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# Associations of Depressive and Anxiety Disorders with Pulmonary Disorders in the Community: The PneumoLaus and PsyCoLaus Studies

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**Keywords**
Lung function · Asthma · Chronic obstructive pulmonary disease · Depression · Anxiety disorders

**Abstract**

***Introduction:*** Mental health disorders figure among the many comorbidities of obstructive respiratory diseases. The multisystemic characteristics of chronic respiratory disease and its impact on quality of life could affect depressive and/or anxiety disorders. We aimed to evaluate the association of spirometric indices, ventilatory disorders, and self-reported respiratory diseases with psychiatric disorders considering potential confounders. ***Methods:*** We analysed data from CoLaus|PsyCoLaus, a Swiss population-based cohort study, consisting of 2′774 participants (56% women; mean age: 62.3 (standard deviation = ±9.9) years) who performed spirometry and completed semi-structured psychiatric interviews. We defined ventilatory disorders using GLI-2012 references. Major depressive episode (MDE) and anxiety disorders were defined using the DSM-IV (Diagnostic and Statistical Manual). ***Results:*** 630 subjects (22.7%) presented a recent MDE. Reversible obstructive ventilatory disorders were associated with recent MDE (OR = 1.94, 95% confidence interval (95% CI) 1.10–3.43) and recent anxiety disorders (2.21 [1.16–4.22]) only in unadjusted model. Self-reported chronic obstructive pulmonary (COPD) and asthma were associated with MDE with ORs of 2.49 (95% CI, 1.19–5.27) and 1.56 (95% CI, 1.04–2.35) after adjustment, respectively. Possible restrictive ventilatory impairment was positively associated with recent anxiety disorders (OR = 2.46, 1.10–5.51). Z-scores of FEV1, FVC, and maximal mid-expiratory flow were not associated with psychiatric

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disorders. There was no association between ventilatory disorders and MDE in adjusted models. ***Conclusions:*** In this cross-sectional population-based study, the association between respiratory disorders and depressive disorders was observed for self-reported COPD and asthma, but not with objective diagnoses based on spirometry. Lung volumes are not associated with psychiatric disorders. Further prospective studies will be necessary to understand the significance of the association.


## Introduction

Mental health disorders figure among the many comorbidities of chronic obstructive pulmonary disease (COPD) and asthma. Major depressive disorder and anxiety disorders account for approximately 60% of all mental disorders [1].

Mental health disorders are common in patients with COPD, although there are important variations in the prevalence of major depressive disorder. Hanania et al. [2], in the ECLIPSE study using self-administered survey to diagnose depression, found a prevalence of depression of 26% in COPD patients and between 7% (non-smokers) to 12% (smokers) in non-COPD patients. However, this association was absent in a matched COPD cohort, within a prevalence of 9.4% in the COPD group and 8.0% in the non-COPD group [3]. A meta-analysis concluded for a depression prevalence of 27% in COPD [4]. The heterogeneity across studies was important and a meta-regression showed that demographic and clinical factors were not the determinants of heterogeneity in prevalence of depressive symptoms [5].

Depressive disorders adversely affected prognosis in COPD, conferring an increased risk of exacerbation and possibly death [6]. Conversely, COPD increased the risk of developing depression [6]. Anxiety disorders were more prevalent in COPD individuals (11.2% vs. 4.0%, OR [95% CI] 2.14 [2.07–2.21]) in a cross-sectional study in primary care in the UK [7].

Asthma control is sometimes difficult to achieve because of the interaction of different causes related to the disease itself, the treatment (e.g., incorrect device utilisation) and patient characteristics. Among comorbidities, mental diseases are frequently observed in asthma patients and depressive symptoms are common [8–10]. However, the prevalence of depressive disorders in this population is not well determined [11]. Prevalence of anxiety disorders in the general population ranged from 0.9% to 4.3% depending on the sort of disorders and from 0.4% to 11.2% in self-reported adult-onset asthma in a multi-continental study [9]. A meta-analysis found that depression was associated with a 43% increased risk of developing adult-onset asthma. However, asthma did not increase the risk of depression [10]. A large cross-national study confirmed in 2007 that depressive disorders occur with greater frequency (sex-adjusted odds of 1.6) among persons with self-reported asthma [12]. A Canadian cross-sectional study reported a prevalence of major depression, diagnosed by structured interviews, higher (17.9%) in individuals with self-reported asthma than in healthy respiratory individuals (11.7%) [8]. In the Severe Asthma Research Population (SARP), patients with depression had a 2.4-fold increased risk for poor asthma control and a 1.5 higher risk for healthcare utilisation, suggesting a significant impact of these conditions on asthma-related outcomes [13].

