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Chronic obstructive pulmonary disease and anxiety disorders: a nationwide population-based study in Taiwan☆

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ABSTRACT

Objective: Few studies have investigated the relationship between chronic obstructive pulmonary disease (COPD) and anxiety disorder outcomes. We sought to investigate the association in a large national sample.
Methods: Cases were identified from Taiwan's National Health Insurance Research Database who were aged 15 years and above, with a new primary diagnosis of COPD (International Classification of Diseases, Ninth Revision codes: 491, 492, 494 and 496) between 2000 and 2007. The 29,951 cases identified were compared to 29,951 controls matched on sex, age, urban/rural residence and socioeconomic status based on insurance premium. Both groups were followed until the end of 2008 for instances of anxiety disorders. Competing risk-adjusted Cox regression analyses were applied, adjusting for matching variables, Charlson comorbidity index, hospital admission days and daily dose of prednisone.
Results: Of the 59,902 subjects, 3951 were found to have anxiety disorders during a mean (SD) follow-up period of 5.5 (2.5) years. COPD, female, urban residence, lower dose of prednisone use, depressive disorders and higher outpatient visits were independent predictors of incident anxiety disorder.
Conclusions: COPD was associated with increased risk of an anxiety disorder diagnosis, independent of a number of potential confounding factors.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease characterized by airflow limitation with a progressive and not fully reversible course [1]. COPD affects 329 million people or nearly 5% of the population worldwide. In 2011, it ranked as the fourth leading cause of death, killing over 3 million people [2]. COPD also impairs daily activities, social functioning and quality of life and is associated with increased healthcare costs due to its complex psychological comorbidities, as well as lengthy disease course [3,4]. Among psychological comorbidities, depression and anxiety [5–7] are frequent and more common in patients with COPD than the general population [8]. Although the relationships between COPD and anxiety have been considered, most research has been limited to cross-sectional studies of relatively small samples and use of screening questionnaires rather than physician diagnoses. A recent systematic review cited 10 studies that had diagnosed anxiety disorders from a clinical interview using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, or previous versions of *Diagnostic and Statistical Manual of Mental Disorders*, or International Classification of Diseases, Tenth Revision [9]. This article concluded that the prevalence of clinical anxiety in patients with COPD ranged from 10% to 55% among inpatients and from 13% to 46% among outpatients. However, among these studies, only four used comparison groups, suggesting raised prevalence in COPD [10–13]. In Asia, a recent case–control study [14] found a 3-fold higher risk of anxiety disorder in COPD than controls (18.3% vs. 5.3%) in China, but no population-based cohort study has yet been reported in Asia. In addition, the association of prednisone with anxiety remains controversial with inconsistent results [15–18] with previous studies limited by cross-sectional design and small sample sizes. We describe what we believe to be the first

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Asian population-based cohort study to investigate the role of COPD in the subsequent development of anxiety disorder, as well as the first population-based cohort study to investigate the association between prednisone and anxiety.

2. Material and methods

2.1. Sample

A retrospective cohort study was assembled using data from the Taiwan's National Health Insurance Research Database (NHIRD) provided by that country's National Health Research Institute (NHRI) that included outpatient, ambulatory and hospital inpatient care, as well as dental services. The National Health Insurance (NHI) program provides compulsory universal health insurance, implemented from March 1995, covering all delivery of healthcare in 98% of the national population. In cooperation with the Bureau of NHI, the NHRI extracted a randomly sampled representative database of 1,000,000 people from the year 2005 registry of all NHI enrollees using a systematic sampling method for research purposes, forming the Longitudinal Health Insurance Database. There are no statistically significant differences in age, sex or healthcare costs between this sample and all enrollees [19].

COPD cases were identified based on recorded International Classification of Diseases, Ninth Revision (ICD-9) codes of 491, 492, 494 and 496. All medical claims made under this diagnostic code from 1997 to 2008 were collected from NHIRD for further analysis. The definition of COPD for this analysis required an inpatient diagnosis and/or at least 1-year duration of diagnosed COPD from outpatient services, a definition consistent with other research using this database [20]. To define new cases, people who had received any COPD diagnosis in the medical claim data from 1997 to 1999 were excluded from the analysis. In this way, 29,951 new COPD cases aged more than 15 years were identified. For assessing the association between COPD and anxiety disorder risk, one control per case was randomly sampled from the remaining sample, matching for sex, age within 1 year, urban/rural residence and insurance premium (a marker of socioeconomic status; see below). Both cases and controls were followed for diagnosed anxiety disorder as an outcome. Anxiety disorders were defined in this study on the basis of ICD-9 codes 300.0, 300.01, 300.02, 300.2, 300.21, 300.23 and 300.3. All study patients without anxiety disorder diagnosis before the index date. The index date was the first COPD diagnosis date, and this was also assigned to the respective matched controls, who were NHI enrollees without an anxiety disorder diagnosis before the index date.

