# ­Unemployment in chronic airflow obstruction around the world: Results from the BOLD study

Running head: Unemployment in CAO

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**Take home message:**

Chronic airflow obstruction increases risk of unemployment, and is a burden to welfare systems worldwide.

# Abstract

**Objectives:** We aimed to examine associations between chronic airflow obstruction (CAO) and unemployment across the world.

**Methods:** Cross-sectional data from 26 sites in the Burden of Obstructive Lung Disease (BOLD) Study were used to analyze effects of CAO on unemployment. Odds ratios (OR) for unemployment in subjects 40-65 years old were estimated with multilevel mixed-effects generalized linear model with study site as random effect. Site-by-site heterogeneity was assessed using individual participant data meta-analyses.

**Results:** Of 18710 participants, 11.3% had CAO. Ratio of unemployed subjects with CAO divided by subjects without CAO showed large site discrepancies, though these were no longer significant after adjusting for age, sex, smoking and education. Site-adjusted OR for unemployment (95%CI) was 1.79 (1.41, 2.27) for CAO cases, decreasing to 1.43 (1.14, 1.79) after adjusting for sociodemographic factors, comorbidities and forced vital capacity. Of other covariates that were associated with unemployment, age and education were important risk factors in high-income sites (OR (95%CI) 4.02 (3.53, 4.57) and 3.86 (2.80, 5.30) respectively), while female gender was important in low-to-middle-income sites (OR 3.23 (2.66, 3.91)).

**Conclusions:** In the global BOLD study, CAO was associated with increased levels of unemployment, even after adjusting for sociodemographic factors, comorbidities and lung function.

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# Introduction

Chronic Airflow Obstruction (CAO) is the primary characteristic of patients with Chronic Obstructive Pulmonary Disease (COPD) and affects up to one in five adults depending on where they live, according to data from the Burden of Obstructive Lung Disease (BOLD) Study (1). COPD is expected to keep its position as the third most important cause of death worldwide (2), and imposes a substantial burden on quality of life (3) and healthcare utilisation (4). So far, data on productivity-related burden of CAO or COPD have been scant (4).

Only three population-based studies have provided employment rates in CAO (5–7). Erdal et al. showed that 55% of individuals with CAO from a general Norwegian population were in a paid job, versus 87% of controls without CAO. However, controls were younger and had higher education, and the authors did not examine employment in multivariate analyses (5) Jansson et al. examined CAO specific disability in northern Sweden, but did not include a control group and did not report employment rates (6). In the PLATINO study carried out in five Latin-American countries, Montes de Oca et al. showed that the workforce participation amongst subjects with CAO was lower than in healthy subjects (41.8% vs 57.1%). However, in multivariable analyses they found that higher age, dyspnea, number of comorbid conditions, female gender and lower education were associated with unemployment, whereas CAO was only of borderline significance (7).

The Burden of Obstructive Lung Disease study is a large international study providing population-based estimates of prevalence and burden of CAO. One of the primary objectives of the BOLD study is to estimate disease burden in terms of activity limitation and economic impact (8). In the current analysis, we have compared estimates of employment status in BOLD participants with and without CAO across the world.

# Methods

The BOLD protocol has been published previously (8). It was written in compliance with the Helsinki declaration and is approved by local ethics committees at all sites. All participants provided written consent.

## Population

All participating sites were recruited from well-defined administrative areas with the goal of providing representative samples of the local population of at least 600 non-institutionalized persons 40 years or older. The current report includes participants from 26 sites (see online supplement). Of 22,118 participants providing interview data, 18,710 performed acceptable post-bronchodilator spirometry and were included in the descriptive part of the current analysis. When analyzing risk for unemployment as outcome, however, all subjects aged 65 or older (defined here as retirees) and homemakers/caregivers were excluded. After excluding these subjects, there were no CAO cases left in Tirana (Albania), so this centre is not part of the analyses assessing the effect of CAO on unemployment. The online repository lists sampling strategy and response rates for all sites (E-table 1).

## Data collection

The BOLD study is a cross-sectional study based on a structured, face-to-face interview using standardized questionnaires and pre/post bronchodilator spirometry. All study coworkers were trained and certified by BOLD coordinating centers.

The interviews gathered information on smoking habits, education, job status, self-reported comorbidities (hypertension, heart disease, diabetes, stroke, lung cancer), and respiratory symptoms (dyspnea, wheezing, chronic bronchitis).