Depressive patients exhibit elevation in inflammation cytokine like TNF-alpha and IL-1β which are associated with impaired bronchodilatation response and airway neutrophilia, skewing the inflammation towards a M1 macrophage and Th1 $CD4^+$ lymphocyte response. This neuro-immune reaction may promote the remodelling of the airways and eventually lead to the development of airway obstruction [14]. A meta-analysis and a systematic review revealed a bidirectional association between psychosocial factors and atopic disorders including self-reported asthma [15]. Using data from a population-based cohort, the purpose of the present paper was to evaluate the association between lung volumes, spirometric ventilatory disorders and self-reported respiratory diseases and major depressive episode (MDE) and anxiety disorders, controlling for potential confounders.

## Methods

*Setting and Selection of Participants*

The data stemmed from the prospective CoLaus|PsyCoLaus cohort study (www.colaus-psycolaus.ch) which assessed the associations between mental disorders and cardiovascular risk factors in the community. The study has been previously described in detail [16, 17]. Briefly, CoLaus|PsyCoLaus includes an original random sample of 6,734 participants (age range 35–75 years) recruited from the residents of the city of Lausanne, Switzerland between 2003 and 2006. After the baseline investigation, the cohort was followed up after approximately 5 (follow-up 1, FU1, 5,064 participants), 9 (follow-up 2, FU2, 4,881 participants), and 13 years (follow-up 3). The spirometry investigation PneumoLaus took place between June 2014 and August 2017, i.e., during the FU2 physical evaluation and 1 year before the FU2 psychiatric evaluation [18]. PneumoLaus included 3,351 participants and FUP2 psychiatric evaluation included 3,493 participants. Our analysis included 2,774 participants who had completed the spirometry investigation as well as the FU2 psychiatric evaluation to determine the MDE and the anxiety status. The CoLaus|PsyCoLaus and

PneumoLaus studies were approved by the local Ethics Committee and all participants provided written informed consent (www.cer-vd.ch; project number PB_2018-00038, reference 239/09).

*Spirometric Manoeuvres and Ventilatory Disorders Definitions*

The Pneumolaus methodology was already described [18]. Briefly, spirometry was assessed using a MasterScreen-PFT spirometer (Carefusion, Hoechberg, Germany), employing the Sentry Suite software (Version 2.17). Measures were repeated to achieve a reproducible spirometry result, until a maximum of eight attempts, or interrupted if the participant was unable to continue. Each manoeuvre was analysed by computer in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) standards published in 2005 [19]. The maximal mid-expiratory flow (MMEF) was defined by the mean forced expiratory flow between 25% and 75% of the FVC. The GLI-2012 reference values were used, adjusted for ethnicity [20]. If FEV1/FVC ratio or FVC were below lower limit of normal (LLN) spirometry was repeated 10–15 min after administration of 400 µg of salbutamol administered via a metered dose inhaler and a spacer. Spirometry was included using recognised acceptability and reproducibility criteria as a reference aid [21].

Normal spirometry was defined by baseline FEV1/FVC ratio and FVC above LLN [22, 23]. We defined a chronic obstructive ventilatory disorder (COVD) as the $FEV_1$/FVC ratio below LLN following bronchodilation (BD). Reversible obstructive ventilatory disorder (ROVD) was defined as the FEV1/FVC ratio below LLN before BD and above LLN after BD using the best FVC [18]. The presence of a FVC below LLN before BD that became above LLN after BD was also assigned as a ROVD because of suspected air trapping [22]. We defined a possible restrictive ventilatory impairment as FVC below LLN before and after BD [22]. In the lack of an internationally accepted gold standard for the definition of small airways dysfunction (SAD) [24], we used the MMEF to define SAD, reflecting the impact of a reduced MMEF highlighted in other studies [25]. We defined SAD when the MMEF before BD was below the LLN according to expert recommendations and local data [24–26].

*Respiratory Risk Factors, Symptoms, and Self-Reported Respiratory Diagnosis*

A face-to-face structured interview with a respiratory practitioner on the day of the spirometry was used to assess respiratory risk factors, respiratory symptoms, and putative prior respiratory diagnoses as self-reported asthma or self-reported COPD, emphysema, or chronic bronchitis [18]. Respiratory symptoms such as cough, sputum production, and breathlessness according to the modified Medical Research Council (mMRC) dyspnoea scale were documented [27].

