

# Neurological and Psychiatric Comorbidities in Chronic Obstructive Pulmonary Disease

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**Background and Purpose:** Chronic obstructive pulmonary disease (COPD) is often accompanied by different neurological and psychiatric comorbidities. The purpose of this study was to examine which of them are the most frequent and to explore whether their manifestation can be explained by underlying latent variables.

**Methods:** Data about patients with COPD and their neurological and psychiatric comorbidities were extracted from an electronic database of the National Health Insurance Fund of Lithuania for the period between January 1, 2012, and June 30, 2014. Exploratory factor analysis (EFA) was used to investigate comorbidity patterns.

**Results:** A study sample of 4834 patients with COPD was obtained from the database, 3338 (69.1%) of who were male. The most frequent neurological and psychiatric comorbidities were nerve, nerve root and plexus disorders (n=1439, 29.8%), sleep disorders (n=666, 13.8%), transient ischemic attack (n=545, 11.3%), depression (n=364, 7.5%) and ischemic stroke (n=349, 7.2%). The prevalence of ischemic stroke, transient ischemic attack, Parkinson's disease, dementia and sleep disorders increased with age. One latent variable outlined during EFA grouped neurological disorders, namely ischemic stroke, transient ischemic attack, epilepsy, dementia and Parkinson's disease. The second encompassed depression, anxiety, somatoform and sleep disorders. While similar patterns emerged in data from male patients, no clear comorbidity profiles among women with COPD were obtained.

**Conclusion:** Our study provides novel insights into the neurological and psychiatric comorbidities in COPD by outlining an association among cerebrovascular, neurodegenerative disorders and epilepsy, and psychiatric and sleep disorders. Future studies could substantiate the discrete pathological mechanism that underlie these comorbidity groups.

**Keywords:** chronic obstructive pulmonary disease, comorbidities, factor analysis, sleep impairment, stroke

## Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most frequent chronic respiratory conditions and a leading cause of death worldwide.<sup>1,2</sup> Its prevalence, mortality and associated burden have been decreasing throughout the years when adjusted for population growth and ageing. However, COPD remains a major contributor to disease burden globally when measured in disability-adjusted life-years (DALYs). Among non-communicable diseases, COPD-related DALYs were surpassed only by ischemic heart disease and stroke, according to data from the Global Burden of Disease Study 2017.<sup>3</sup> Patients suffering from COPD are also more likely to be diagnosed with various comorbidities, such as allergic,

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cardiovascular or cerebrovascular disease, different neurological and psychiatric conditions.<sup>4–8</sup> Therefore, COPD can lead to high medical expenses and challenges in providing multidisciplinary care.<sup>9</sup>

Controlled studies provide information about the specific neurological or psychiatric risks that patients with COPD face (eg increased risk of stroke). However, the interpretation of reports addressing the increased prevalence of individual comorbidities is often limited because of methodological issues.<sup>10</sup> Non-identical definitions of COPD, variability in data sources, selected patient samples and measured outcomes render very different comorbidity prevalence results. As current findings indicate that comorbidities in COPD tend to cluster in discrete groups, it might be thus more beneficial to examine multimorbidity patterns among patients with COPD rather than the risks of the discrete comorbidities themselves.<sup>11–13</sup> Further examination of such clustering may evade some of the limitations of prevalence studies by allowing qualitative analysis of the underlying multimorbidity profiles. A similar approach has already led to the identification of different clinical patterns of COPD.<sup>14–18</sup> Outlining the comorbidity profiles in patients with COPD could help to acknowledge the additional health conditions that may be present in these individuals. This could improve personalization of care and facilitate a multidisciplinary approach in treatment protocols.<sup>19</sup>

Most studies exploring comorbidities in COPD include heterogeneous disorder groups and consequently report broad patterns of disease clustering (eg “cardiovascular” or “metabolic” profiles). This current study seeks to narrow the analysis down and focuses on neurological and psychiatric comorbidities in COPD. It is already known that psychiatric disorders (eg depression, anxiety), impaired cognition, poor sleep and an increased risk of stroke are relevant issues among patients with COPD.<sup>4,7,20–26</sup> However, it is not entirely clear, whether different neurological and psychiatric comorbidities tend to manifest together and in what patterns they emerge among individuals with COPD. Such information could prove to be valuable for neurologists and psychiatrists when providing medical services to patients with COPD. The aims of this study were (1) to evaluate the frequency of neurological and psychiatric comorbidities in a sample of patients with COPD and (2) to explore the associations among the comorbidities by extracting underlying factors that are common for several comorbid disorders.