Participants indicated whether they worked for income at any time in the preceding year or if they served as full-time homemakers/caregivers during that timeframe. Since retirement was not formally captured under occupation, we excluded anyone aged 65 or older from analyses involving employment status. All other individuals not being categorized as working, homemakers/caregivers or retirees were defined as unemployed. The main outcome for the current study was a dichotomous employment status where retirees (65 years or older) and homemakers/caregivers were excluded.

Never-smokers were individuals who had smoked <20 packs of cigarettes during their lifetime, or <1 cigarette daily for a year. Ex-smokers were those who reported an age at which they had stopped smoking. Education was categorized according to highest level of completed schooling and divided into no schooling, primary school, middle school, high school, some college, and completed college/university.

Dyspnea was defined using the modified Medical Research Council questions (grades 0-4, see online supplement for details) (9). Subjects reporting being unable to walk for reasons other than breathing problems were excluded from the dyspnea variable. Wheezing was defined as attacks of wheezing associated with dyspnea in the last 12 months. Chronic bronchitis was defined as productive cough on most days in three months a year for at least two consecutive years.

Post-bronchodilator spirometry was performed by a hand-held spirometer (EasyOne, ndd Medizintechnik AG, Zürich, Switzerland) according to ATS standards (10), before and at least 15 minutes after inhalation of 200 mcg salbutamol through a large-volume spacer. For quality control, all individual maneuvers were reviewed by a pulmonary function reading centre.

Predicted values of forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC were estimated from equations for Caucasians from the third National Health and Nutrition Examination Survey (NHANES-III) (11). Spirometric CAO was defined as post-bronchodilator FEV1/FVC < lower limit of normal (LLN).

## Analysis

The sample size of the BOLD study was set to be able to provide robust CAO prevalence estimates at the individual sites (8). No power calculations were performed *a priori* for employment status.

For unadjusted comparisons of individuals with and without CAO, we used Pearson chi-square (categorical variables) and t-tests (continuous variables). To illustrate differences in unemployment and CAO in different parts of the world, we stratified descriptive analyses by high-income sites (Sydney, Salzburg, Vancouver, London, Tartu, Hannover, Reykjavik, Maastricht, Bergen, Krakow, Lisbon, Uppsala, Lexington) and low-to-middle-income sites (Guangzhou, Mumbai, Pune, Manila, Nampicuan Talugtug, Annaba, Cape Town, Adana, Kashmir, Sousse, Ife, Fes). Income categories were based on the Gross National Income Per Capita of the country (GNIPC), with the cut point between low-to-middle income and high-income being GNIPC 10 000 US$. (12). We also calculated a risk ratio for unemployment associated with CAO as the prevalence of unemployment in CAO-subjects divided by the prevalence of unemployment in non-CAO subjects, using a log-binomial generalized linear model (in Stata specified as *glm* with *fam(bin)* and *link(log)*). A risk ratio >1 indicates higher risk of unemployment associated with CAO, while a ratio <1 indicates lower risk of unemployment associated with CAO. To illustrate gender differences in CAO status across sites, we tabulated study sites and CAO status, stratified by gender.

Multivariable analyses for the pooled data-set were conducted using multilevel mixed-effects generalized linear model (see online supplement for details). An alternative approach would be a fixed-effect model. The difference to the chosen mixed-effects approach, would be that the latter treats the sites as a random sample of all possible sites, whereas the former would tend to focus more exclusively on the sites that were included in the study. The BOLD sites are in some sense a random sample of sites more broadly to which we wish to make an inference.

The main predictor variable was spirometric CAO. We fitted 5 mixed models, all adjusting for site as a cluster level variable. We first identified the total effect of CAO on unemployment in a model with no additional covariates included (Model 1). Model 2 added demographic variables (age, gender, education) and smoking habits. Model 2 was extended into Model 3 by adding comorbidities. Model 4 included FVC in addition to Model 3 covariates. As our multivariable analyses include height, age, and gender, which are the main components when using percent of predicted values, we thus chose to analyze lung function in terms of absolute values. In addition, a recent publication from the ECRHS-III study has indicated that FVC in absolute values (lung size) is able to explain most of the difference in symptom burden between men and women (13). FVC is a robust indicator of lung disease, especially when obstruction is already taken into account. In the online supplement, we also included a model 5 with respiratory symptoms in addition to the Model 4 covariates. For details on comorbidities and symptoms, please see online supplement. Covariates added in each model were added not as independent risk factors for unemployment, but as potential confounding or mediating factors influencing the effect of CAO on unemployment. Models 2-5 were also performed separately for high-income sites and for low-to-middle-income sites.

