, asthma affects 2.2 million Canadians and over 20.3 million Americans. Even more startling is the extent of the increase in morbidity associated with asthma. U.S. figures for the year 2000 showed that asthma accounted for over 465,000 hospitalizations, 1.8 million emergency department (ED) visits, and over 10.4 million physician office visits.[4] Data from the National Population Health Survey (NPHS)[2] revealed a similar pattern of morbidity in Canada. In 1997, 56% of asthmatics had an asthma attack in the previous year and 60% visited a physician, with as many as 17% visiting a physician four times or more. The survey also found that 18% of asthmatics had visited the ED at least once in the past year, and over 5.3% of asthmatics required hospitalization. Finally, although mortality rates have decreased since the mid-1980s, recent mortality rates are just as high as those reported over 30 years ago, indicating that we have failed to obtain important decreases in asthma mortality in the last 3 decades.

1.2 Personal, social and economic impact of asthma

Asthma is a multifactorial lung disease that is associated not only with significant morbidity, but also has important personal, social and economic impacts. According to the 1996-97 NPHS,[2] 35% of Canadians with asthma were restricted in their daily activities as a result of their asthma. In the previous year, 22% were restricted for one to five days and 13% were restricted for more than five days. Asthma has been directly related to increased work and school absences, an inability to perform household chores, and restriction of social activities.[5] U.S. statistics show that each year, approximately 14 million days of school absences and 100 million days of restricted activity are attributed to asthma.[4] In addition to significant indirect costs, direct health care costs for asthma are also substantial. The cost of caring for asthma has been calculated by the World Health Organization to exceed that of AIDS/HIV and tuberculosis combined.[6] In 1990, a Canadian study estimated the total cost of asthma to be $504-648 million per year, $306 million of which was attributed to direct costs (e.g., inpatient care, emergency services, physician services, drugs, diagnostic tests).[5] In the same year, it was estimated that approximately 1% of all U.S. health care costs (representing nearly $6.2 billion) were spent on asthma-related health care.[7] Hospitalization charges alone exceeded $2.6 billion. These figures highlight the scope of the burden associated with this disease and its impact on quality of life.

1.3 Asthma in the workplace

A significant proportion of adult-onset asthma is related to workplace exposure. A population-based study recently carried out in six communities across Canada (Vancouver, Montreal, Winnipeg, Halifax, Hamilton, Prince Edward Island) estimated that 36.1% (31.3 to 41.0%, 95% confidence interval (CI)) individuals mentioned that their asthma worsened at work.[8] Other studies using a stricter definition have concluded that 5 to 10% of all adult-onset asthma was work-related.[9,10] occupational asthma (OA) is a type of work-related asthma that is caused by the workplace. It is defined as a "disease characterized by variable airflow limitation or airway hyperresponsiveness due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace".[11] Two types of OA have been identified: 1) immunological, in which a latency period is required for acquiring "sensitization"; and 2) non-immunological, also known as irritant-induced asthma (IrIA), which follows exposure to irritant materials in high concentrations. The frequency of OA among adult asthmatics, confirmed by objective testing, is of the order of 20% (medicolegal statistics in Québec). [5] Over 250 different agents present in the workplace can cause OA with a latency period (see www.asthme.csst.qc.ca); these include high-(proteinaceous) and low-(chemical)-molecular-weight agents. The most common causal agents in developed countries are isocyanates, flour, various chemicals, wooddusts, drugs, various proteins, metals, resins and glues, latex, cereals and grains.[11,12] Irritant-induced asthma can be caused by a variety of agents with irritant properties if they are generated at high concentrations.[11,12]

1.4 Psychological factors in asthma

The scope of the burden associated with asthma is multifactorial; health, personal, social and economic impacts have been well established. However, living with asthma may also have significant psychological impacts, the study of which has received increased attention in recent years. The idea that asthma may be related to psychological factors is not new. Psychological stress has long been considered an important asthma trigger, with references to asthma as being "passion-induced" and related to mood dating back as far as 200 B.C.[13] By the late 19th and early 20th centuries, Sir William Osler viewed asthma as a "neurotic affection" in which imbalances of the nervous system and emotional factors played a fundamental role.[14] Since then, the field of psychosomatic medicine has evolved into an established branch of medicine, with a growing number of studies providing evidence of a link between various psychosocial factors and asthma.[13]

More recently, data from both clinical and community settings suggest that psychiatric disorders, and mood and anxiety disorders in particular, are disproportionately more prevalent among asthmatics relative to the general population.[a] Point prevalence rates of anxiety disorders (e.g., panic disorder, generalized anxiety disorder, social phobia) and mood disorders (e.g., major and minor depressive disorder) are especially high among asthmatics, ranging from 16 to 52% for anxiety disorders[16-18] and from 14 to 41% for mood disorders.[16,17,19,20] Results from our own investigation including over 400 asthma outpatients indicate that 34% of asthmatics meet criteria for one or more *current* mood (20%) or anxiety (25%) disorders.[21] Rates of certain disorders (i.e.,

[a] General population prevalence rates for anxiety (1-13%) and mood (2-9%) disorders, respectively.[15]

panic disorder and major depressive disorder) are as much as *six times* more prevalent among asthmatics relative to the general population.[16-18,20]

1.5 Impact of psychiatric disorders and psychological stress on asthma

There is a vast literature linking symptoms of psychological stress to increased asthma morbidity. For example, symptoms of anxiety and depression have been associated with increased asthma severity, increased use of emergency services, increased symptom reporting, poorer pulmonary function, lengthier hospital stays, and increased use of reliever medication.[22-26] To date, relatively few studies have evaluated associations between asthma morbidity and an actual psychiatric disorder (which imply experiencing psychological stress at a level that is clinically significant and impairs daily functioning). However, those that have have yielded similar results. One recent study found associations between major depressive disorder (assessed using the Primary Care Evaluation for Mental Disorders, PRIME-MD) and worse nocturnal asthma symptoms, worse waking asthma symptoms, and worse quality of life.[19] A related study found that asthmatics identified as having a psychiatric disorder (according to the Structured Clinical Interview for DSM-III-R) were more likely to have poorly controlled asthma, to demonstrate worse medication adherence, and to have greater drop-out rates from asthma management programs relative to patients without a psychiatric disorder.[25] Collectively, these studies indicate a strong association between both psychological stress and psychiatric disorders and increased asthma morbidity.

1.6 Psychiatric disorders, psychological stress and occupational asthma

Despite strong associations between psychiatric disorders, high levels of psychological stress, and asthma morbidity, these associations remain totally unexplored in patients with OA. Given the high rate of asthma-related morbidity among non-occupational asthma patients with psychiatric disorders and in those experiencing high levels of psychological stress, it seems vital to explore these associations in OA patients. They may experience additional psychological stress by virtue of the fact that their symptoms are hypothesized to be related to their workplace, which may threaten their ability to work and make a living. When one also considers the scope of the burden associated with non-occupational asthma and applies those potential impacts to patients who were for years disease-free, an additional psychological burden associated with OA that surpasses that of non-OA can be hypothesized.

2. OBJECTIVES

The primary objective of the present study was to determine the prevalence of psychiatric disorders (i.e., mood and anxiety disorders, and hypochondriasis) and the levels of psychological distress among patients referred for evaluation of OA, and the extent to which having a psychiatric disorder was associated with a lower likelihood of receiving a diagnosis of OA (suggesting that psychiatric morbidity may be a plausible differential diagnosis for OA).

The secondary objective of the present study was to assess the impact of having one or more psychiatric disorder(s) at baseline (i.e., having a mood or anxiety disorders, or hypochondriasis) on employment status, health service utilization, and quality of life at 12-18 month follow-up, after adjustment for covariates. It was hypothesized that 1) a diagnosis of one or more psychiatric disorder at baseline would be associated with a lower likelihood of receiving a final diagnosis following evaluation for OA and that 2) having one or more psychiatric disorder at baseline would be associated with worse outcomes (i.e., more unemployment, greater health service use, and worse quality of life) in this population, at follow-up, after covariate adjustment.