*Psychiatric Evaluation*

The PsyCoLaus methodology was already described [17]. Information on mental disorders was elicited at each psychiatric evaluation using the French version [28] of the Diagnostic Interview for Genetic Studies (DIGS) [29]. The DIGS was completed by the French version [30] of the sections on generalised anxiety disorder (GAD), post-traumatic stress disorder, and phobia disorders of the Schedule for Affective Disorders and Schizophrenia-Lifetime and Anxiety disorders (SADS-LA) [31]. Anxiety disorders included GAD, social phobia, panic disorder, and agoraphobia. At the follow-up evaluations, a shortened version of the DIGS was used focusing on the period since the last assessment. Mental disorders were assigned according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) [32]. MDE and anxiety disorders were subdivided in three categories: (1) "recent," i.e., reported for the 5 years preceding the spirometry investigation (between the FU1 psychiatric evaluation and the spirometry investigation [FU2]), (2) "remote" i.e., for the period earlier than the 5 years preceding the spirometry investigation (prior to the FU1 psychiatric evaluation), or (3) never i.e., having never met lifetime criteria for the disorder up to the spirometry investigation. For those who have not participated in the FU1 psychiatric evaluation, the cut-off to decide whether MDE or any anxiety disorders have taken place for or earlier than the 5 years preceding the spirometry investigation was based on the mean interval of 4.7 years between FU1 psychiatric evaluation and the spirometry investigation.

Interviews were conducted by master-level psychologists, who had been trained for a period of 1–2 months. All interviews were reviewed by an experienced senior psychologist.

*Covariates*

Demographic characteristics (age, sex) and smoking history were assessed using a standardised interview during the spirometry investigation. The socio-economic status was defined according to the Hollingshead scale [33]. The FU2 physical investigation included anthropometric measurements. Height was measured using a vertical stadiometer (Seca) and weight was measured using a calibrated scale to within 0.1 kg (Seca), these values were used to calculate the body mass index (BMI in $kg/m^2$).

*Statistical Analysis*

Participant characteristics were expressed as numbers (percentage) for categorical variables, and as mean ± standard deviations (SDs) for continuous variables. Univariate comparisons were performed using $\chi^2$ test and Student test for continuous variables as appropriate. Associations of the spirometric indices, the objectively measured ventilatory disorders (COVD, ROVD, or possible restricted ventilatory impairment, and SAD) and the self-reported respiratory diseases (COPD/emphysema/chronic bronchitis, and asthma), as the independent variables, with MDE and anxiety disorders (agoraphobia, panic disorder, GAD, social phobia) since and prior to the FU1 psychiatric evaluation, as the dependent variables, were assessed using multinomial logistic regression involving the three diagnostic groups with "never" as the reference. Each independent variable was included separately in the models. Firstly, all models were unadjusted. In a second step, each model was adjusted for age, sex, socio-economic status, BMI, and smoking status. In a third step, each model was adjusted for the same covariates plus anxiety disorders if the dependent variable was MDE or MDE if the dependent variable was anxiety disorders. Statistical significance was considered for a two-sided test with $p$ value <0.05. Stata™ software (version 17.0, StataCorp, College Station, TX, USA) was used for all statistical analyses.

## Results

*Characteristics of the Study Sample*

The characteristics of the participants are summarised in Table 1. In total, 1,552 (56.0%) were women, 1,390 (50.1%) were ever smokers and 503 (18.1%) were current smokers.