## Materials and Methods

### Data Sources

The data of this current study were part of a database from the project “The Joint Action on Chronic Diseases and Promoting Healthy Ageing Across the Life Cycle (JA-CHRODIS)” co-funded by the European Union. The initial project dealt with analyzing prevention and management of chronic diseases using data about chronic conditions from large populations by using national electronic health records. Selected variables (eg presence of different disorders, demographic variables, information about hospital admissions etc.) were extracted from electronic health records of the National Health Insurance Fund of Lithuania for the period from January 1, 2012, to June 30, 2014. The Lithuanian national healthcare system relies on compulsory health insurance and seeks to provide universal access for all country’s residents. Therefore, the records covered almost all primary care visits and up to 98% of all inpatient visits in the country’s territory during the study period. Comprehensive methods and results involving data from Lithuania have already been presented elsewhere.<sup>27</sup> An approval from the Vilnius Regional Biomedical Research Ethics Committee has been acquired for this study (approval number 2020/3-1207-692) and it was conducted according to guidelines and principles outlined in the Declaration of Helsinki. No consent from individual participants was deemed necessary for the Committee’s approval, because all analysis was based on anonymous data from electronic health records. Researchers of this study received permission to use the database, which is comprised of anonymous data only.

### Study Sample

The initial patient cohort consisted of 452 769 patients and was composed of all individuals (18 years or older) that had been diagnosed with at least one chronic condition from the 32 chronic diseases list used by Barnett et al and, thus, involved chronic diseases with the highest prevalence and the highest impact on patients.<sup>28</sup> During the first step of patient selection for the current study, data of patients aged from 40 to 79 have been extracted, resulting in a sample of 353 780 individuals. The group of patients aged 80 and older was small; data variation in the group was high and many outliers were observed. Because of these reasons, we decided to exclude patients older than 79 years from the analysis. To include only patients with a reliable diagnosis of COPD, we used several criteria

during the following step. To be regarded as having COPD, the patients had to be diagnosed with this disorder (code J44.8 in the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification [ICD-10-AM], “Other specified chronic obstructive pulmonary disease”), have a record of being prescribed medication for COPD (for at least 6 months a year) and have had at least one consultation by a specialist in pulmonology. There were 4834 such individuals (1.37% of the initial sample aged 40 to 79) and only their data were used for further analysis. Among the excluded patients, 316 463 had no diagnosis of COPD, 17,466 had a diagnosis of COPD, but did not meet the required criteria and 15,017 had COPD codes that were not J44.8.

## Variable Selection

To better differentiate among the conditions that co-occur with COPD during the second half of adulthood from those existing over the course of an individual’s life, all comorbid disorders had to be recorded during the study period (during medical visits or hospitalizations). All neurological and psychiatric comorbidities were identified only by diagnostic ICD-10-AM codes throughout the medical record data. Some disorders, however, were present in single cases (eg obsessive compulsive or eating disorders) and/or were judged to have too little value to be explored in the context of COPD (eg tic disorder). We chose to omit such disorders from the analysis. Stroke was classified as either ischemic or hemorrhagic by using codes I63-I64 and I60-I61, respectively, as proposed by Woodfield et al (presuming that most undetermined strokes are ischemic).<sup>29</sup>

Additional variables have been selected for context (eg as risks factors to be associated with stroke). They included diagnosis of tracheal or lung cancer (C33-C34), hypertension (I10-I15), type II diabetes mellitus (E11.01–E11.9, only with prescribed medication and a recorded endocrinologist consultation), ischemic heart disease (I20-I25, only with a recorded cardiologist consultation), arrhythmias (I44–I49, only with a recorded cardiologist consultation) or heart failure (I50.0–I50.9, only with a recorded cardiologist consultation). Information about the number of hospital admissions, total hospital stay and patient disability status was also available.