3. METHODS

3.1 Patient selection

Patients were recruited from Hôpital du Sacré-Cœur de Montréal when presenting for evaluation of OA. They were included if they were over 18 years of age and could speak either English or French. Patients were excluded if they had co-morbid condition (e.g., cancer, cardiovascular disease) that could have conferred greater risk for morbidity than OA. A total of 247 patients presented for evaluation of OA between January 2006 and December 2008. Of these, 241 were approached to participate (98%). A total of 19 refused to participate and three were excluded due to language deficits, yielding a sample of 219 patients (91% participation rate). Following the evaluation, 23 patients were excluded for having been exposed to a single industrial accident, making them ineligible and resulting in a final baseline sample of 196 patients. A total of 149 patients (76%) completed the follow-up (Figure 1). This study was approved by the research ethics committee of Hôpital du Sacré-Coeur de Montréal, and written informed consent was obtained from all participants.

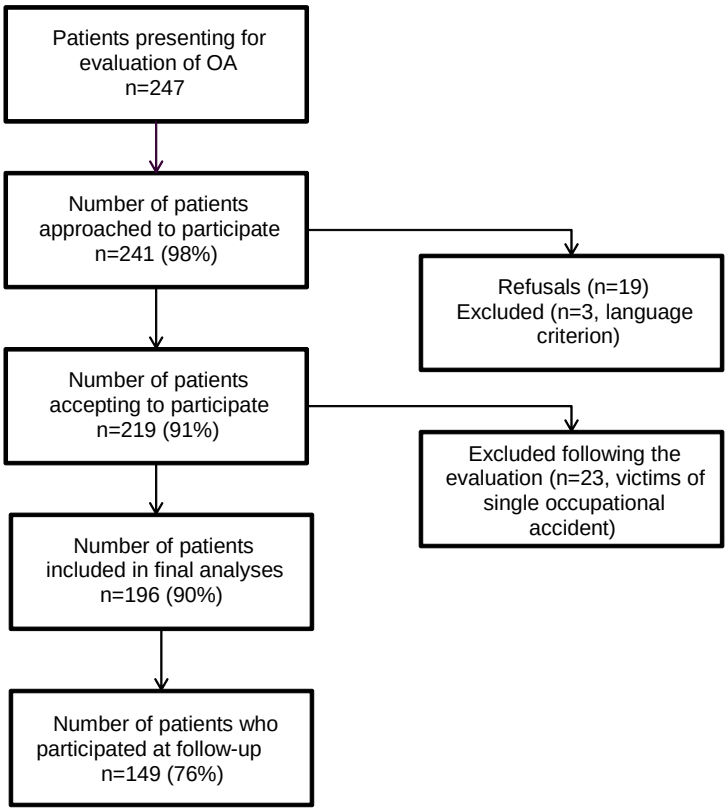

Figure 1: Flow chart of study participation.

3.2 Study design and procedures

3.2.1 Baseline evaluation

A total of 219 consecutive patients presenting to Hôpital du Sacré-Cœur de Montréal for the evaluation of OA participated in the present study. Patients were contacted following their physician visit (but prior to undergoing their OA tests), and underwent a brief sociodemographic and medical history interview, followed by a brief, structured psychological interview (PRIME-MD). The PRIME-MD (as well as all interviews) was administered by a single, trained clinical research assistant with over six years of experience. Patients then completed the battery of questionnaires assessing psychological stress (including depression, anxiety, anxiety sensitivity and hypochondriasis), asthma symptoms, and quality of life. All participants then underwent the standard medical evaluation including pulmonary function testing (measures of forced expiratory volume in one second (FEV_1)) and specific inhalation challenge (SIC) tests as part of the standard OA assessment. A physician-verified report of the medical findings was obtained for each participant to determine each patient's final diagnosis.

3.2.2 Follow-up evaluation

Patients were re-contacted between 12 and 18 months post-evaluation to undergo a telephone follow-up assessment. Patients underwent a brief, structured socio-demographic and medical interview where they were asked to update their medical status, report on the status of their employment (currently employed/working, not currently employed), and report on their health service utilization (in general, and for asthma) since their baseline evaluation. Interviewers were blind to patients' initial (baseline) PRIME-MD diagnoses. Patients were then mailed a self-report questionnaire assessing quality of life that they were asked to complete and return in a pre-addressed stamped envelope.

3.3 Baseline measures

3.3.1 Socio-demographic and medical history interview

Baseline socio-demographic information (including age, sex, ethnicity, and marital status), socioeconomic status (derived from measures of education level), relevant work-related variables (occupation, duration of exposure, time since symptom onset, nature of workplace symptoms), health behaviours (current/past tobacco and alcohol consumption), body mass index (BMI), and general medical and asthma history were collected using a structured interview by a single, trained clinical research assistant.

3.3.2 Pulmonary function testing

All patients underwent standard pulmonary function testing to yield measures of FEV_1 and metacholine challenge to yield measures of PC_{20}, according to ATS/European Respiratory Society (ERS) guidelines[27,28] at baseline and following SIC testing. Predicted values of FEV_1 were calculated from reference values for patients less than 70 years[29] and greater than[30] 70 years respectively, yielding % predicted FEV_1.

3.3.3 Specific inhalation challenge (SIC) testing and sputum induction

All patients presented for evaluation of OA and as such, underwent laboratory SIC testing according to standard procedures. Specifically, all patients were exposed to increasing doses of the occupational agent suspected to be causing their symptoms (which have been previously described)[12,31], over 3 to 4 days until a 20% fall in FEV_1 occurred. Methacholine challenge and sputum induction were performed at the end of each day of exposure. Sputum induction was conducted using normal saline administered via aerosol. If well tolerated, hypertonic saline was administered at increasing concentrations (3%, 4%, and 5%) via ultrasonic nebuliser, according to the procedure described by Pin et al.[32] After each period of inhalation, FEV_1 was measured for safety. Subjects were given inhaled salbutamol (200µg) prior to testing. Patients were then asked to blow their nose, rinse their mouth with water and then swallow the water in order to reduce contamination with saliva and postnasal drip. Patients were then instructed to cough into a sterile container, and the expectorate was processed within two hours. The sputum was processed as previously described.[33] The cell pellet was suspended in PBS and cytospins were prepared using a Shandon cytocentrifuge. The preparations were stained with Diff Quik and differential cell counts were determined on a count of 300 cells. Sputum samples were assessed for total cell count by weight (10^6 c/ml), and the respective percentages of neutrophils, eosinophils, and lymphocytes.

3.3.4 Asthma symptom burden

To assess asthma symptom burden, patients completed the Asthma Control Questionnaire (ACQ) and the Asthma Quality of Life Questionnaire (AQLQ).

ACQ: The ACQ evaluates levels of asthma control according to standard criteria specified by international guidelines.[34] Respondents were asked to recall their asthma symptoms (shortness of breath, wheezing, waking dyspnea, and nocturnal dyspnea), activity limitations, and bronchodilator use in the last week. One additional question assessing spirometry results (FEV_1, % predicted) was completed by the research assistant, following pulmonary function testing. The ACQ contains 7 items rated on a 7-point scale (0 = good control, 6 = poor control) to yield a mean score out of 6. The ACQ has demonstrated very good measurement properties, including high intra-class correlation coefficients between 0.90 and 0.95, a good construct, as well as cross-sectional and longitudinal validity.[35,36]

AQLQ: The AQLQ was modified[b] for use with patients who have yet to confirm a diagnosis of asthma. The AQLQ evaluates asthma-related quality of life across four domains: activity limitations, symptoms, emotional distress, and environmental stimuli. It contains 32 items rated on a 7-point scale (1 = maximal impairment, 7 = no impairment) to yield a mean score out of 7. The AQLQ has demonstrated very good measurement properties, including high intra-class correlation coefficients between 0.90 and 0.95, a good construct, as well as cross-sectional and longitudinal validity.[37,38]

[b] Items referring to “asthma” were replaced with “respiratory symptoms”.

3.3.5 Psychiatric interview

In order to evaluate the prevalence of current psychiatric disorders (including mood disorders: major depression, minor depression, dysthymia, and bipolar disorder; and anxiety disorders: panic disorder, panic attacks, generalized anxiety disorder, social anxiety disorder[c], and 'other' anxiety disorder), all patients underwent a brief, structured psychiatric interview called the *The Primary Care Evaluation of Mental Disorders (PRIME-MD).*[41] The PRIME-MD is a well validated screening instrument designed to detect the most common disorders that present in primary and tertiary care settings (Diagnostic and Statistical Manual of Mental Disorders - 4th Edition (DSM-IV)[25]). The PRIME-MD uses diagnostic algorithms to generate diagnoses based on DSM-IV criteria that have been shown to be of comparable reliability, sensitivity and specificity as longer structured psychological interviews.[41]

The interview begins with a series of screening questions followed by structured interview questions that are used to follow up patient responses. The PRIME-MD takes between 10 and 15 minutes to administer and score, and has been used successfully in previous studies (including our own study of over 700 non-occupational asthma patients)[21] assessing the prevalence of psychiatric disorders in asthma patients. [17,19] The PRIME-MD was administered by a trained clinical research assistant to determine the prevalence of current psychiatric disorders (specifically, the mood and anxiety disorders presented above).