Covariates considered in this analysis included age, sex, area of residence (urban/rural), insurance premium, prednisone use, Charlson comorbidity index and hospital admission days. The insurance premium served as an indicator of economic status and was classified into one of three categories: fixed premium and dependent, monthly income less than 20,000 New Taiwan Dollars (NTD) and 20,000 NTD or more (1 USD = 32.1 NTD in 2008). The fixed premium group comprised those requiring social welfare support, which included low-income citizens and veterans. The 'dependent' insurance group referred to family members who did not have a fixed salary income. Only prednisone use for at least 1 year was classified as use. The annual average cumulative defined daily dose (DDD) of prednisone was calculated and divided into three groups (0, 1–29 and 30 +). The DDD recommended by the WHO is a unit for assessing the standard dose of drug. Cumulative DDD, which indicates the exposed duration of drug use for a period, was estimated as the sum of dispensed DDDs of a drug within a time period. The annual average cumulative DDD was used to assess the dose usage of prednisone in the follow-up time period. General physical health was quantified using the Charlson comorbidity index that comprises a summation of diseases weighted on the basis of their association with mortality [21] as of the index date "Hospital admission days" for any disorder during any period was also included as an indicator of general health. The Charlson comorbidity index and hospital admission days were measured prior to the outcome since 1997.

2.2. Statistical analysis

Death prior to anxiety disorder was considered as a competing risk event. The death date was retrieved from the national mortality database. The death-adjusted cumulative incidences of anxiety disorder were calculated using the Fine and Gray method [22]. Each person's first presentation within the study period was used in the calculation of outcome risk over given time intervals. The risk of anxiety disorder during the follow-up period was calculated using survival analysis, with the time function represented by the number of years from the index date of COPD diagnosis to December 31, 2008 (end of follow-up) or until the date of death or migration if earlier. Competing risk-adjusted Cox regression models [22] were fitted to estimate associations between COPD and anxiety disorder, adjusting for covariates. All data management was performed using SAS 9.3 software (SAS Institute Inc., Cary, NC, USA). Calculations of cumulative incidences and Cox models in the competing risk analysis were carried out using the R package "cmprsk" [23].

Time-dependent Cox regression model was used for multivariate assessment of prednisone use on anxiety disorder by controlling the potential confounding covariates. Instead of modeling prednisone as a cumulative effect by calculating the cumulative annual average DDD during the follow-up period, time-dependent model can take dynamic changing of prednisone use into account by assessing the yearly DDD of prednisone use effect during the following period in this study. Hazard ratios (HRs) and 95% confidence interval (CI) for bipolar were reported and comparing to the main analysis.

We classified anxiety diagnosis as two categories: (1) 300.0 (anxiety state) (2) 'specified anxiety', including 300.01 (panic disorder), 300.02 (generalized anxiety disorder), 300.2 (phobic disorders), 300.21 (agoraphobia), 300.23 (social anxiety disorder) and 300.3 (obsessive–compulsive disorder). Besides, we also classified anxiety diagnosis as 'diagnosed by psychiatrist' and 'diagnosed by other physician'. The frequency of these two kinds of classification was reported. In order to reveal these diagnosis effects on our results, we performed sensitivity analysis that only focused on 'specified anxiety' and 'diagnosed by psychiatrist', respectively. The anxiety state and 'diagnosed by other physician' type of anxiety were considered as competing event and adjusted by competing Cox regression model.

3. Results

The two cohorts consisted of 29,951 people with newly diagnosis COPD and 29,951 matched controls ascertained from the database covering 2000–2007. Cohort characteristics are described and compared in Table 1. Of the COPD cases, 60% were male and highest numbers were in the 65 + year range. More than 70% were urban residents and one third were receiving social welfare support or were dependent on their family. The COPD cohort used steroid during follow-up more frequently than the control cohort. The mean Charlson comorbidity index, hospital admission days and outpatient visits were higher in the COPD cohort than in the control cohort (t test $P<.001$).

Of the total 59,902 subjects, 3951 received a diagnosis of an anxiety disorder during the surveillance period: 2735 (9.13%) in the COPD cohort and 1216 (4.06%) in the control cohort. The mean (SD) follow-up interval for all subjects was 5.5 (2.5) years (Table 1). The anxiety disorder incidence for the COPD cohort was 1674.3 per 10^5 person-years (95% CI: 1612.1–1738.3) and that for the control cohort was 744.4 per 10^5 person-years (95% CI: 703.2–787.5). Kaplan–Meier analysis of cumulative incidence showed that patients with COPD had a significantly higher rate of incident anxiety disorders than the non-COPD group ($P<.001$; modified log-rank test) (Fig. 1).

Analyses of associations of interest are summarized in Table 2. In the fully adjusted Cox regression model from the competing risk analysis,