## Statistical Analysis

Exploratory factor analysis (EFA) was performed in search of variables underlying the neurological and

psychiatric multimorbidity profiles in COPD. EFA is the proposed method when it is assumed that distinct health conditions are causally related and represent a continuum of pathological processes.<sup>30</sup> EFA was based on a tetrachoric correlation matrix from the binary comorbidity data (“1” – a condition is present, “0” – a condition is absent). To be included as variables, comorbidities had to be present in two or more percent of the patient sample or the patient subgroup in question. Being unaware of any existing guidelines for methods of selection of distinct diagnostic categories for EFA, we grouped diagnoses by ICD-10-AM codes according to two principles. First, if one condition was predominant in a group of ICD-coded disorders, we sought not to group it with other disorders that are heterogeneous in their etiology, mechanism and/or manifestation. For example, the group of different movement disorders was largely represented by Parkinson’s disease, which was thus selected for EFA. Secondly, we combined the coded disorders into groups if they have a similar impact on the patient’s health or have a similar etiology. For instance, nerve, nerve root or plexus disorders mostly manifest as pain or reduced mobility almost irrespectively of the affected region (eg whether they are cervical, thoracic or lumbar root disorders).

The number of factors extracted was based on Eigenvalues exceeding the value of 1.0 and the evaluation of a scree plot. The factor loadings were interpreted after performing an oblique oblimin rotation. A cutoff value of  $>0.30$  was used to determine the inclusion of factor loadings into a comorbidity profile. If the Heywood phenomenon occurred (factor loading  $\geq 1.00$ ), the variable in question was eliminated and the procedure repeated to improve model fit. To state the obtained sampling adequacy, we employed the Kaiser-Meyer-Olkin (KMO) criterion ( $<0.50$  being unacceptable).

The benefits of additional stratification by age in EFA of multimorbidity profiles is unclear.<sup>30</sup> Given that the patient sample was already limited to ages between 40 and 79, we did not split the study sample into additional age groups. However, we anticipated variation in the discrete COPD comorbidities between genders. Therefore, additional EFA was performed for male and female subgroups.

Microsoft Excel 16.0 was used for descriptive statistics and the creation of graphs. IBM SPSS 23.0 was used for  $\chi^2$  and Mann–Whitney *U*-tests. We employed STATA 13.0 for EFA.

## Results

In the sample of 4834 patients with COPD, around two thirds were male. The number of patients in different age groups is seen in Figure 1. Patient characteristics and comorbidity data are presented in Table 1. We identified 2767 (57.2%) patients that had been diagnosed with at least one neurological or psychiatric disorder (including stroke). Among the neurological and psychiatric comorbidities, most prevalent were nerve, nerve root and plexus disorders (n=1439, 29.8%), sleep disorders (n=666, 13.8%), transient ischemic attack (n=545, 11.3%), depression (n=364, 7.5%) and ischemic stroke (n=349, 7.2%). Being diagnosed with a transient ischemic attack was associated with hypertension (OR=2.218, 95% CI from 1.429 to 3.443). Recorded ischemic stroke episodes were related to both hypertension (OR=2.117, 95% CI from 1.262 to 3.754) and arrhythmias (OR=1.343, 95% CI from 1.030 to 1.752). The rate of distinct neurological and psychiatric comorbidities varied between men and women, the former more frequently presenting with alcohol-use related disorders ( $p<0.0001$ ) and ischemic stroke ( $p=0.001$ ), the latter – with depression, anxiety and somatoform disorders, sleep, headache, nerve, nerve root and plexus disorders, and transient ischemic attack ( $p<0.0001$  for all). Trends of comorbidity frequency and prevalence throughout age groups are presented in Table 2 and Figure 2, respectively.