3.3.6 Hypochondriasis assessment

The Whiteley Hypochondriasis Index (WI)[40] is a 14-item self-report questionnaire designed to assess levels of hypochondriasis, which is a common somatoform disorder characterized by excessive anxiety and worry about having a serious illness despite physician reassurance of the absence of medical illness or biological causes for the patients' symptoms.[15] Fourteen items are rated on a 5-point Likert-type scale from 1 (not at all) to 5 (a great deal), with higher scores indicating higher levels of hypochondriasis (range 14-70). Scores between 14 and 28 are considered within the normal range (average = 21 ±7), whereas scores between 32 and 55 are indicative of hypochondriasis (average = 44 ±11).[40] Sample items include: "Do you often worry about the possibility that you have a serious illness?" and "Is it hard for you to believe the doctor when he tells you there is nothing for you to worry about?" This questionnaire has demonstrated good psychometric properties, including good internal consistency, test-retest reliability (r=.83), and discriminant and convergent validity[41]. The WI has also been used in previous studies to screen for hypochondriasis among primary health care patients.[40,42]

3.3.7 Levels of psychological distress

In order to assess levels of psychological distress, patients completed the Beck Depression Inventory-II (BDI-II), the Beck Anxiety Inventory (BAI), and the Anxiety Sensitivity Index (ASI) in the clinic waiting room, which collectively took approximately 10-15 minutes to complete.

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[c] Due to the relative frequency of social anxiety disorder in asthma samples, we also administered questions from the Anxiety Disorders Interview Schedule for DSM-IV (ADIS)[39] to evaluate diagnoses of social anxiety disorder, a disorder that is not specifically assessed by the PRIME-MD.

***BDI-II*[43]:** The BDI-II is a 21-item self-report questionnaire designed to measure the intensity of depressive symptoms. The BDI-II has excellent internal consistency (alpha = .90-.91) and high construct validity (r = .89) with the depression scale of the SCL-90-R.[43]

***BAI*[44]:** The BAI is a 21-item self-report questionnaire measuring common symptoms of anxiety, such as nervousness and fear of losing control. The BAI has excellent internal consistency with psychological patients (alpha = .92) and good factorial validity.[44]

***ASI*[45]:** The ASI is a 16-item self-report questionnaire designed to measure patients' fear of anxiety symptoms. The ASI has a high degree of internal consistency (alpha=0.82 to 0.91) and satisfactory test-retest reliability (r=0.71).[45]

3.4 Follow-up measures

3.4.1 Telephone interview

Patients were contacted by telephone between 12 and 18 months after their initial evaluation, to undergo a follow-up interview which took approximately 20-30 minutes. Patients provided information about any changes in socio-demographics (e.g., changes in marital status), changes in medical status (e.g., diagnoses of new medical disorders, changes in medications), and on their current employment status (currently employed/not employed). They also provided information about their health service utilization over the course of the follow-up period, including information regarding the number of physician visits (general practitioner + pneumologists + other specialists), the number of emergency visits, and the number of hospitalizations.

3.4.2 Quality of life

Following the interview, patients were mailed the AQLQ to measure follow-up quality of life.

3.4.3 Statistical analyses

Group differences were examined using χ^2 test statistics (categorical variables) and General Linear Models (GLM: continuous variables), and means (SD) and proportions (%, n) were presented to describe continuous and categorial variables, respectively. To examine the likelihood of not receiving a diagnosis as a function of having a psychiatric diagnosis (yes/no, including mood or anxiety disorders, or hypochondriasis), multivariate logistic regression analyses were performed adjusting for age and sex. A series of GLMs or multivariate logistic regressions were used to examine the extent to which having a psychiatric disorder (yes/no) at baseline was associated with employment status (yes/no) at follow-up, health service use over the course of the follow-up, which included any health service visit (yes/no), any physician visits (including general practitioner and specialists: yes/no), any emergency visits (yes/no), and any hospitalizations (yes/no), and follow-up levels of quality of life (modified AQLQ scores). All tests were two-tailed and the level of significance was set at 0.05. Data analysis was performed using SAS v.9.3 (SAS Institute, Cary, NC).

4. RESULTS

4.1 Sample sociodemographic characteristics and baseline data

A summary of the sample characteristics is presented in Table 1. Participants were 57% male and had a mean age of 41.8 (± 11.2) years. Participants had an average of 11.6 (± 2.7) years of education, 65% (n=127) were cohabitating, and 55% (n=107) were employed (working) at the time of baseline evaluation. The majority of the sample (90%, n=175) were Caucasian. Participants had an average body mass index (BMI) of 27.1 kg/m2 (± 5.6), had smoked an average of 12.6 (± 11.8) pack-years, and 26% (n=51) of the sample were current smokers.

Table 1: Sample sociodemographic characteristics and baseline data.

	Mean ±SD or % (n) (n=196)
Sociodemographic characteristics	
Age (yrs)	41.8 ±11.1
Sex (male)	57 (112)
Caucausian	90 (175)
Years of education	11.6 ±2.7
Cohabitating	65 (127)
Employed at baseline evaluation	55 (107)
BMI (kg/m^2)	27.1 ±5.6
Smoking amount (pack-years)	12.6 ±11.8
Current smoker	26 (51)
Baseline data	
FEV_1 (% predicted, baseline)	93.7 ±17.0
Short-acting bronchodilator use (#/week preceding evaluation)	8.3 ±13.8
ACQ score	1.4 ±1.1
AQLQ score (modified version)	5.1 ±1.2
Time working before symptom onset (months)	77.9 ±103.4
Time between symptom onset and evaluation (months)	46.0 ±55.7
Depression score (BDI-II)	9.6 ±8.1
Anxiety score (BAI)	10.7 ±10.5
Anxiety sensitivity score (ASI)	16.5 ±10.5

BMI = body mass index; FEV1 = forced expiratory volume in one second; ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; BDI-II = Beck Depression Inventory; BAI = Beck Anxiety Inventory; ASI = Anxiety Sensitivity Index

At the time of baseline evaluation, participants had an average FEV_1 (% predicted) of 93.7 (±17.0), had taken their short-acting bronchodilators, on average, 8.2 (± 13.8) times in the past week, and had scores of 1.4 (± 1.1) and 5.1 (± 1.2) on the ACQ and on the modified AQLQ, respectively. These scores indicate, with the exception of pulmonary function which was normal, moderately poorly controlled symptomatic asthma-like symptoms and asthma-like symptom burden. Participants had been working for an average of 77.9 (± 103.4) months prior to the onset

of asthma-like symptoms, and were evaluated for OA an average of 46 (± 55.7) months after symptom onset. Finally, BDI-II, BAI and ASI results indicated scores in the normal range.

4.2 Diagnostic classification

Following completion of all testing, results showed that 152 out of 196 participants (78%) met criteria for at least one diagnosable disorder and 44 (22%) did not. Participants were grouped according to whether or not they met diagnostic criteria for the following disorders as their primary diagnosis: (1) OA, (2) asthma (i.e., non-occupational asthma) or work-exacerbated asthma (work-exacerbated asthma was classified in the asthma group because they do not represent true cases of OA[46]), (3) another inflammatory disorder (neither OA nor asthma), (4) non-inflammatory disorder, (5) no diagnosable disorder. As presented in Table 2, final diagnostic results revealed that 26% (n=50) of patients were classified in the 'OA' group, 25% (n=48) were classified in the 'asthma' group, 14% (n=28) were classified in the 'other inflammatory disorder' group, 13% (n=26) were classified in the 'other non-inflammatory disorder' group, and 22% (n=44) were classified in the 'no diagnosable disorder' group. As can be seen in Table 2, there were significant comorbidities within all groups except for the 'no diagnosable disorder group'.

Table 2: Diagnostic classification.