In individual participant data meta-analyses, we estimated site-specific and overall OR for CAO on unemployment in forest plots, with increasing adjustment corresponding to models 1 to 5 described above (except for the site adjustment). The STATA command used was *ipdmetan* which performs a two-stage individual participant data meta-analysis using the inverse-variance method. Unlike traditional meta-analysis, the individual participant data meta-analysis in *ipdmetan* fits a specified model to the data of one site at a time, making use of all individual participants within the sites. The two-stage approach derives aggregate data in each site separately and then combines these in a traditional meta-analysis model. The I2 statistic was reported to display the percentage of total variation across sites which was due to true site-by-site heterogeneity rather than what would be expected by chance alone (for more details, see online supplement) (14).

All analyses were performed using Stata SE version 14 for Macintosh OSX (Stata Corp, College Station, TX, USA).

# Results

Of 18,710 participants, 2,123 (11.3%) had CAO. Compared to subjects without CAO, those with CAO were older, had lower education, more smoking exposure, more comorbidities, more respiratory symptoms, and substantially lower FEV1 (Table 1). Overall, CAO was more common in men than in women. However, site-specific prevalence estimates stratified by gender showed that for some centers the gender ratio was reversed (e-Table 2). Excluding those aged 65 and older, 36.7% of participants with CAO reported paid work the preceding year, whereas 53.2% of participants without CAO had paid work the preceding year.

**Table 1. Study participant characteristics in the Burden of Obstructive Lung Disease study (BOLD) by chronic airflow obstruction (CAO), proportion with 95% confidence intervals for categorical variables and mean with standard deviation for continuous variables, N = 18 710 subjects from 26 study sites.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Spirometric CAO | No spirometricCAO | Total |
| N | 2123 | 16587 | 18710 |
| Female gender, % | 46.4 (44.2, 48.5) | 51.9 (51.1, 52.6) | 51.3 (50.5, 52.0) |
| Age, mean (SD) years | 60.7 (11.9) | 55.2 (11.0) | 55.8 (11.3) |
| Smoking habit |  |  |  |
|  Never-smoker, % | 33.9 (32.0, 36.0) | 57.2 (56.4, 58.0) | 54.6 (53.8, 55.3) |
|  Ex-smoker, % | 31.0 (29.1, 33.0) | 23.9 (23.2, 24.5) |  24.7 (24.1, 25.3) |
|  Current smoker, % | 35.1 (33.1, 37.1) |  18.9 (18.4, 19.5) | 20.8 (20.2, 21.4) |
| Education |  |  |  |
|  None, % | 14.7 (13. 2, 16.3) | 12.1 (11.6, 12.6) | 12.4 (11.9, 12.9) |
|  Primary school, % | 21.7 (20.0, 23.5) | 15.7 (15.2, 16.3) | 16.4 (15.9, 16.9) |
|  Middle school, % | 17.0 (15.5, 18.7) | 16.0 (15.5, 16.6) | 16.1 (15.6, 16.7) |
|  High school, % | 24.7 (22.9, 26.6) | 26.2 (25.5, 26.8) | 26.0 (25.4, 26.6) |
|  Some college, % | 11.1 (9.8, 12.5) | 12.8 (12.3, 13.4) | 12.6 (12.2, 13.1) |
|  College/university, % | 10.9 (9.6, 12.3) | 17.2 (16.6, 17.8) | 16.5 (15.9, 17.0) |
| Job status |  |  |  |
|  Paid work, % | 36.7 (34.7, 38.8) | 53.2 (52.4, 53.9) | 51.3 (50.6, 52.0) |
|  Homemaker/caregiver, % | 14.8 (13.3, 16.4) | 13.5 (13.0, 14.0) | 13.7 (13.2, 14.1) |
|  Unemployed, % | 19.6 (18.0, 21.4) | 16.2 (15.6, 16.8) | 16.6 (16.1, 17.1) |
|  Above retirement age, % | 28.9 (27.0, 30.8) | 17.1 (16.6, 17.7) | 18.5 (17.9, 19.0) |
| Lung function |  |  |  |
|  FVC % predicted, mean (SD) | 89.2 (21.8) | 90.3 (16.1) | 90.2 (16.9) |
|  FEV1 % predicted, mean (SD) | 69.2 (21.4) | 92.0 (16.7) | 89.4 (18.7) |
| Self-reported doctor’s diagnosis |  |  |  |
|  COPD, % | 15.3 (13.8, 16.9) | 2.4 (2.2, 2.6) | 3.9 (3.6, 4.2) |
|  Hypertension, % | 32.9 (30.9, 34.9) | 26.2 (25.6, 26.9) | 27.0 (26.3, 27.6) |
|  Heart disease, % | 14.3 (12.9, 15.9) | 10.0 (9.5, 10.4) | 10.5 (10.0, 10.9) |
|  Diabetes, % | 7.2 (6.1, 8.3) | 7.5 (7.1, 7.9) | 7.5 (7.1, 7.9) |
|  Stroke, % | 3.1 (2.4, 3.9) | 1.9 (1.7, 2.1) | 2.0 (1.8, 2.2) |
|  Lung cancer, % | 0.7 (0.4, 1.1) | 0.2 (0.1, 0.3) | 0.3 (0.2, 0.3) |
| Dyspnea |  |  |  |
|  mMRC 0, % | 55.8 (53.5, 58.0) | 78.8 (78.1, 79.4) | 76.2 (75.6, 76.9) |
|  mMRC 1, % | 17.1 (15.5, 18.9) | 12.1 (11.6, 12.6) | 12.7 (12.2, 13.2) |
|  mMRC 2, % | 13.2 (11.7, 14.8) | 5.6 (5.2, 5.9) | 6.4 (6.1, 6.8) |
|  mMRC 3, % | 8.5 (7.3, 9.8) | 2.7 (2.5, 3.0) | 3.3 (3.1, 3.6) |
|  mMRC 4, % | 5.5 (4.5, 6.6) | 0.9 (0.7, 1.0) | 1.4 (1.2, 1.6) |
| Attack of wheezing 12 months, % | 22.3 (20.6, 24.1) | 6.3 (5.9, 6.6) | 8.1 (7.7, 8.5) |
| Chronic bronchitis, % | 15.4 (13.9, 17.0) | 5.1 (4.8, 5.5) | 6.3 (5.9, 6.6) |