Results from EFA of comorbidity patterns based on data from all patients are seen in Table 3. The Kaiser-Meyer-Olkin (KMO) measure was 0.6738 (mediocre). Based on Eigenvalues, two factors have been extracted. The first factor groups disorders whose prevalence increases with age (except

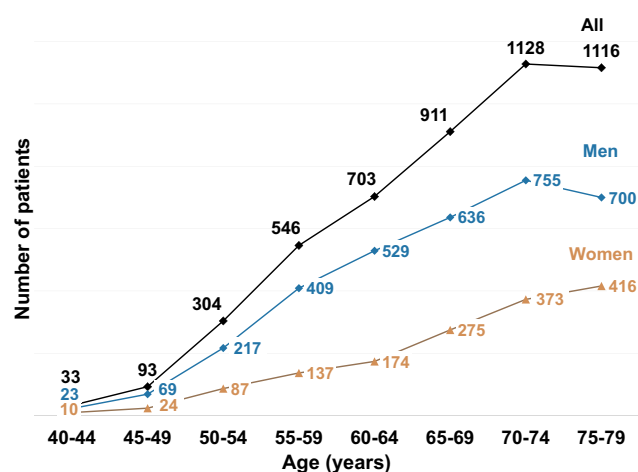


Figure 1 Patients with confirmed COPD in different age groups.

for epilepsy) and reveals a pattern of mostly neurodegenerative-cerebrovascular comorbidities. The second pattern matrix included psychiatric and sleep disorders. To better quantify the relationship between the neurodegenerative-cerebrovascular disorders and epilepsy (variables in the first factor), odds ratios were calculated. The odds ratios of being diagnosed with epilepsy were significantly increased with co-existent Parkinson's disease (OR=3.624, 95% CI from 1.903 to 6.903), dementia (OR=4.130, 95% CI from 2.352 to 7.253), transient ischemic attack (OR=2.440, 95% CI from 1.606 to 3.707) and ischemic stroke (OR=3.051, 95% CI from 1.931 to 4.819).

When performing EFA with data from male patients, a Heywood case was obtained for Parkinson's disease. After omitting this variable, patterns of dementia-sleep-psychiatric comorbidities and dementia-epilepsy-cerebrovascular disease emerged with a KMO measure of 0.5923 (Table 4) and were similar to those obtained from EFA of all patient data. While EFA results from female individuals (Table 5) pointed to a mediocre sampling adequacy (KMO=0.6957), two variables had been excluded before the analysis. Besides, only one factor was extracted and factor loadings in the matrix did not outline a clear clinical profile.

## Discussion

### General Findings

The prevalence of COPD (1.37%) was lower than could be expected from other reports, probably because of the conservative inclusion criteria in the current study.<sup>1,31</sup> By including only patients who required medical consultations and treatment for COPD, we shifted the focus towards exploring comorbidities among individuals with more active forms of COPD. The male/female ratio was 2.2 – higher than that of around 1.5 observed in other studies and could also be partly explained by the sample selection strategy (ie more severe COPD).<sup>32,33</sup> Our findings indicate a relatively sharp increase in both COPD and some of its neurological and psychiatric comorbidities with older age. Cerebrovascular, neurodegenerative and sleep disorders followed a positive trend when presented both in absolute estimates and in relative measures of prevalence among individuals in selected age groups. Gender differences were consistent with findings from other studies: women were more likely to suffer from sleep, anxiety problems, mood disorders and headaches.<sup>32,34</sup> Evaluating the prevalence of the neurological and psychiatric disorders in COPD in comparison to a control group was beyond the scope of our study.