	OA (n=50)	**Asthma (n=48)**	**Other inflammatory disorder (n=28)**	**Non-inflammatory disorder (n=26)**	**No diagnosable disorder (n=44)**
Primary diagnosis	Occupational asthma (n=50)	Asthma (n=44) Work-exacerbated asthma (n=4)	Rhinitis (n=15) Eosinophilic bronchitis (n=6) Rhinoconjuctivitis (n=4) Alveolitis (n=2) RADS (n=1)	HVS (n=19) Other non-inflammatory disorder (not specified) (n=7)	No diagnosable disorder (n=44)
Secondary diagnosis	Rhinitis (n=5) Asthma (n=3) Rhinoconjunctivitis (n=3) Eosinophilic bronchitis (n=2)	COPD (n=3) HVS (n=2) Eosinophilic bronchitis (n=2) Rhinitis (n=2) Rhinoconjuctivitis (n=2)	HVS (n=2) Vocal cord dysfunction (n=1)	Other non-inflammatory disorder (not specified) (n=5)	NA

COPD = chronic obstructive pulmonary disease; HVS = hyperventilation syndrome; RADS = reactive airway dysfunction syndrome

In cases where patients met criteria for more than one diagnosis, the following algorithm was used: if they met criteria for OA + another disorder, they were classified in the 'OA' group; if

they met criteria for asthma + another disorder, they were classified in the 'asthma' group; if they met criteria for at least one other inflammatory disorder, they were classified in the 'other inflammatory disorder' group; if they met criteria for a non-inflammatory disorder, they were classified in the 'non-inflammatory disorder' group; if they did not meet criteria for any diagnosis explored as part of the standard evaluation for OA, they were classified in the 'no diagnosable disorder' category. A complete list of the disorders classified within each diagnostic group can be found in Table 2.

4.3 Sociodemographic and occupational characteristics as a function of diagnostic group

Sociodemographic and occupational characteristics presented as a function of diagnostic group are presented in Table 3. Patients in the 'other inflammatory disorder' group were significantly more likely to have been exposed to high (relative to low) molecular weight agents in the workplace compared to patients in the 'non-inflammatory disorder' and the 'no diagnosable disorder' groups ($F=4.68$, $p<0.001$). Although the overall model suggested group differences in time delays between symptom onset and evaluation for OA ($F=3.45$, $p = 0.009$), post-hoc analyses revealed only non-significant trends indicating that patients in the 'OA' group had larger delays than patients in the 'non-inflammatory disorder' and 'no diagnosable disorder' groups. There were no other significant differences on any socio-demographic or occupational variable between diagnostic groups.

Table 3: Sociodemographic and occupational characteristics as a function of diagnostic group.

Variable (Mean ±SD or %)	OA (n=50)	Asthma (n=48)	Other inflammatory disorder (n=28)	Non-inflammatory disorder (n=26)	No diagnosable disorder (n=44)	F	p
Age	41.1 ±11.7	42.1 ±11.7	43.6 ±9.6	41.1 ±12.2	41.81 ±10.5	0.27	0.895
Sex (male)	62	56	46	62	57	0.50	0.738
Caucasian	88	88	96	92	88	0.51	0.730
Education (years)	11.2 ±3.1	11.4 ±2.9	12.1 ±2.7	11.6 ±2.3	11.7 ±2.4	0.54	0.706
Cohabitating	58	63	82	58	68	1.14	0.233
Employed at baseline evaluation	46	65	57	46	57	1.08	0.368
HMW exposure	**48**	**26**	**63**	**11**	**18**	**4.68**	**<0.001**
Time working before symptom onset (months)	66.4 ±79.7	79.2 ±107.0	86.2 ±115.5	101.2 ±134.6	68.4 ±95.2	0.71	0.585
Time between symptom onset and OA evaluation (months)	**59.1 ±59.7**	**57.1 ±59.4**	**54.4 ±78.5**	**24.2 ±20.3**	**28.8 ±34.4**	**3.45**	**0.009**

HMW = high molecular weight agent exposure in the workplace

4.4 Clinical, respiratory, and immune characteristics as a function of diagnostic group

Clinical, respiratory, and immune characteristics presented as a function of diagnostic group are presented in Table 4. Patients in 'asthma' group had significantly worse baseline FEV_1 (% predicted) compared to those in the 'other inflammatory', 'non-inflammatory' and 'no diagnosable disorder' groups ($F=6.47$, $p<0.001$). Similarly, patients in the 'OA' and 'asthma' groups had significantly worse baseline PC_{20} ($F=30.54$, $p<0.001$) compared to patients in all other groups. Patients in the 'OA' and 'asthma' groups were significantly more likely to be prescribed ICS medication ($F=9.87$, $p<0.001$) and at higher doses ($F=12.54$, $p<0.001$) than patients in the 'non-inflammatory' and 'no diagnosable disorder' groups. Finally, patients in the 'OA' group had significantly higher post-SIC test % eosinophils ($F=9.35$, $p<0.001$) compared to patients in all other groups.

There were no other significant differences on any clinical, respiratory, or immune variable between diagnostic groups. Overall, this pattern of results validates our classification of patients, as respiratory and immune parameters in the 'OA' and 'asthma' groups were consistent with expected value ranges for patients with these disorders.[31]

Table 4: Clinical, respiratory and immune characteristics as a function of diagnostic group.

Variable (Mean ±SD or %)	OA (n=50)	Asthma (n=48)	Other inflammatory disorder (n=28)	Non-inflammatory disorder (n=26)	No diagnosable disorder (n=44)	F	p
Clinical characteristics							
BMI (kg/m^2)	28.1 ±6.2	28.0 ±6.0	26.0 ±3.6	25.3 ±4.6	26.6 ±5.9	1.83	0.126
Somking amount (pack-year)	11.8 ±10.5	14.4 ±14.1	13.3 ±14.7	14.6 ±10.1	9.8 ±8.5	0.69	0.601
Current smoker	26	31	18	28	25	0.42	0.792
Respiratory characteristics							
Bronchodilator use (#/week preceding OA evaluation)	9.1 ±15.3	10.5 ±15.7	2.0 ±2.5	1.8 ±2.9	4.6 ±6.7	0.94	0.447
ACQ score	1.3 ±1.2	1.7 ±1.2	1.3 ±1.1	1.1 ±1.1	1.5 ±1.0	1.57	0.188
AQLQ§ score	5.2 ±1.2	5.0 ±1.1	5.3 ±1.1	5.2 ±1.6	4.8 ±1.1	0.74	0.565
FEV_1, at baseline (% predicted)	**90.6 ±14.1**	**85.6 ±19.9**	**97.6 ±18.0**	**100.8 ±12.7**	**99.4 ±14.0**	**6.47**	**<0.001**
FVC (% predicted)	98.6 ±15.0	97.9 ±16.2	102.9 ±17.9	102.6 ±11.0	102.0 ±14.2	0.94	0.443
FEV_1/FVC at baseline	**77.2 ±8.2**	**72.3 ±10.8**	**78.8 ±5.7**	**81.3 ±6.7**	**81.0 ±5.9**	**8.64**	**<0.001**
PC_{20} geometric mean, at baseline [95% CI]	**4.6 [2.7;7.7]**	**2.3 [1.4;3.4]**	**28.5 [14.7;55.3]**	**59.7 [37.2;95.5]**	**54.2 [37.8;77.6]**	**30.54**	**<0.001**
ICS prescribed	**82**	**85**	**68**	**31**	**50**	**9.87**	**<0.001**
ICS dose (µg)¶	**597 ±525**	**866 ±727**	**325 ±364**	**120 ±260**	**155 ±343**	**12.54**	**<0.001**
Immune characteristics							
% sputum neutrophils, at baseline	39.3 ±23.0	38.6 ±27.5	39.2 ±22.5	42.5 ±19.0	44.6±24.6	0.29	0.883
% sputum neutrophils, post-SIC	46.0 ±24.9	43.1 ±26.2	50.5 ±23.4	47.8 ±19.7	41.7 ±23.7	0.48	0.753
% sputum eosinophils, at baseline	2.1 ±3.2	2.7 ±5.2	2.5 ±3.6	0.56 ±1.1	2.1 ±5.6	0.89	0.469
% sputum eosinophils, post-SIC	**11.3 ±14.4**	**2.4 ±5.4**	**2.9 ±4.0**	**0.1 ±.24**	**0.9 ±1.8**	**9.35**	**<0.001**

BMI = body mass index; ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; § modified AQLQ; ¶ fluticasone equivalent; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; ICS = inhaled corticosteroids; SIC = specific inhalation challenge; PC_{20} = provocative concentration of methacholine causing a 20% fall in FEV_1

4.5 Prevalence of psychiatric disorders

The prevalence of psychiatric diagnoses for the entire sample is presented in Table 5. Results of the PRIME-MD interviews and WI questionnaire indicated that a total of 67 out of 196 patients (34%) met diagnostic criteria for one or more psychiatric disorders (mood or anxiety disorders, or hypochondriasis). A total of 56 patients (29%) met criteria for one or more mood disorders, with major depression being the most common (n=47, 24%). A total of 47 patients (24%) met criteria for one or more anxiety disorders, with panic disorder being the most common (n=14, 7%). Finally, a total of 12 patients (6%) met cutoff criteria on the WI, suggesting probable diagnoses of hypochondriasis.