All comparisons between CAO and non-CAO were significant (p<0.01, Pearson chi square test for categorical variables, t test for continuous variables) except for self-reported diabetes. Missing data: Smoking habits - 11 individuals (1 CAO, 10 non-CAO); education – 25 individuals (4 CAO, 21 non-CAO); hypertension, diabetes, stroke, lung cancer, heart disease – 1 individual (1 CAO); dyspnea – 1834 missing (258 CAO, 1576 non-CAO) – mostly because of other reasons of trouble walking; wheezing – 11 missing (2 CAO, 9 non-CAO); Chronic bronchitis – none missing.

Figure 1 shows that more men than women reported current paid employment in both high- and low-to-middle income countries, but the difference was larger in low-to-middle income countries. This appeared to be explained by a substantial proportion of female unpaid homemakers/caregivers in low-to-middle-income countries. More details on gender differences in employment status are given in e-Table 3.

Table 2 shows unemployment by CAO-status in each study site, excluding homemakers, caregivers, and retirees (subjects aged 65 years and older). Despite a wide variation in unemployment rates by site, there was a fairly consistent pattern of higher unemployment among individuals with CAO in high-income sites. This pattern was less clear in the low-to-middle-income sites.

**Table 2: Unemployment rates: Prevalence of unemployment by site and spirometric CAO status.**

**N = 11 675\*.**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Unemployment (%)** |  |
| **Site** | **N** | **CAO**  | **No** **CAO** | **Crude Risk Ratio (95%CI)\*\*** |
| **HIGH INCOME** |  |  |  |  |
| Bergen, Norway | 397 | 20.0 | 9.5 | 2.1 (1.0, 4.2) |
| Hannover, Germany | 361 | 25.0 | 20.8 | 1.2 (0.6, 2.5) |
| Krakow, Poland | 350 | 57.9 | 41.4 | 1.4 (1.0, 1.9) |
| Lexington, USA | 305 | 61.0 | 27.7 | 2.2 (1.6, 3.0) |
| Lisbon, Portugal | 320 | 53.9 | 39.8 | 1.4 (0.9, 2.0) |
| London, UK | 427 | 40.4 | 24.3 | 1.7 (1.1, 2.4) |
| Maastricht, Netherlands | 396 | 31.3 | 20.4 | 1.5 (1.0, 2.3) |
| Reykjavik, Iceland | 557 | 14.0 | 3.3 | 4.2 (1.8, 10.1) |
| Salzburg, Austria | 860 | 35.2 | 25.4 | 1.4 (1.1, 1.8) |
| Sydney, Australia | 339 | 20.0 | 15.3 | 1.3 (0.6, 3.0) |
| Tartu, Estonia | 348 | 20.0 | 7.8 | 2.6 (0.9, 7.5) |
| Uppsala, Sweden | 371 | 23.8 | 6.0 | 4.0 (1.7, 9.5) |
| Vancouver, Canada | 594 | 21.8 | 11.5 | 1.9 (1.1, 3.3) |
| **LOW-TO-MIDDLE INCOME** |  |  |  |  |
| Adana, Turkey | 487 | 41.1 | 45.4 | 0.9 (0.7, 1.2) |
| Annaba, Algerie | 408 | 50.0 | 24.6 | 2.0 (1.2, 3.3) |
| Cape Town, South Africa | 510 | 52.2 | 33.5 | 1.6 (1.2, 2.0) |
| Fes, Morocco | 335 | 41.7 | 53.7 | 0.8 (0.5, 1.3) |
| Guangzhou, China | 359 | 35.7 | 49.9 | 0.7 (0.4, 1.5) |