**Table 1** Patient Characteristics and Comorbidity Data by Gender (Disorders with Prevalence <1% Have Been Omitted)

		All Patients	%	Men	%	Women	%	Significance
		4834		3338	69.1	1496	30.9	
Continuously using COPD medication for 180 days		761	15.7	588	17.6	173	11.6	<0.0001
Recorded disability with COPD being the primary of secondary cause		428	8.9	343	10.3	85	5.7	<0.0001
		Median	Range	Median	Range	Median	Range	
Age		69	40–79	68	40–79	70	40–79	<0.0001
Hospital admissions		1	0–26	1	0–26	0	0–19	<0.0001
Total hospital stay (days)		4	0–273	6	0–273	0	0–209	<0.0001
Selected comorbidities (not neurological or psychiatric)	Code (ICD-10-AM)	N	%	N	%	N	%	
Type 2 diabetes	E11.01–E11.9	609	12.6	419	12.6	190	12.7	0.886
Heart failure	I50.0– I50.9	698	14.4	491	14.7	207	13.8	0.425
Arrhythmias	I44–I49	846	17.5	605	18.1	241	16.1	0.088
Ischemic heart disease	I20–I25	1869	38.7	1326	39.7	543	36.3	0.024
Hypertension	I10–I15	4446	92.0	3012	90.2	1434	95.9	<0.0001
Tracheal and lung cancer	C33–C34	186	3.8	159	4.8	27	1.8	<0.0001
<b>Neurological and psychiatric comorbidities</b>								
Dementia (including Alzheimer's disease)	F00–F03, G30	159	3.3	104	3.1	55	3.7	0.312
Mental and behavioral disorders due to psychoactive substance use	F10–F19	88	1.8	78	2.3	10	0.7	<0.0001
Alcohol related disorders	F10	71	1.5	66	2.0	5	0.3	<0.0001
Mood disorders	F30–F39	370	7.7	165	4.9	205	13.7	<0.0001
Depression	F32–33	364	7.5	162	4.9	202	13.5	<0.0001
Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders	F40–F48	292	6.0	144	4.3	148	9.9	<0.0001
Phobic and other anxiety disorders	F40–F41	158	3.3	84	2.5	74	4.9	<0.0001
Somatoform disorders	F45	98	2.0	37	1.1	61	4.1	<0.0001
Sleep disorders (all)	F51, G47	666	13.8	408	12.2	258	17.2	<0.0001
Sleep disorders not due to a substance or known physiological condition	F51	298	6.2	185	5.5	113	7.6	0.007
Sleep disorders	G47	403	8.3	244	7.3	159	10.6	<0.0001
Extrapyramidal and movement disorders	G20–G26	185	3.8	107	3.2	78	5.2	0.001
Parkinson's disease	G20	128	2.6	69	2.1	59	3.9	<0.0001
Epilepsy	G40	130	2.7	95	2.8	35	2.3	0.314
Headache disorders	G43–G44	119	2.5	49	1.5	70	4.7	<0.0001
Headache disorders others than migraine	G44	110	2.3	48	1.4	62	4.1	<0.0001
Nerve, nerve root and plexus disorders	G50–G59	1439	29.8	911	27.3	528	35.3	<0.0001
Lower back pain	G54.1; G54.4; G55.1	877	18.1	555	16.6	322	21.5	<0.0001
Brachial plexus disorders	G54.0	75	1.6	41	1.2	34	2.3	0.007
Cervical root disorders	G54.2	290	6.0	155	4.6	135	9.0	<0.0001
Thoracic root disorders	G54.3	213	4.4	122	3.7	91	6.1	<0.0001

(Continued)



**Table 1** (Continued).

		All Patients	%	Men	%	Women	%	Significance
		<b>4834</b>		<b>3338</b>	<b>69.1</b>	<b>1496</b>	<b>30.9</b>	
Carpal tunnel syndrome	G56.0	76	1.6	49	1.5	27	1.8	0.384
Other mononeuropathies	G58	93	1.9	65	1.9	28	1.9	0.860
<b>Polyneuropathies and other disorders of the peripheral nervous system</b>	G60-G64	124	2.6	93	2.8	31	2.1	0.147
<b>Transient ischemic attack</b>	G45	545	11.3	290	8.7	255	17.0	<0.0001
<b>Ischemic stroke</b>	I63, I64	349	7.2	269	8.1	80	5.3	0.001

**Abbreviations:** ICD-10-AM, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification; N, number of patients, broader disease categories are presented in bold.

Nevertheless, national prevalence data from the Health Statistics Portal of Institute of Hygiene of Lithuania from 2014 pointed to large differences in the rate of most neurological and psychiatric diseases between our sample and the general population of the same age. To name some, the estimates were 3.3% vs 0.8% for dementia, 7.5% vs 2.5% for depression, 2.7% vs 1.0% for epilepsy, 29.8% vs 8.5% for nerve, nerve root and plexus disorders, 2.6% vs 0.4% for polyneuropathies, 11.3% vs 1.8% for transient ischemic attack, 7.2% vs 0.9% for stroke, respectively.<sup>35</sup> The extent of these dissimilarities indicates that disorders from the whole spectrum of neurological and psychiatric disease, rather than distinct conditions, can be relevant in COPD.