Table 5: Prevalence of psychiatric disorders among all participants.

Variable	% (n) n=196
Any psychiatric disorder	**34 (67)**
Any mood disorder	**29 (56)**
Major depression	24 (47)
Minor depression	21 (41)
Dysthymia	3 (6)
Any anxiety disorder	**24 (47)**
Panic disorder	7 (14)
Generalized anxiety disorder	5 (10)
Social anxiety disorder	1 (1)
Other anxiety disorder	14 (27)
Hypochondriasis	**6 (12)**

The prevalence of psychiatric disorders presented as a function of whether or not patients received a final diagnosis is presented in Table 6. Interestingly, patients who did not receive at least one diagnosis (i.e., those in the ‘no diagnosable disorder’ group) were significantly more likely to meet criteria for hypochondriasis relative to those who did receive at least one diagnosis ($F=5.71$, $p=.018$). Although not significant, patients who did not receive at least one final diagnosis were also more likely to meet criteria for a mood disorder (major depression) and anxiety disorder (panic disorder, generalized anxiety disorder, other anxiety disorder) relative to patients who did receive at least one diagnosis.

The prevalence of psychiatric disorders presented as a function of diagnostic group is presented in Table 7. Although there were no significant differences in the prevalence of psychiatric disorders across the five diagnostic groups, prevalence rates were generally higher in the ‘no diagnosable disorder’ group relative to the others for any psychiatric disorder, any anxiety disorder, major depression, panic disorder, other anxiety disorder, and hypochondriasis.

Table 6: Prevalence of psychiatric disorders as a function of having received at least one diagnosis.

Variable (% (n))	Received at least one diagnosis		F	p
	Yes (n=151)	No (n=44)		
Any psychiatric disorder	31 (47)	45 (20)	3.12	0.079
Any mood disorder	28 (42)	34 (15)	0.64	0.423
Major depression	19 (28)	27 (12)	1.59	0.209
Minor depression	9 (13)	7 (3)	.014	0.705
Dysthymia	3 (5)	0	1.49	0.223
Any anxiety disorder	22 (33)	30 (13)	1.11	0.293
Panic disorder	6 (9)	11 (5)	1.49	0.224
Generalized anxiety disorder	5 (7)	7 (3)	0.33	0.566
Social anxiety disorder	1 (1)	0	0.58	0.456
Other anxiety disorder	13 (20)	18 (8)	0.67	0.414
Hypochondriasis	**4 (6)**	**14 (6)**	**5.71**	**0.018**

Table 7: Prevalence of psychiatric disorders as a function of diagnostic group.

Variable (%)	OA (n=50)	Asthma (n=48)	Other inflammatory disorder (n=28)	Non-inflammatory disorder (n=26)	No diagnosable disorder (n=44)	F	p
Any psychiatric disorder	32	32	26	35	46	0.89	0.472
Any mood disorder	28	29	19	35	34	.059	0.669
Major depression	20	19	15	19	27	0.47	0.760
Minor depression	8	10	4	12	7	0.38	0.825
Dysthymia	4	2	4	4	0	0.47	0.755
Any anxiety disorder	24	23	15	23	30	0.50	0.734
Panic disorder	8	2	7	8	11	0.76	0.550
Generalized anxiety Disorder	4	8	0	4	7	0.73	0.573
Social anxiety disorder	4	0	0	0	0	1.47	0.212
Other anxiety disorder	14	13	11	15	18	0.22	0.925
Hypochondriasis	5	5	0	9	16	1.77	0.137

4.6 Levels of psychological distress

Levels of psychological distress presented as a function of diagnostic group are presented in Table 8. There were no significant differences in levels of depression, anxiety, or anxiety sensitivity between the five diagnostic groups. Overall, levels of depression and anxiety were in the normal range, and levels of anxiety sensitivity (which assesses fear of physical and mental symptoms of anxiety) were normal (14-18) to moderate (19-20).

Table 8: Levels of psychological distress as a function of diagnostic group (Mean ±SD).

Variable	OA (n=50)	Asthma (n=48)	Other inflammatory disorder (n=28)	Non-inflammatory disorder (n=26)	No diagnosable disorder (n=44)	F	p
Depression (BDI-II scores)	10.8 ±9.7	8.7 ±6.7	9.5 ±7.9	8.5 ±7.4	9.8 ±8.4	0.44	0.777
Anxiety (BAI scores)	11.3 ±11.5	9.9 ±8.5	9.9 ±9.3	11.3 ±11.4	11.2 ±12.1	0.17	0.955
Anxiety sensitivity (ASI scores)	19.0 ±12.6	15.9 ±9.5	19.9 ±8.6	14.9 ±10.2	14.4 ±10.1	1.22	0.304

4.7 Likelihood of NOT receiving a diagnosis as a function of the presence of a psychiatric disorder

In order to assess the extent to which having a psychiatric disorder can predict the likelihood of not receiving a diagnosis, multivariate logistic regression was carried out with presence/absence of a psychiatric disorder (including any mood or anxiety disorder, or hypochondriasis) as the independent variable, and presence/absence of a final diagnosis (yes/no) as the outcome variable. Results indicated that after adjustment for age and sex, the odds of not receiving a diagnosis if a psychiatric disorder was present was 1.85 (95% CI .93 – 3.67, p = .080) (Table 9). This suggests that patients under investigation for OA who met criteria for a psychiatric disorder were over 80% more likely to not receive a final diagnosis relative to patients without a psychiatric disorder. Although this finding was a non-significant trend, the range of the confidence interval suggests that the overall risk of not receiving a diagnosis is higher when a psychiatric disorder is present.

Interestingly, although having a mood (adjusted OR = 1.34, 95% CI = .66 – 2.75, p= 0.42) or an anxiety (adjusted OR = 1.50, 95% CI = .71 – 3.19, p = 0.29) disorder did not significantly increase the likelihood of not receiving a final diagnosis, meeting criteria for hypochondriasis significantly increased the likelihood of not receiving a final diagnosis by nearly 4-fold (adjusted OR = 3.92, 95% CI = 1.18 – 13.05, p = .026) (Table 9). This suggests that patients under investigation for OA with a diagnosis of hypochondriasis are nearly four times more likely not to have OA or any other diagnosable non psychiatric disorder, relative to those without hypochondriasis.

Table 9: Odds of not receiving a final diagnosis as a function of the presence of a psychiatric disorder.

Variable	OR	Adjusted OR	95% CI	p
Any psychiatric disorder	1.84	1.85	[0.93;3.67]	0.080
Any mood disorder	1.34	1.34	[0.65;2.75]	0.421
Any anxiety disorder	1.50	1.50	[0.71;3.19]	0.292
Hypochondriasis	**3.90**	**3.92**	**[1.18;13.05]**	**0.026**

Overall, this pattern of results suggests that hypochondriasis may explain a certain proportion of undiagnosable cases among patients referred for evaluation of OA, but that in general, psychiatric morbidity is more common in these patients compared to the general population[15], irrespective of the diagnostic group.

4.8 Follow-up sample characteristics

A total of 149 patients (76%) completed the follow-up assessment (see Figure 1), of which 57% (n=85) were employed (working) at follow-up. Due to the high rate of attrition from baseline to follow-up, we conducted analyses (GLM and chi-square analyses) to determine if there were any systematic differences between patients who completed versus those who did not complete the follow-up assessment, based on the following variables: age, sex, psychiatric disorder (yes/no), diagnostic group. As presented in Table 10, patients who completed the follow-up were significantly older (43.0 ±11.2 years vs. 38.2 ±10.2 years, F=6.78, p=0.010) and more likely to have been classified in the 'asthma' and 'other inflammatory disorder' groups, and less likely to have been classified in the 'no diagnosable disorder' groups, relative to non-completers. Though not significant, patients who completed the follow-up assessment tended to be male in a lower proportion (54% vs. 68%, χ^2 = 3.04, p=0.083) and tended to have lower rates of psychiatric disorders (31% vs. 45%, χ^2 = 2.94, p=0.088) relative to those who did not complete the follow-up assessment.