| Ile-Ife, Nigeria | 667 | 5.1 | 7.6 | 0.7 (0.2, 2.7) |
| Kashmir, India | 366 | 7.6 | 1.3 | 5.8 (1.5, 22.9) |
| Manila, Philippines | 594 | 10.3 | 19.5 | 0.5 (0.2, 1.4) |
| Mumbai, India | 250 | 17.7 | 10.3 | 1.7 (0.6, 5.1) |
| Nampicuan Talugtug, Philippines | 493 | 23.2 | 14.7 | 1.6 (0.9, 2.7) |
| Pune, India | 671 | 6.5 | 4.1 | 1.6 (0.4, 6.4) |
| Sousse, Tunisia | 390 | 53.3 | 46.1 | 1.2 (0.7, 1.9) |
| Tirana, Albania | 520 | 0.0 | 5.0 | - |

## \*Retirees (age limit defined as 65 years old) and homemakers/caregivers were excluded from the analysis. \*\*Ratio is calculated based on prevalence of unemployment among subjects with CAO divided upon prevalence of unemployment among subjects without CAO. A ratio above 1 indicates higher unemployment prevalence among CAO subjects than among non-CAO subjects, while a ratio below 1 indicates lower unemployment prevalence among CAO subjects.

In multivariable analyses, we assessed the odds ratio (OR) of being unemployed by CAO status and an increasing number of covariates (Table 3). The first model showed that when we adjusted for site, the OR (95% confidence interval (CI)) of being unemployed was 1.79 (1.41, 2.27) for participants with CAO. Adding the traditional confounders gender, age, smoking habits and education in model 2 decreased the OR for unemployment in participants with CAO (OR reduction from 1.79 to 1.44), but the effect remained statistically significant. Further addition of comorbidities (model 3) and FVC (model 4) had little effect on the association between unemployment and CAO, even when these variables themselves were significantly associated with unemployment: the presence of comorbidities and declining FVC were all associated with increased odds of being unemployed. Table 3 shows that excess unemployment among those with CAO is partially explained by sex, age, smoking, and education, but not explained additionally by comorbidities and FVC. When respiratory symptoms were added (e-Table 4) these were also significantly associated with unemployment and appeared to explain some of the effects of CAO. In this model, the odds ratio for CAO independent of reported symptoms fell to 1.26 (95%CI: 1.00, 1.57). Substituting self-reported COPD for LLN-defined CAO in our analyses increased the odds ratio of not being in paid work (95% CI) from 1.43 (1.14, 1.79) to 3.31 (2.17, 5.05) (additional analysis, data not shown). However, while the prevalence of spirometry-defined CAO was 11.3% in BOLD, the prevalence of self-reported COPD was only 1.2%, and while 36.7% of the spirometry-defined participants with CAO were in paid employment, the corresponding figure for the self-reported COPD cases was only 25% (results not shown).