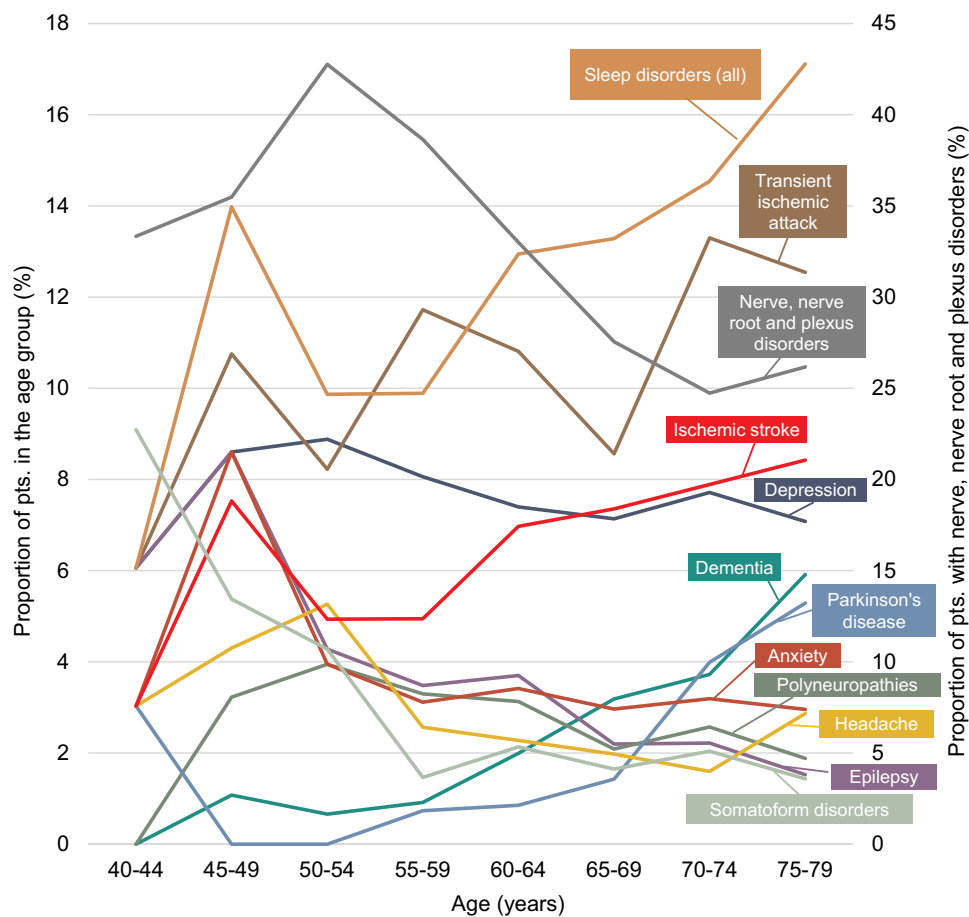
### The Pattern of Epilepsy, Neurodegenerative and Cerebrovascular Disease

Exploratory factor analysis revealed two possible latent variables that underlie the neurological and psychiatric

comorbidities in COPD. One of them grouped dementia, Parkinson's disease, epilepsy, ischemic stroke and transient ischemic attack. A question regarding this factor could be whether it represents mainly the process of ageing with COPD or some discrete pathological mechanisms. The two explanations are probably interrelated, especially if ageing is understood as progressive decline in body function. In this sense, patients with COPD have been shown to age faster because of the earlier onset of COPD comorbidities.<sup>12,36</sup> The specific pathways associating COPD and its comorbidities have not been fully elucidated. It is hypothesized that shared risk or genetic factors, chronic hypoxia, oxidative stress and systemic inflammation underlie the increased risk of co-occurring pathologies in COPD. The link between COPD and cerebrovascular disease is probably easier to explain because of the evidence of vascular impairment in COPD. Increase in molecules related to inflammation "spill-over" from the lungs