Table 10: Comparisons of follow-up completers vs. non-completers.

Variable	Completers (n=149)	Non-completers (n=47)	χ^2	p
Age (years)	**43.0 ±11.2**	**38.2 ±10.2**	**6.78**	**0.010**
Sex (% male)	54	68	3.04	0.083
Psychiatric disorder (baseline %)	31	45	2.94	0.088
Diagnostic group (baseline, %)				
OA	24	30	**10.09**	**0.040**
Asthma	27	17		
Other inflammatory disorder	17	4		
Non-inflammatory disorder	13	15		
No diagnosable disorder	19	34		

4.9 Impact of psychiatric disorders on employment status at follow-up

A series of GLM analyses were conducted to assess the impact of having a psychiatric disorder at baseline (including a mood or anxiety disorders, or hypochondriasis) on the likelihood of being employed (working, yes/no) at 12-18 month follow-up. Two models were analyzed: one adjusting for age, sex, baseline employment status, follow-up time and diagnostic group (to determine the extent to which psychiatric disorders predict employment status at follow-up irrespective of the diagnostic group); and a second examining the interaction between psychiatric status and diagnostic group on the follow-up employment status (using the same covariates).

Results of Model 1 indicated that after adjustment for covariates, patients with a psychiatric disorder at baseline were significantly less likely to be employed (working) at follow-up (44%) compared to those without a psychiatric disorder (64%) (F=7.02, p=0.009) (Figure 2). This indicates that after adjustment for covariates, including baseline employment status and diagnostic group, psychiatric morbidity at the time of evaluation of OA is a significant predictor of being unemployed within 12-18 months. Results of Model 2 revealed a significant interaction effect showing that after adjustment for the same covariates as in Model 1 (with the exception of the diagnostic group), patients in the 'OA', 'non-inflammatory disorder' and 'no diagnosable disorder' groups, with a psychiatric disorder at baseline, were more likely to be unemployed relative to patients in the same groups but without a psychiatric disorder at baseline (F=6.10, p=0.015) (Figure 3).

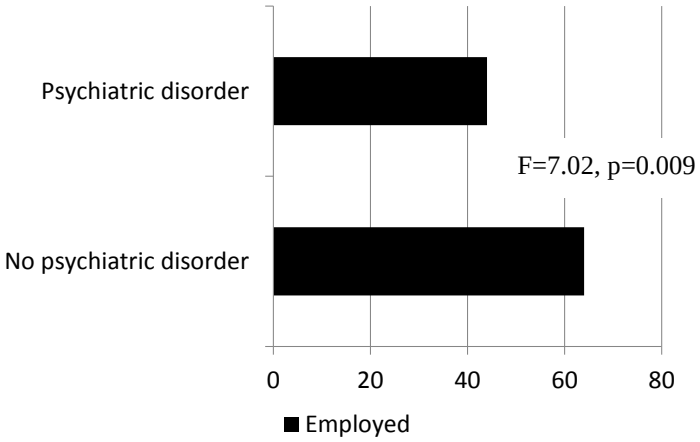

Figure 2: Follow-up employment rates as a function of baseline psychiatric group.

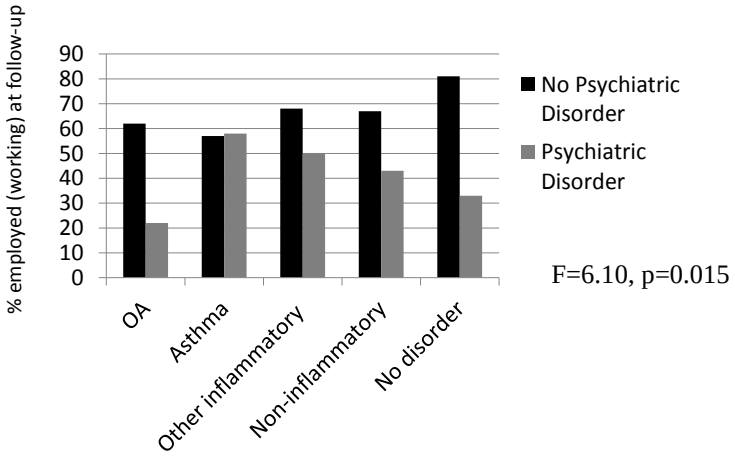

Figure 3: Follow-up employment rates as a function of baseline psychiatric group and diagnostic group.

4.10 Impact of psychiatric disorders on health service use over the follow-up period

A series of multivariate logistic regression analyses were conducted to determine the impact of having a psychiatric disorder at baseline on health service use over the 12-18 month follow-up period, after adjustment for the following covariates: age, sex, follow-up time, and diagnostic group. Overall, there was a relatively low incidence of health service use over the follow-up period (Table 11). Results revealed that patients with a psychiatric disorder at baseline were significantly more likely to have an emergency visit during the follow-up period compared to patients without a psychiatric disorder (35% vs. 19%, F=4.19, p =0.042). There were no other significant differences in health service use during the follow-up period in patients with versus without a psychiatric disorder at baseline (Table 12).

Table 11: Number of health service visits during the follow-up period, per category, as a function of the psychiatric group.

Variable (Mean ±SD)	Presence of a psychiatric disorder at baseline*	
	Yes (n=46)	No (n=102)
Total # health service visits	5.04 ±5.7	5.61 ±7.9
# physician visits	4.36 ±5.3	5.20 ±7.9
# emergency visits	0.63 ±1.1	0.37 ±1.2
# hospitalizations	0.04 ±0.2	0.05 ±0.2

* Total number of follow-up respondants, n=148, due to missing data from one participant

Table 12: Rates of health service use during the follow-up period, per category, as a function of the psychiatric group.

Variable	Presence of a psychiatric disorder at baseline*		F	p
	Yes (n=46)	No (n=102)		
Any health service visits	84%	90%	1.38	0.242
Physician visits	78%	8%	2.39	0.125
Emergency visits	**35%**	**19%**	**4.19**	**0.042**
Hospitalizations	<1%	<1%	0	0.967

* Total number of follow-up respondants, n=148, due to missing data from one participant

4.11 Impact of psychiatric disorders on quality of life at follow-up

GLM analyses were conducted to determine the impact of having a psychiatric disorder at baseline on the quality of life (modified AQLQ scores) at 12-18 month follow-up, after adjustment for the following covariates: age, sex, follow-up time, baseline modified AQLQ scores, and diagnostic group. The analyses revealed no differences in follow-up quality of life scores after adjustment for covariates between patients with (5.45 ±0.19) versus without (5.65 ±0.13) a psychiatric disorder at baseline ($F=0.76$, $p = 0.386$) (Table 13). Interestingly, even though absolute follow-up modified AQLQ scores were lower in patients with psychiatric disorders at baseline, the largest predictor of follow-up modified AQLQ score was baseline modified AQLQ score, which was also lower among patients with psychiatric disorders (data not shown). This indicates that patients with psychiatric disorders have lower quality of life scores at baseline which do not improve over the follow-up period.

Table 13: Predictors of follow-up modified AQLQ scores.