To examine how the observed associations varied by country income, we performed multivariable analyses separately for high-income and low-to-middle-income sites (Table 4). CAO was a significant risk factor for unemployment in all models in high-income sites, but not in low-to-middle-income sites. While age and lower education were important risk factors for unemployment in high-income sites, female gender was the most pronounced risk factor for unemployment in low-to-middle income sites. To further depict the gender variation in job status, we created e-Table 3 that shows the prevalence of job status categories among men and women in each site. This table points out that nearly no country had more women than men in paid work (with Lexington, Lisbon and Ile-Ife as the only three exceptions). Further on, focusing on the low-to-middle-income sites, this table demonstrates that the difference between the genders having the job status “unemployed” were in some sites very high with the mean difference being 46.1% more women than men unemployed. There were some sites having more men than women unemployed, but these were few (Annaba, Cape Town, Kashmir, Mumbai, and Pune), and the mean difference was low (5.5%). In model 5, dyspnea also was an important risk factor for unemployment in high-income sites together with age and education (e-Table 4).

## Table 3: Odds ratios (OR) with 95% confidence intervals (95%CI) for unemployment for LLN-defined CAO and other risk factors, with increasing degree of adjustment (demographic characteristics, comorbidities and FVC\*). N = 11 675\*\*.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Model 1** | **Model 2** | **Model 3** | **Model 4** |
| Spirometric CAO | 1.79 (1.41, 2.27) | 1.44 (1.15, 1.81) | 1.45 (1.15, 1.82) | 1.43 (1.14, 1.79) |
| FVC, 10 percentage points decrease in %predicted |  |  |  | 1.08 (1.04, 1.12) |
| Female gender |  | 2.07 (1.85, 2.32) | 2.10 (1.87, 2.36) | 2.10 (1.87, 2.35) |
| Age, 10yrs increment |  | 3.09 (2.85, 3.35) | 2.91 (2.68, 3.15) | 2.90 (2.67, 3.15) |
| Smoking Status |  |  |  |  |
|  Current-smoker |  | 0.96 (0.83, 1.10) | 0.98 (0.85, 1.13) | 0.98 (0.85, 1.13) |
|  Ex-smoker |  | 1.15 (1.01, 1.32) | 1.13 (0.99, 1.30) | 1.14 (0.99, 1.30) |
| Education |  |  |  |  |
|  Some college |  | 1.51 (1.23, 1.85) | 1.49 (1.22, 1.84) | 1.49 (1.21, 1.83) |
|  High school |  | 2.03 (1.71, 2.42) | 2.02 (1.69, 2.41) | 2.01 (1.68, 2.39) |
|  Middle school |  | 2.24 (1.83, 2.73) | 2.20 (1.80, 2.69) | 2.18 (1.79, 2.67) |
|  Primary school |  | 2.78 (2.27, 3.41) | 2.76 (2.25, 3.39) | 2.72 (2.22, 3.35) |
|  No education |  | 2.73 (2.09, 3.57) | 2.69 (2.05, 3.51) | 2.66 (2.03, 3.49) |
| Hypertension |  |  | 1.29 (1.13, 1.46) | 1.26 (1.10, 1.43) |
| Heart disease |  |  | 1.54 (1.27, 1.86) | 1.51 (1.25, 1.83) |
| Diabetes |  |  | 1.51 (1.23, 1.85) | 1.47 (1.19, 1.80) |
| Stroke |  |  | 1.82 (1.16, 2.86) | 1.80 (1.15, 2.83) |
| Lung Cancer |  |  | 2.34 (0.81, 6.76) | 2.38 (0.82, 6.93) |

\*Adjustment variables: no fixed effects (model 1); age, gender, education and smoking (model 2); model 2 adjustment + comorbidities (model 3); model 3 adjustment + FVC (model 4). All five models were fit using multilevel mixed-effects generalized linear model with study site included as random effect to account for within site clustering. Reference values for categorical variables: no CAO, males, never-smokers, university education, no hypertension, no heart disease, no diabetes, no stroke, no lung cancer. \*\*Retirees (age limit defined as 65 years old) and homemakers/caregivers were excluded from the analysis.