**Table 1.** Characteristics of the study participants ($n$ = 2,774)

| | |
|---|---|
| Socio-demographic characteristics at the time of the spirometry investigation | |
| Age, mean (SD), years | 62.3 (9.9) |
| Female sex, *n* (%) | 1,552 (56.0) |
| Socio-economic status[a], mean (SD) | 3.5 (1.2) |
| Caucasian, *n* (%) | 2,708 (97.6) |
| Characteristics at the time of the spirometry investigation | |
| BMI (kg/m$^2$), mean (SD) | 26.3 (4.7) |
| Ever smoked, *n* (%) | 1,390 (50.1) |
| Current smokers, *n* (%) | 503 (18.1) |
| Pack-years if ever smoked, mean (SD) | 24.3 (22.4) |
| Spirometric indices | |
| FEV1 (L), mean (SD) | 2.87 (0.79) |
| FEV1 (% predicted), mean (SD) | 100.1 (14.5) |
| FVC (L), mean (SD) | 3.73 (0.99) |
| FVC (% predicted), mean (SD) | 101.8 (14.5) |
| MMEF (L/s), mean (SD) | 2.59 (1.08) |
| MMEF (% predicted), mean (SD) | 104.7 (36.9) |
| Spirometric ventilatory disorders | |
| Ventilatory impairment, *n* (%) | |
| Possible restrictive ventilatory impairment | 48 (1.7) |
| ROVD | 66 (2.4) |
| COVD | 104 (3.8) |
| Normal lung function[b] | 2,556 (92.1) |
| Small airway dysfunction, *n* (%) | 131 (4.7) |
| Self-reported respiratory disorders | |
| COPD, emphysema, chronic bronchitis, *n* (%) | 43 (1.6) |
| Asthma, *n* (%) | 156 (5.6) |
| Psychiatric disorders | |
| MDE | |
| Since FU1 psychiatric evaluation (recent) | 630 (22.7) |
| Prior to FU1 psychiatric evaluation (remote) | 775 (27.9) |
| Anxiety disorders[c] | |
| Since FU1 psychiatric evaluation (recent) | 243 (8.8) |
| Prior to FU1 psychiatric evaluation (remote) | 325 (11.7) |

Descriptive statistics are presented as mean (SD) for continuous variables and *n* (percentage) for categorical variables. SD, standard deviation; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow; COVD, chronic obstructive ventilatory disorder; ROVD, reversible obstructive ventilatory disorder; COPD, chronic obstructive pulmonary disease; BMI, body mass index. [a]A value of 3 represents a socio-economic status of III (middle class) on the Hollingshead Scale. [b]Defined by FVC and FEV1/FVC > LLN (lower limit of normal, utilising GLI 2012 reference). [c]Generalised anxiety disorder, social phobia, panic disorder, or agoraphobia.

Among ever smokers, mean pack-years were 24.3 (SD = 22.4). 2708 (97.6%) of participants were Caucasian. The mean age was 62.3 years (SD = 9.9). Compared to participants who could not be included, participants in our study were younger, more likely to be women, with a lower BMI, required less social assistance, had a higher level of education, and were in better psychological health (online supplementary Table S1; for all online suppl. material, see https://doi.org/10.1159/000537918).

Spirometry showed that 104 (3.8%) of the subjects had COVD, 66 (2.4%) had ROVD, 48 (1.7%) had possible restrictive ventilatory impairment, and 131 (4.7%) had SAD (Table 1). A total of 156 (5.6%) subjects had self-reported asthma and 43 (1.5%) had self-reported medically diagnosed COPD, emphysema, or chronic bronchitis. Finally, MDE and anxiety disorders were reported by 50.6% and 20.5% of the participants, respectively.

**Table 2.** Association between spirometric indices, objectively measured ventilatory disorders and self-reported respiratory diseases and recent MDE and recent anxiety disorders