Variable	F	p
Psychiatric disorder	0.076	0.386
Baseline modified AQLQ score	**30.56**	**<0.001**
Diagnostic group	2.22	0.141
Age	0.05	0.817
Sex	**4.44**	**0.039**
Follow-up time	1.01	0.319

5. DISCUSSION

5.0 Rates of psychiatric morbidity and psychological distress

This study examined the prevalence of psychiatric disorders in patients under investigation for OA, and the impact on their employment, health service use, and quality of life outcomes at 12-18 month follow-up. Results revealed that rates of psychiatric diagnoses were relatively high in this population, reaching 34%. Mood and anxiety disorders affected 29% and 24% of the sample respectively, which is at least 2-4 times higher than rates observed in the general population[47] but generally comparable to rates observed among nonoccupational asthmatics.[17,48-51] Major depressive disorder was the most commonly diagnosed mood disorder (24%) and panic disorder was the most commonly diagnosed specific anxiety disorder (7%). Rates of hypochondriasis were disproportionately elevated in this sample (6%), which is considerably higher than prevalence rates found in the general population (0.6%)[52] and over 1.5 times higher than average rates observed in primary care populations (4.2%).[53-55] Despite relatively high rates of psychiatric disorders, average levels of psychological distress (i.e., symptoms of depression and anxiety) were within the normal range, and levels of anxiety sensitivity (a trait that measures fear of symptoms of anxiety) were normal to moderate. Overall, this pattern of results indicates that rates of psychiatric morbidity, which reflect clinically significant levels of psychological distress, were slightly higher than for nonoccupational asthma cohorts (though comparable),[48] but that levels of psychological distress were generally within the normal range.[40,44,45,56]

To our knowledge, this is the first study to evaluate rates of psychiatric disorders and levels of psychological distress in patients referred for evaluation of OA (thus patients not yet diagnosed as having or not having OA). Aside from two review articles,[46,57] we are aware of only four studies to date that have specifically assessed levels of psychological distress or psychiatric morbidity in cohorts of patients with OA or work-related asthma,[58-61] and our results are generally consistent with these reports. Yacoub et al. found that workers with possible (at the time of investigation) or confirmed OA had high levels of anxiety and depression measured using the Millon Clinical Multiaxial Inventory-III (MCMI-III)[62], a self-report questionnaire. [58] Anxiety disorders were most commonly diagnosed, with 14 subjects (35%) having a possible (n=5) or probable (n=9) anxiety disorder. Rates of possible or probable mood disorders were also high at 35%, and dysthymia (a chronic form of depression) was found to be the most common mood disorder, with 22.5% of subjects having possible (n=7) or probable (n=2) dysthymia. Finally, 5% of patients had possible (n=1) or probable (n=1) somatoform disorders, of which hypochondriasis is a sub-type.[63] The rates of anxiety and mood disorders reported by Yacoub et al. were slightly higher, and the rates of somatoform disorder somewhat lower than the rates of mood and anxiety disorders and hypochondriasis observed in the present study. This may be explained by the fact that Yacoub et al. used a self-report questionnaire that generates probable as well as possible diagnoses, which may inflate rates of overall psychiatric morbidity or may lack sensitivity to detect some disorders.

In the present study, we relied upon the use of a structured interview which is generally more sensitive and specific than self-report questionnaires, and tends to produce more reliable and valid diagnoses. Two studies by Miedinger et al.[59,60] assessed rates of psychiatric disorders (using the PRIME-MD)[60] and levels of psychological distress[59] among 60 patients with OA two

years after cessation of exposure to their sensitizing agent. They found that anxiety disorders affected 15% of patients, and rates of mood disorders were as high as 32%, with major and minor depressive disorder affecting 13% and 18% of patients, respectively. Miedinger et al.[59] also found that at least 50% of patients experienced clinically significant levels of psychological distress (i.e., anxiety, anger, depression and cognitive disturbance) according to the self-reported Psychiatric Symptom Index (PSI)[64]. Although rates of mood disorders observed by Miedinger et al. (32%) were similar to those observed in the present study (29%), rates of anxiety disorders (15%) were lower than in our study (24%). This may be explained by the fact that Miedinger et al.'s subjects all had confirmed OA at the time of their evaluation, whereas our subjects were under investigation for OA at the time of their evaluation, thus assessed at a time of high uncertainty. This may have increased the rates of anxiety disorders observed in the present study.

Finally, one study of individuals with work-related asthma found that depression (measured using the Asthma and Depression Modules as part of the Behavioral Risk Factor Surveillance System Asthma Call-Back Survey) was more prevalent among those with work-related asthma, relative to those with non work-related asthma.[61]

5.1 Psychiatric morbidity and final diagnosis

When rates of psychiatric morbidity were examined as a function of having received at least one diagnosis following evaluation for OA at baseline, only diagnoses of hypochondriasis were found to be significantly more prevalent among patients who *did not* receive any final diagnosis following testing (i.e., 16% vs. 5%). Interestingly, having hypochondriasis was associated with a nearly 4-fold increased risk of not receiving a final diagnosis, suggesting that this psychiatric disorder may account for a significant number of 'undiagnosable' cases of patients who present for evaluation of OA. To our knowledge, this is the first study to examine the extent to which a psychiatric disorder may account for the symptom presentation of patients suspected of having OA, but who are not found to have OA or any other diagnosable disorder evaluated as part of the standard evaluation of OA. According to the DSM-IV-R,[47] the core feature of hypochondriasis is a persistent fear (despite medical assurance following appropriate examinations) of having serious illness based on a misinterpretation of bodily symptoms. Hypochondriasis in the general population is associated with significant functional impairment and greater health care utilization,[65,66] even after controlling for clinical and sociodemographic factors. This suggests that some patients experiencing respiratory symptoms in the workplace may have misinterpreted their symptoms as reflecting asthma, which may be better explained by hypochondriasis or health anxiety than OA or related respiratory or inflammatory disorders. The fact that a greater proportion of patients who did not receive a diagnosis of any disorder had scores on the WI in the range consistent with a probable diagnosis of hypochondriasis provides support for this hypothesis.

Although psychiatric disorders in general were not significantly associated with a greater likelihood of not receiving a final diagnosis, this analysis revealed a trend ($p=0.079$) suggesting that this association was close to reaching significance. In fact, an examination of the absolute rates of psychiatric morbidity in those *without* a final diagnosis after evaluation for OA was 45%, compared to only 31% in those *with* a final diagnosis. Moreover, proportions were in the expected direction for any mood disorder (34% vs. 28%, *without* vs. *with*) [major depression

(27% vs. 19%)]; any anxiety disorder (30% vs. 22%) [panic disorder (11% vs. 6%), generalized anxiety disorder (7% vs. 5%) and other anxiety disorder (18% vs. 13%)]. The reasons why these differences did not reach statistical significance are not known. However, it is possible that despite having a relatively large sample size (in the context of a highly specialized population), we lacked power to detect differences between groups in a sample where psychiatric morbidity was overall quite high.

Another potential explanation lies in the nature of some of the confirmed diagnoses within the group of patients who received a diagnosis following evaluation of OA. Table 2 reveals that within the groups of patients who received a diagnosis, one of the most commonly diagnosed disorders was Hyperventilation Syndrome (HVS), affecting 23 patients or 12% of the sample. HVS is characterized by frequent episodes of breathing faster than necessary, which reduces blood carbon dioxide concentrations to below normal. This may result in dizziness, tingling sensations in the hands, feet, and lips, headache, chest pain, and occasional fainting.[67] Of note is that the vast majority of symptoms observed in HVS are also observed among patients with anxiety disorders (e.g., panic disorder).[47] Moreover, one of the most common causes of hyperventilation is stress or anxiety.[67] Although a well-established clinical diagnosis that is distinct from anxiety disorders, their shared clinical features suggest that the patients diagnosed with HVS may have suffered from higher levels of anxiety, potentially masking the detection of significant group differences across the diagnostic groups. It is noteworthy that the majority of patients diagnosed with HVS were classified in the 'non-inflammatory disorder' group, who had the second highest rates of psychiatric disorders relative to the 'no diagnosable disorder' group, providing partial support for this hypothesis. Finally, group differences in rates of psychiatric disorders may have failed to reach statistical significance due to some degree of reporting bias (i.e., symptom under-reporting) on the part of some participants, who may have been reluctant to divulge information related to psychological factors. This is understandable given that patients were, at the time of the evaluation, under investigation for OA, and may have been concerned about being labeled, or not having their symptoms being taken seriously (despite a reassurance that their research participation and their psychological evaluation would remain strictly confidential). However, if there was symptom under-reporting, it suggests that the present findings were at worst, under-estimates of the true rates of psychiatric morbidity or psychological distress.

5.2 Psychiatric morbidity and outcomes

Results of follow-up analyses revealed that patients with psychiatric disorders at baseline compared to those without a psychiatric disorder were significantly less likely to be employed (working) at follow-up, independent of baseline employment status and diagnostic group. Interestingly, there was a significant interaction between baseline psychiatric status and diagnostic group, such that differences in rates of employment at follow-up between patients with versus without a psychiatric disorder were most striking in the 'OA' and in the 'no diagnosable disorder' groups. This indicates that for patients who end up with a final diagnosis of OA, psychiatric morbidity has a significant impact on their likelihood of working within 12-18 months, which goes beyond simply having an occupational lung disease. In fact over 60% of workers with OA but without a psychiatric disorder were working at follow-up while only 20% of workers combining OA and a psychiatric disorder were working at follow-up. This indicates

that having a psychiatric disorder at the time patients are being investigated for OA may have important consequences for likelihood of being employed at follow-up. To our knowledge, this is the first study to evaluate the impact of psychiatric morbidity on employment outcomes among patients referred for evaluation of OA, and points to a novel association between psychiatric morbidity and worse occupational outcomes.