## Table 4: Odds ratios (OR) with 95% confidence intervals (95%CI) for unemployment for CAO and other risk factors, stratified by country income category, with increasing degree of adjustment (demographic characteristics, comorbidities and FVC\*). N = 11 675\*\*.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **High income** | **Low to middle income** | **High income** | **Low to middle income** | **High income** | **Low to middle income** |
|  | **Model 2** | **Model 2** | **Model 3** | **Model 3** | **Model 4** | **Model 4** |
| Spirometric CAO | 1.71 (1.17, 2.49) | 1.16 (0.78, 1.73) | 1.63 (1.16, 2.28) | 1.18 (0.79, 1.76) | 1.68 (1.16, 2.45) | 1.15 (0.77, 1.71) |
| FVC, 10 percentage points decrease in %predicted |  |  |  |  | 1.09 (1.03, 1.15) | 1.08 (1.02, 1.14) |
| Female gender | 1.36 (1.16, 1.59) | 3.34 (2.76, 4.04) | 1.43 (1.23, 1.68) | 3.25 (2.68, 3.94) | 1.44 (1.23, 1.68) | 3.23 (2.66, 3.91) |
| Age, 10yrs increment | 4.28 (3.77, 4.86) | 2.31 (2.06, 2.59) | 4.04 (3.55, 4.59) | 2.21 (1.96, 2.48) | 4.02 (3.53, 4.57) | 2.20 (1.96, 2.47) |
| Current-smoker | 1.34 (1.09, 1.65) | 0.88 (0.72, 1.09) | 1.36 (1.11, 1.68) | 0.89 (0.72, 1.10) | 1.36 (1.10, 1.67) | 0.89 (0.72, 1.10) |
| Ex-smoker | 1.31 (1.09, 1.56) | 1.15 (0.90, 1.47) | 1.28 (1.07, 1.53) | 1.13 (0.88, 1.44) | 1.29 (1.08, 1.54) | 1.12 (0.88, 1.43) |
| Some college | 1.85 (1.45, 2.38) | 0.96 (0.60, 1.52) | 1.83 (1.43, 2.36) | 0.95 (0.60, 1.52) | 1.83 (1.42, 2.35) | 0.97 (0.61, 1.54) |
| High school | 2.30 (1.84, 2.88) | 1.26 (0.92, 1.73) | 2.27 (1.81, 2.84) | 1.28 (0.93, 1.76) | 2.24 (1.79, 2.81) | 1.30 (0.94, 1.78) |
| Middle school | 3.65 (2.73, 4.87) | 1.23 (0.89, 1.70) | 3.54 (2.64, 4.74) | 1.26 (0.91, 1.74) | 3.49 (2.60, 4.67) | 1.26 (0.91, 1.75) |
| Primary school | 4.14 (3.02, 5.66) | 1.52 (1.10, 2.10) | 3.90 (2.84, 5.37) | 1.56 (1.13, 2.16) | 3.86 (2.80, 5.30) | 1.56 (1.13, 2.16) |
| No education | 1.96 (0.61, 6.32) | 1.61 (1.13, 2.30) | 2.01 (0.62, 6.43) | 1.64 (1.15, 2.34) | 1.98 (0.61, 6.43) | 1.65 (1.15, 2.35) |
| Hypertension |  |  | 1.25 (1.05, 1.49) | 1.25 (1.02, 1.53) | 1.22 (1.02, 1.45) | 1.22 (0.99, 1.50) |
| Heart disease |  |  | 1.56 (1.22, 2.00) | 1.20 (0.86, 1.67) | 1.53 (1.19, 1.96) | 1.18 (0.85, 1.64) |
| Diabetes |  |  | 1.53 (1.14, 2.04) | 1.39 (1.01, 1.92) | 1.46 (1.09, 1.95) | 1.38 (1.00, 1.91) |
| Stroke |  |  | 2.17 (1.14, 4.13) | 1.58 (0.83, 3.02) | 2.15 (1.13, 4.10) | 1.56 (0.82, 2.99) |
| Lung Cancer |  |  | 2.87 (0.89, 9.30) | 1.01 (0.04, 28.54) | 2.86 (0.89, 9.26) | 1.03 (0.04, 28.37) |

\*Adjustment variables: no fixed effects (model 1); age, gender, education and smoking (model 2); model 2 adjustment + comorbidities (model 3); model 3 adjustment + FVC (model 4). All five models were fit using multilevel mixed-effects generalized linear model with study site included as random effect to account for within site clustering. Separate analyses performed for high-income-countries and low-to-middle-income-countries. Reference values for categorical variables: no CAO, males, never-smokers, university education, no hypertension, no heart disease, no diabetes, no stroke, no lung cancer. \*\*Retirees (age limit defined as 65 years old) and homemakers/caregivers were excluded from the analysis