| | MDE | | | | Anxiety disorders[b] | | | |
|---|---|---|---|---|---|---|---|---|
| | recent | | | never | recent | | | never |
| | *n* (%)/ mean (SD) | unadjusted, OR [95% CI] | model 1, OR [95% CI] | *n* (%)/ mean (SD) | *n* (%)/ mean (SD) | unadjusted, OR [95 CI] | model 1, OR [95 CI] | *n* (%)/ mean (SD) |
| Spirometric indices | | | | | | | | |
| FEV1 (L) | 2.83 (0.79) | **0.88* [0.78-0.99]** | 0.91 [0.75–1.10] | 2.91 (0.82) | 2.90 (0.81) | 1.05 [0.89–1.24] | 1.05 [0.81–1.37] | 2.87 (0.79) |
| FEV1 (% predicted) | 100.3 (16.4) | 1.00 [0.99–1.00] | 1.00 [0.99–1.01] | 100.7(16.8) | 99.9(17.0) | 1.00 [0.99–1.01] | 1.00 [0.99–1.00] | 100.8 (16.6) |
| FEV1 (z-score) | 0.02 (1.10) | 0.98 [0.90–1.07] | 0.98 [0.89–1.08] | 0.05 (1.06) | 0.00 (1.12) | 0.96 [0.85–1.08] | 0.95 [0.84–1.07] | 0.05 (1.07) |
| FVC (L) | 3.63 (0.96) | **0.85* [0.77-0.93]** | 0.88 [0.74–1.03] | 3.80 (1.03) | 3.76(1.00) | 1.03 [0.90–1.17] | 1.06 [0.85–1.31] | 3.73 (1.00) |
| FVC (% predicted) | 101.3 (14.1) | 1.00 [0.99–1.00] | 1.00 [0.99–1.00] | 101.8(15.0) | 101.4(14.5) | 1.00 [0.99–1.01] | 1.00 [0.99–1.01] | 101.9 (14.6) |
| FVC (z-score) | 0.09 (0.97) | 0.97 [0.88–1.07] | 0.95 [0.86–1.06] | 0.12 (0.98) | 0.10 (0.99) | 0.97 [0.85–1.12] | 0.94 [0.82–1.09] | 0.12 (0.97) |
| MMEF (L/s) | 2.64 (1.12) | 1.04 [0.96–1.14] | 1.02 [0.91–1.14] | 2.59 (1.09) | 2.64(1.12) | 1.05 [0.93–1.18] | 0.99 [0.85–1.16] | 2.59 (1.08) |
| MMEF (% predicted) | 103.6 (36.5) | 1.00 [0.99–1.00] | 1.00 [1.00–1.00] | 105.1(37.0) | 102.5(38.2) | 1.00 [1.00–1.00] | 1.00 [0.99–1.00] | 105.0 (37.0) |
| MMEF (z-score) | 0.12 (1.22) | 0.97 [0.90–1.06] | 1.01 [0.93–1.11] | 0.16 (1.14) | 0.08 (1.22) | 0.94 [0.84–1.05] | 0.96 [0.85–1.08] | 0.16 (1.17) |
| Objectively measured ventilatory disorders | | | | | | | | |
| Ventilatory impairment | | | | | | | | |
| Possible restrictive ventilatory impairment | 12 (1.9) | 0.88 [0.45–1.73] | 0.95 [0.46–1.98] | 30 (2.2) | 8 (3.3) | 1.98 [0.91–4.30] | 2.37* [1.07–5.24] | 38 (1.7) |
| ROVD | 23 (3.7) | **1.94* [1.10 – 3.43]** | 1.80 [0.99–3.26] | 26 (1.9) | 12 (4.9) | 2.21* [1.16–4.22] | 2.10* [1.09–4.04] | 51 (2.3) |
| COVD | 21 (3.3) | 0.85 [0.51–1.43] | 0.92 [0.55–1.58] | 54 (3.9) | 7 (2.9) | 0.78 [0.35–1.70] | 0.76 [0.34–1.62] | 85 (3.9) |
| Normal lung function[a] | 574 (91.1) | 1 (ref.) | 1 (ref.) | 1,259 (92.0) | 216 (88.9) | 1 (ref.) | 1 (ref.) | 2032 (92.1) |
| Small airways dysfunction[c] | 32 (5.1) | 1.21 [0.78–1.88] | 1.17 [0.73–1.86] | 58 (4.2) | 17 (7.0) | 1.60 [0.94–2.73] | 1.57 [0.91–2.71] | 99 (4.5) |
| No small airways dysfunction | 598 (94.9) | 1 (ref.) | 1 (ref.) | 1,331 (95.8) | 226 (93.0) | 1 (ref.) | 1 (ref.) | 2107 (95.5) |
| Self-reported respiratory disorders | | | | | | | | |
| COPD, emphysema, chronic bronchitis | 16 (2.5) | **2.20* [1.09–4.44]** | **2.61* [1.25–5.47]** | 16 (1.2) | 6 (2.5) | 1.72 [0.72–4.16] | 1.90 [0.77–4.67] | 32 (1.5) |
| No COPD, emphysema, chronic bronchitis | 614 (97.5) | 1 (ref.) | 1 (ref.) | 1,352 (98.8) | 237 (97.5) | 1 (ref.) | 1 (ref.) | 2173 (98.6) |
| Asthma | 53 (8.4) | **2.00* [1.37–2.94]** | **1.59* [1.06–2.38]** | 60 (4.4) | 16 (6.6) | 1.25 [0.73–2.14] | 1.17 [0.68–2.02] | 118 (5.4) |
| No asthma | 577 (91.6) | 1 (ref.) | 1 (ref.) | 1,308 (95.6) | 227 (93.4) | 1 (ref.) | 1 (ref.) | 2087 (94.7) |