**Table 2** Frequencies of the Selected Disorders (Overall Prevalence  $\geq$  2%) in Different Age Groups

Disorders	Age Group (Years)								Total
	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	
Nerve, nerve root and plexus disorders	11	33	130	211	232	251	279	292	1439
Sleep disorders (all)	2	13	30	54	91	121	164	191	666
Transient ischemic attack	2	10	25	64	76	78	150	140	545
Ischemic stroke	1	7	15	27	49	67	89	94	349
Depression	2	8	27	44	52	65	87	79	364
Dementia	0	1	2	5	14	29	42	66	159
Parkinson's disease	1	0	0	4	6	13	45	59	128
Anxiety	1	8	12	17	24	27	36	33	158
Headache	1	4	16	14	16	18	18	32	119
Polyneuropathies	0	3	12	18	22	19	29	21	124
Epilepsy	2	8	13	19	26	20	25	17	130
Somatoform disorders	3	5	13	8	15	15	23	16	98



**Figure 2** Prevalence of the selected disorders (overall prevalence  $\geq 2\%$ ) in different age groups. Please note that nerve, nerve root and plexus disorders are plotted on a secondary axis.

(eg C reactive protein, interleukin-6) or reactive oxygen species might represent damage to the endothelium, which promotes atherosclerosis and results in an increased risk of

stroke.<sup>37,38</sup> It can only be speculated what groups ischemic stroke and transient ischemic attack with Parkinson’s disease, dementia and epilepsy. Systemic inflammation and

**Table 3** Factor Loadings for the Selected Variables (Disorders with Prevalence  $\geq 2\%$ ) When Analysis Was Performed with Data from All Patients in the Sample (KMO=0.6738)

Comorbidity	Factor 1	Factor 2
Dementia	<b>0.5595</b>	0.0492
Depression	0.2760	<b>0.4929</b>
Phobic and other anxiety disorders	-0.1090	<b>0.7867</b>
Somatoform disorders	0.0546	<b>0.5256</b>
Sleep disorders (all)	0.2165	<b>0.4225</b>
Parkinson’s disease	<b>0.4702</b>	-0.0415
Epilepsy	<b>0.5087</b>	-0.1395
Headache disorders	0.2710	0.2425
Nerve, nerve root and plexus disorders	0.1476	0.2385
Polyneuropathies, other PNS disorders	0.0458	0.1190
Transient ischemic attack	<b>0.5882</b>	0.0944
Ischemic stroke	<b>0.5686</b>	-0.0842

**Note:** Factor loadings  $>0.30$  are highlighted.  
**Abbreviation:** PNS, peripheral nervous system.

**Table 4** Factor Loadings for the Selected Variables (Disorders with Prevalence  $\geq 2\%$  in the Group) When Analysis Was Performed with Data from Male Patients (KMO=0.5923)

Comorbidity	Factor 1	Factor 2
Dementia	<b>0.3461</b>	<b>0.4680</b>
Alcohol related disorders	<b>0.3731</b>	0.2229
Depression	<b>0.6467</b>	-0.0107
Phobic and other anxiety disorders	<b>0.6380</b>	-0.1237
Sleep disorders (all)	<b>0.5231</b>	0.0844
Epilepsy	-0.0996	<b>0.5860</b>
Nerve, nerve root and plexus disorders	0.1602	0.0324
Polyneuropathies, other PNS disorders	0.1482	-0.0445
Transient ischemic attack	-0.0252	<b>0.5618</b>
Ischemic stroke	-0.0219	<b>0.6768</b>

**Notes:** Note that Parkinson’s disease has been excluded because it yielded a Heywood case (factor loading  $>1.0$ ). Factor loadings  $>0.30$  are highlighted.  
**Abbreviation:** PNS, peripheral nervous system.