Although patients with psychiatric disorders at baseline did not present with a greater overall health service use over the course of the follow-up period relative to patients without psychiatric disorders, they were almost twice as likely to have had an emergency visit. To our knowledge, this is the first study to specifically examine the risk for increased health service use as a function of psychiatric status in patients referred for evaluation of OA. This finding is consistent with the results of at least one similar study among patients with work-related asthma in a large community cohort (greater need for urgent treatment, more emergency department visits, and more hospitalizations).[61] This finding is also consistent with the general psychiatric and chronic disease literature showing that patients with psychiatric disorders, alone or in the context of another chronic disease (e.g., non-occupational asthma, cardiovascular disease) are more likely to visit the emergency than their non-psychiatric counterparts.[68-72]

This study was not designed to examine the mechanisms linking psychiatric morbidity to worse health outcomes in this population, but we can still speculate on some potential explanations for this finding. First, the rates of overall psychiatric morbidity in this cohort were relatively high, affecting more than one third of the patients. Given that one of the cardinal features of mood and anxiety disorders, and hypochondriasis is a range of chronic somatic complaints, which may include breathlessness, heart palpitations, chest pain, dizziness, lack of energy and fatigue, sleep and appetite disturbances, and chronic pain,[47] it is perhaps not surprising that many of these patients would present to the emergency department with the fear of having a serious medical disorder. Moreover, given that one of the characterizing features of hypochondriasis is a tendency for patients to persist in their fears of having a serious illness despite receiving medical confirmation to the contrary, it is possible that the higher rates of emergency visits among patients with a psychiatric disorder was related to failing to receive a diagnosis or any other explanation for their asthma-like symptoms. The fact that the highest rates of psychiatric disorders were observed in the ‘no diagnosable disorder’ group provides partial support for this hypothesis, and suggests that psychiatric disorders should be evaluated in this population, so that appropriate treatment can be offered.

Finally, contrary to our initial hypotheses, we did not find a prospective association between baseline psychiatric status and follow-up quality of life. Though no previous study has examined this association in patients under investigation for OA, it is generally inconsistent with previous reports linking psychiatric disorders (i.e., mood and anxiety disorders) to worse quality of life among occupational[59] and non-occupational asthmatics.[19,21,48,73-75] The reasons for this finding are not known. However, it is noteworthy that even though absolute follow-up modified AQLQ scores were lower in patients with psychiatric disorders at baseline, the largest predictor of follow-up modified AQLQ score was baseline modified AQLQ score, which was also lower among patients with psychiatric disorders. This indicates that patients with psychiatric disorders have lower quality of life scores at baseline that do not improve over the follow-up period, which is generally consistent with what has been found in the literature.

5.3 Study limitations and strengths

This study needs to be interpreted in light of some methodological limitations. First, although this study is the largest to date to assess psychiatric morbidity and levels of psychological distress in patients under investigation for OA, it remains modest with 196 patients at baseline and 149 patients at follow-up, which may have reduced power to detect group differences. Second, psychiatric disorders were evaluated while patients were being evaluated for OA, which could have been considered a “high stress” period and contributed to inflated rates of psychiatric morbidity. However, the fact that rates of psychiatric disorders were comparable to those observed among other OA cohorts and asthma populations in general, as well as the use of a psychometrically valid and reliable interview to assess psychiatric morbidity, suggests that rates were unlikely to have been inflated. Third, despite efforts to retain all baseline subjects across the follow-up, we were only able to retain 76% of patients, and follow-up participants differed significantly from non-participants in terms of age and baseline diagnostic group, suggesting there may have been a selection bias in the follow-up sample. However, given the highly specialized nature of the population and the fact that patients came from a large geographical area, we are confident that our results are generalizable to patients suspected of having OA. Fourth, it is possible that due to limitations in the diagnostic methods used to diagnose OA (including rare difficulties isolating a single agent as responsible for their symptoms), some patients may have been misclassified. Finally, outcome measures used in this study were self-reported, which may have introduced some reporting biases (e.g., recall bias). However, we are fairly confident in the acurracy of employment status outcomes, as patients only had to indicate if they were currently employed (working) at the time of the follow-up assessment. Also, given the short duration of the follow-up period and the relative infrequency of health service use, we are confident that self-reports of health service use are accurate. Finally, even though the modified AQLQ was self-reported, it has demonstrated excellent psychometric properties, so we are confident in the reliability and validity of this measure.

Despite these limitations, this study also has a number of strengths. First, it is, to our knowledge, the first study to date to assess rates of psychiatric disorders in patients under investigation for OA. Its particularity arises also from the extent to which psychiatric disorders may account for the symptom presentation of patients suspected of having OA, but who are not found to have OA or any other diagnosable disorder evaluated as part of the standard evaluation of OA. Second, this study used a well-validated, structured psychiatric interview (PRIME-MD) to assess psychiatric morbidity, rather than self-report questionnaires which cannot provide clinical diagnoses, and which tend to over or underestimate rates of psychiatric morbidity. Third, we collected a range of relevant socio-demographic and clinical variables using established methods that provide a very well characterized sample of participants. Finally, this study successfully recruited 91% of all presenting patients and retained over three quarters of participants for the follow-up assessment, which support the generalizability of the results considering the above metionned limits.

6. APPLICABILITY OF RESULTS

The results of this study have the potential to impact clinical practice. First, they suggest that systematic evaluations of psychiatric morbidity (hypochondriasis in particular) may be warranted among patients referred for evaluation of OA, particularly those who do not meet criteria for any diagnosable disorder following OA testing. The systematic assessment of psychological factors in these patients may help ensure that a subset of those who remain symptomatic but who do not meet criteria for OA or any other diagnosable disorder does not “fall through the cracks” and go without available treatment, and that those with psychiatric disorders that are comorbid to other medical diagnoses (including OA) receive appropriate treatment.

The overall high prevalence of psychiatric morbidity in this population relative to the general population also suggests that irrespective of their final diagnosis (i.e., OA or other disorder or no diagnosable disorder), referral and treatment of psychiatric morbidity in this population may be warranted in order to improve occupational, health, and quality of life outcomes, which were generally found to be worse among patients with a psychiatric disorder at baseline. As such, this study may contribute to improved diagnostic efficiency and effectiveness, appropriate treatment, reduced functional impairment, and improved patient quality of life. Though treatment of psychiatric morbidity has been shown to improve psychosocial outcomes in other disease populations, this remains to be tested in an OA population.

We have intentionally used measurement tools (e.g., PRIME-MD, Beck Depression Inventory-II, Whiteley Index) to assess psychiatric morbidity and psychological distress that can be easily administered and scored. We believe these tools can be readily incorporated into existing evaluation protocols that will encourage their uptake in clinical practice.

Finally, we believe the results of this study will help inform the development and testing of interventions designed to improve psychiatric morbidity in patients with OA and patients with asthma-like symptoms at work. The goal of these interventions would be improved psychological, health (asthma), and occupational functioning (e.g., more rapid return to work or work re-orientation). There are already existing empirically-validated psychotherapeutic and pharmacological interventions for psychiatric morbidity (e.g., cognitive-behavioural therapy, CBT) that could be adapted and implemented in this unique population. This represents the next step in our research program.

7. CONCLUSION

The results of our study revealed that rates of psychiatric disorders are disproportionately high (2-10 times greater than rates observed in the general population) in patients presenting for evaluation of OA. Though rates of mood or anxiety disorders and levels of psychological distress were comparable among patients with and without an eventual diagnosis of OA or of another diagnosable disorder, hypochondriasis was more common among patients not receiving a final diagnosis, suggesting that it may underlie a significant proportion of 'un-diagnosable' cases of suspected OA. Follow-up results indicate that irrespective of diagnostic group, patients with a psychiatric disorder at baseline have less favorable 12-18 month outcomes, including being less likely to be employed and showing a greater use of health services (emergency visits). Overall, the results of this study suggest that greater efforts should be made to assess (and treat) psychiatric disorders in this population.

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