Model 1 was adjusted for age, sex, socio-economic status, BMI, and smoking status. FU1, follow-up 1; SD, standard deviation; OR, odd ratio; 95% CI, 95% confidence interval; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow; COVD, chronic obstructive ventilatory disorder; ROVD, reversible obstructive ventilatory disorder; COPD, chronic obstructive pulmonary disease. *$p < 0.05$. [a]Defined by FVC and FEV1/FVC > LLN (lower limit of normal, utilising GLI 2012 reference). [b]Generalised anxiety disorder, social phobia, panic disorder, or agoraphobia. [c]Defined by MMEF < LLN.

*Association between Objectively Measured Ventilatory Disorders and Mental Disorders*

The associations between objectively measured ventilatory disorders and recent depression or recent anxiety disorders are summarised in Tables 2 and 3. COVD was not associated with recent MDE nor with recent anxiety disorders. Participants with ROVD reported twice as often recent MDE or recent anxiety disorder in the unadjusted models compared to normal spirometry (Table 2, unadjusted). Only the association between ROVD and recent anxiety disorder remained statistically significant in the adjusted model (Table 2, Model 1, OR 2.10 [1.09–4.04]). However, when adjusting for the presence of MDE, this association failed to reach statistical significance (Table 3, Model 2). Possible restrictive ventilatory impairment was associated with an increased risk of reporting a recent anxiety disorder in the adjusted model 1 (OR 2.37 [1.07–5.24] and after adjustment for the presence of MDE (Table 3, OR 2.45 [1.10–5.51]). No association between ROVD or COVD and remote MDE or remote anxiety disorders was detected (online suppl. Table S2 and S3). There was a negative association between possible restrictive ventilatory impairment and remote MDE (online suppl. Table S2, model 1) (OR 0.41 [0.17–0.99]; however, after adjustment for anxiety disorder, this association disappeared (online suppl. Table S3, model 2). Finally, we found no association between SAD and any recent or remote depression or any anxiety disorders.

*Association between Self-Reported Respiratory Diagnoses and Mental Disorders*

Self-reported COPD, emphysema or chronic bronchitis, and self-reported asthma were associated with an increased risk of reporting recent MDE (Table 2, unadjusted and model 1). These associations persisted after adjustment for anxiety disorder (Table 3, with self-reported COPD OR 2.49 [1.18–5.27], self-reported asthma OR 1.56 [1.04–2.35]). In contrast, we found no association between self-reported respiratory diagnoses and anxiety disorders (Tables 2, 3; online suppl. Table S2 and S3).

*Association between Lung Volume and Mental Disorders*

The results of the associations between spirometry indices as absolute volume, % of predicted or z-score and depression or anxiety disorders are summarised in Table 2 (for recent diagnosis) and online supplementary Table S2 (for remote diagnosis). As absolute volumes, but not % predicted and z-scores, higher volumes of FEV1 and FVC were associated with a lower risk of recent and remote MDE in the unadjusted analysis. These associations failed to reach statistical significance in the adjusted models. There was no association between MMEF in absolute value, % of predicted or z-score and MDE or anxiety disorder.

## Discussion

Using a population-based study, the four salient key findings of the present analyses emerged: firstly, possible restrictive ventilatory impairment was the only objectively measured ventilatory disorders associated with an increased risk of reporting recent anxiety disorder. Secondly, self-reported COPD, emphysema or chronic bronchitis were associated with an increased risk of reporting a recent MDE. Thirdly, self-reported asthma was associated with an increased risk of reporting a recent MDE. Fourthly, objective spirometry indices were not associated with MDE or anxiety disorders.

Surprisingly, there was no association between COVD and MDE or anxiety disorders, whereas COVD is related to COPD in spirometry. This could be due to a selection bias excluding subjects with severe COPD, given the low prevalence of obstructive ventilatory disorder in our cohort. This lack of association is consistent with the absence of a shared genetic architecture between these 2 disorders, as previously described [34]. However, self-reported COPD was associated with recent MDE as previously described with a known diagnosis of COPD [35]. There could be a difference in the impact of mental health between symptomatic subjects with known diagnosis compared to subjects with few symptoms with unknown COPD diagnosis because subjects with few respiratory symptoms will not visit a physician to obtain their respiratory diagnosis. Similarly, a respiratory diagnosis may be more frequently investigated and obtained in subjects with psychiatric complaints who consult a physician more than in others. There was no association with remote psychiatric disorders possibly because the interval between the period of psychiatric disorders and the detection of a respiratory disorder might be too long. The remote psychiatric disorders occurred before the respiratory impact. This may have reduced the likelihood to perform spirometry or develop respiratory disorders associated with psychiatric disorders.