**Table 5** Factor Loadings for the Selected Variables (Disorders with Prevalence  $\geq 2\%$  in the Group) When Analysis Was Performed with Data from Female Patients (KMO=0.6957)

Comorbidity	Factor I
Dementia	<b>0.3970</b>
Depression	<b>0.4011</b>
Somatoform disorders	<b>0.4118</b>
Sleep disorders (all)	<b>0.3445</b>
Parkinson's disease	<b>0.3931</b>
Epilepsy	<b>0.5853</b>
Headache disorders	<b>0.3809</b>
Nerve, nerve root and plexus disorders	<b>0.3511</b>
Transient ischemic attack	<b>0.3952</b>
Ischemic stroke	-0.0089

**Notes:** Note that disorder groups of "phobic and other anxiety disorders" and "polyneuropathies and other disorders of the peripheral nervous system" have been excluded because they yielded Heywood cases (factor loading > 1.0). Factor loadings > 0.30 are highlighted.

a dysfunctional reaction to hypoxia (eg lower levels of hypoxia inducible factor-1) might contribute to the more frequent development of Parkinson's disease in COPD.<sup>39</sup> Similar pathological pathways, including systemic inflammation, oxidative stress, chronic hypoxia, hypercapnia, previous cerebrovascular events, could be important in developing dementia.<sup>40,41</sup> Epilepsy may be thought to represent seizures associated with neurodegeneration, those secondary to cerebrovascular events or both (as in vascular dementia).<sup>42-46</sup> Overall, the relationship between the discrete pathologies grouped under this factor is probably highly complex with multiple features causing vascular and neural impairment. Future research could investigate mitigation strategies for vascular damage and associated neurological outcomes in COPD.

## The Pattern of Psychiatric and Sleep Comorbidities

Both anxiety and depression are known to be frequent in COPD. While being distinct psychiatric disorders, they are often present at the same time and have also been found to be related to the level of manifestation of somatic symptoms.<sup>20,47,48</sup> Impaired sleep is also a significant comorbidity of COPD.<sup>22</sup> An obstructive sleep apnea-COPD overlap syndrome can even be recognized as a separate diagnostic entity with effects common for both conditions, such as increased hypoxia and propagation of inflammatory processes.<sup>49</sup> The link between sleep disorders, depression and anxiety in COPD has already been proven earlier and replicated in the exploratory analysis of

this current study.<sup>50,51</sup> Further, sleep disturbances in COPD can also be associated with cognitive deficits.<sup>25</sup> We revealed the possibility of such a relationship only among men with COPD – in their case, dementia was included in both factor matrices (along both neurological and psychiatric conditions). The psychiatric-sleep pattern of COPD comorbidities could be relevant from a purely practical standpoint: targeting poor sleep in COPD might be directly beneficial in reducing the patient's psychiatric symptoms.<sup>52</sup>

## Study Limitations

Numerous limitations ought to be stated regarding our study. The source of our data consisted of medical records from the database of the National Health Insurance Fund of Lithuania, which had not been intentionally designed for observational studies. It is thus possible that some conditions were under- or overreported because of various reasons, including insurance policy to reimburse services only after a specific diagnosis is made, presumable stigmatization of some conditions (eg depression) and less accurate reporting in case of multimorbidity. The retrospective nature of our study did not allow selecting patients with COPD according to clinical criteria. Consequently, some patients with less severe forms of COPD had possibly been excluded from the sample. Associations between the various disorders in COPD should be regarded with caution as they depend on ad hoc grouping of nosological entities and a subjective interpretation of the possible underlying latent factors. That is, the statistical methods employed do not provide direct evidence of causative relationships between comorbidities.

## Conclusion

This study reveals that the prevalence of ischemic stroke, transient ischemic attack, sleep disorders, dementia and Parkinson's disease tends to increase with age in patients with COPD. There are two possible patterns grouping neurological and psychiatric comorbidities in COPD. One consists of cerebrovascular events, neurodegenerative disorders (dementia and Parkinson's disease) and epilepsy, the other comprises psychiatric comorbidities and sleep disorders. While these comorbidity profiles were similar in the male subgroup, our study did not manage to prove their existence among women with COPD. Our findings point to the need for further evaluation, whether inflammatory determinants, reactive oxygen species, vascular damage or some other pathological mechanisms could be



central to the co-occurrence of neurological disorders in COPD. Impaired sleep in COPD might influence worse psychiatric outcomes, although a bidirectional relationship between the two should be considered as well. Recognition of the neurological and psychiatric comorbidity patterns in neurological practice could direct care towards preventing vascular events and consider more attention to psychiatric conditions alongside complaints of impaired sleep (and vice versa).

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## Disclosure

The authors report no conflicts of interest for this work.

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