**Table 3.** Association between objectively measured ventilatory disorders and self-reported respiratory diseases and recent major depressive episode and recent anxiety disorders adjusted for comorbid psychiatric disorder

| | Recent major depressive episode | Recent anxiety disorders[b] |
|---|---|---|
| | model 2[d], OR [95% CI] | model 2[e], OR [95% CI] |
| Objectively measured ventilatory disorders | | |
| Ventilatory impairment | | |
| Possible restrictive ventilatory impairment | 0.91 [0.44–1.91] | **2.46* [1.10-5.51]** |
| ROVD | 1.75 [0.95–3.22] | 1.90 [0.98–3.71] |
| COVD | 0.96 [0.44–1.91] | 0.78 [0.35–1.75] |
| Normal lung function[a] | 1 (ref.) | 1 (ref.) |
| Small airways dysfunction[c] | 1.13 [0.70–1.81] | 1.55 [0.83–2.69] |
| No small airways dysfunction | 1 (ref.) | 1 (ref.) |
| Self-reported respiratory disorders | | |
| COPD, emphysema, chronic bronchitis | **2.49* [1.18-5.27]** | 1.58 [0.63–3.94] |
| No COPD, emphysema, chronic bronchitis | 1 (ref.) | 1 (ref.) |
| Asthma | **1.56* [1.04-2.35]** | 1.07 [0.62–1.87] |
| No asthma | 1 (ref.) | 1 (ref.) |

FU1, follow-up 1; OR, odd ratio; 95% CI, 95% confidence interval; COVD, Chronic obstructive ventilatory disorder; ROVD, reversible obstructive ventilatory disorder; COPD, chronic obstructive pulmonary disease. *$p < 0.05$. [a]Defined by FVC and FEV1/FVC > LLN (lower limit of normal, utilising GLI 2012 reference). [b]Generalised anxiety disorder, social phobia, panic disorder, or agoraphobia. [c]Defined by MMEF < LLN. [d]Model 2 adjusted for age, sex, socio-economic status, BMI, smoking status, and anxiety disorders. [e]Model 2 adjusted for age, sex, socio-economic status, BMI, smoking status, and major depressive episode.

We observed associations between ROVD and recent anxiety disorders as well as recent MDE which were confirmed for ROVD and recent anxiety disorders only in our adjusted model 1. A similar association between airflow obstruction and anxiety disorders had previously been described [36]. These associations could be due to the dyspnoea induced by an obstructive ventilatory disorder, which would increase the development of depression or an anxiety disorder [37]. Given the link between breathing and anxiety described especially in anti-anxiety therapies, the association between ROVD and anxiety disorders may be due to variations in obstructive respiratory volumes, which may promote anxiety and lead to the development of anxiety disorders [38, 39]. A neuro-immune reaction may also promote the remodelling of the airways and lead to the development of airway obstruction [14].

The association of self-reported asthma with recent MDE may confirm that subjects with respiratory symptoms are more likely to be diagnosed with psychiatric disorders, and vice versa with the possible bias of the respiratory diagnosis retained more frequently in symptomatic subjects. This confirms the association between known asthma and major depression in the general population [8, 9, 12, 36].

The surprising association between possible restrictive ventilatory impairment and anxiety disorders may be due to the small number of subjects with a possible restrictive ventilatory impairment and recent anxiety disorders ($n = 8$), and its clinical relevance is not straightforward to understand. A possible impact of the limitation of respiratory capacity (e.g., to carry out an exercise) may promote an anxiety disorder due to the theoretic inability to carry out more difficult physical activities. Similarly, we found a protective association of possible restrictive ventilatory disorders with remote probably to a small-size effect ($n = 6$).

The association between FEV1 or FVC and recent MDE was only found with absolute values in the unadjusted analysis. This is probably due to the impact of female sex on MDE, explaining the absence of association in % predicted, in z-score and in the adjusted models. The possible ventilatory impact on psychiatric disorders did not seem to be continuous. The association described between FEV1 and depression by self-report score was not found in our study [40]. SAD, which is currently of increasing interest, does not appear to have any influence on psychiatric disorders. We described here the first lack of association between SAD or MMEF and psychiatric disorders.

The results of this study must be interpreted with an understanding of the inherent limitations including a small number of abnormal spirometry and a probable cohort selection bias. The low number of abnormal spirometry tests and self-reported COPD may be due to the lower prevalence of participants who had ever smoked compared with to other studies [18]. People with low spirometry values might not have participated in our cohort due to their symptom burden. Moreover, this was a cross-sectional study; therefore, it was only possible to confirm a temporal association between mental disorders and airways impairment, without being able to analyse a potential causality due to a period of only 1 year between the spirometry and the psychiatric assessment. Self-reported respiratory diagnoses may also not have been recognised by sick participants. Nevertheless, this is the first population-based study focused on the association between spirometry indices, ventilatory disorders, and psychiatric disorders as defined by a semi-structured interview.

## Conclusions

In this cross-sectional population-based study, the association between respiratory disorders and depressive disorders is found only with self-reported diagnoses and not with objective ventilatory diagnoses. Lung volumes are not associated with depressive or anxiety disorders. Knowing the diagnosis of respiratory diseases seems to influence the likelihood of having a psychiatric diagnosis, and vice versa. Prospective studies are needed to understand the significance of the association.


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## Statements of Ethics

The baseline CoLaus|PsyColaus study protocol was reviewed and approved by the Institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of the Canton of Vaud (www.cer-vd.ch), approval number reference 16/03; 134–03,134-05bis, 134–05-2to5 addenda 1–4. The study protocol was renewed and approved by the Institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of the Canton of Vaud (www.cer-vd.ch) for the first follow-up, approval number reference 33/09; 239/09, for the second follow-up, approval number reference 26/14; 239/09 addendum 2, the third follow-up, approval number PB_2018-00040; 239/09 addenda 3–4. A renewal of the approval for the whole cohort and to conduct the fourth follow-up was obtained by the Ethics Commission of the Canton of Vaud (www.cer-vd.ch) in 2021, approval number PB_2018-0038,239/09. All participants signed a written informed consent to participate in the study. The study was performed in agreement with the Helsinki Declaration and its former amendments and in accordance with the applicable Swiss legislation.

## Conflict of Interest Statement

C.V.G. had grants and contracts with OM Pharma. C.V.G. received consultation fees from AstraZeneca, G.S.K., Boehringer Ingelheim, and OM Pharma. C.V.G. received Payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from AstraZeneca, G.S.K., and OM pharma. The other authors declared no conflicts of interests.


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## Author Contributions

B.T. and A.L. designed the study. B.T. analysed the data with particularly input of A.C., C.V.G., M.P., and M.-P.F.S. B.T. drafted the original manuscript. B.T., A.C., S.J., and M.-P.F.S. participated to write the manuscript. All authors reviewed and edited the writing manuscript. A.C., C.V.G., L.P.N., M.P., and M.-P.F.S. did the supervision of study and manuscript. B.T., C.V.G., and L.P.N. did the project administration of the study. J.V., P.V., C.V.G., M.-P.F.S., and L.P.N. participated to obtain the found of the study. All authors have read and agreed to the published version of the manuscript.

## Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary material files. The data of CoLaus|PsyCoLaus and PneumoLaus studies used in this article cannot be fully shared as they contain potentially sensitive personal information on participants. According to the Ethics Committee for Research of the Canton of Vaud, sharing these data would be a violation of the Swiss legislation with respect to privacy

protection. However, coded individual-level data that do not allow researchers to identify participants are available upon request to researchers who meet the criteria for data sharing of the CoLaus|PsyCoLaus Datacenter (CHUV, Lausanne, Switzerland). Any researcher affiliated to a public or private research institution who complies with the CoLaus|PsyCoLaus standards can submit a research application to or research.psycolaus@chuv.ch. Proposals requiring baseline data only will be evaluated by the baseline (local) Scientific Committee (SC) of the CoLaus and PsyCoLaus studies. Proposals requiring follow-up data will be evaluated by the follow-up (multicentric) SC of the CoLaus|PsyCoLaus cohort study. Detailed instructions for gaining access to the CoLaus|PsyCoLaus data used in this study are available at www.colaus-psycolaus.ch/professionals/how-to-collaborate/.

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