To present the association between CAO and unemployment by site, and to examine site heterogeneity, we performed individual participant data meta-analyses with forest plots of ORs and overall I2 statistics (Figure 2, e-Figures 1-4). The overall OR (95%CI) for unemployment among CAO subjects after adjusting for gender, age, smoking, education, comorbidities and FVC (i.e., the equivalent of model 4, but without site adjustment) was 1.41 (1.18, 1.69) with site-by-site heterogeneity (I2) of 12.9%, p=0.279. Meta-analyses with covariates corresponding to models 1, 2, 3 and 5 are shown in the online supplement (e-Figures 1-4), and show that there is no significant site heterogeneity in the association between airflow obstruction and unemployment when adjusting for the covariates in models 2, 3 and 5. However, in crude analysis (model 1), there is significant site heterogeneity (I2 49.1%, p=0.003).

# Discussion

The unweighted prevalence of spirometry-defined CAO was 11.3% in this sample of almost 19,000 participants from the global BOLD study. The association between CAO and unemployment varied across sites in crude analyses, but the site heterogeneity lost significance after adjustment for relevant covariates: CAO was an overall important risk factor for unemployment after adjusting for gender, age, smoking, education, comorbidities and even FVC. When looking at high-income and low-to-middle-income sites separately, this association was only statistically significant in high-income sites. Regarding other covariates, age and education were important risk factors for unemployment in high-income sites, while female gender was important for unemployment in low-to-middle-income sites.

Comparable population-based studies have previously observed similar prevalence rates of COPD as the CAO-rates found in the present study. The PLATINO-study found the prevalence to be within the range of 7.8% to 19.7 (15), Hansen et al found the overall COPD prevalence in a Danish general population to be 12% (16), and the systematic review by Adeloye et al found the global prevalence of population-based spirometrically defined COPD to be 11.7% (17).

Only one multicenter study has previously provided population-based estimates of unemployment in CAO, identifying CAO by spirometry. In accordance with our findings, the PLATINO study, carried out in five Latin-American countries, estimated that 41.8% of participants with CAO and 57.1% of those without CAO had a paid job the preceding year (7). In the multivariable analysis of the PLATINO study they found a borderline lower probability of paid work (odds ratio (95% CI) 0.83 (0.69 to 1.00)) for CAO patients, and as in our study they found significant effects of age, sex, education, dyspnea and comorbidities. However, the PLATINO study adjusted for dyspnea in their main model, and this has probably reduced the effect of spirometry-defined CAO on the probability of having paid work. We observed the same pattern in our study; while CAO was significantly associated with unemployment in our main model with OR 1.43 (adjusting for gender, age, smoking, education, comorbidities and FVC), the OR decreased to 1.26 (although still remaining significant with 95%CI 1.00-1.57) after adding reported dyspnea and other respiratory symptoms. In line with this, one may speculate that symptoms and severity of CAO would most likely explain the majority of unemployment, and that it would be better to study these disease aspects than the mere spirometry measurement. However, even after adjusting for mMRC, wheezing together with dyspnoea, and symptoms of chronic bronchitis in our study, the effect of spirometry-defined CAO on unemployment was still significant (model 5 online supplement). This suggests that there are other properties than the burden of current wheezing, dyspnea and bronchitis that leads to unemployment, and adding objectively measured CAO identifies the magnitude of these. For instance, the patient might experience other symptoms (e.g. asthenia), be a frequent exacerbator, or there might be some degree of reporting bias.

Other studies on workforce-participation in CAO have been based on self-reported COPD diagnosis and not spirometry (18–22). Studies of self-reported COPD observe stronger associations between the disease and participation in the work place than the current study. This difference might be due to a bias towards more severely affected patients in studies based on self-reports (23). Lamprecht and co-workers (24) showed that over 80% of subjects with post-bronchodilator FEV1/FVC<LLN were undiagnosed, and that less severe airflow obstruction was an important predictor lack of diagnosis.

The inclusion of un-diagnosed CAO-patients by state-of-the-art spirometric case-detection in representative population-based samples is the main strength of the current study. All epidemiological studies are to some degree subject to selection bias, and the use of representative samples and mostly high cooperation rates (over half above 70%), reduce the likelihood of strong biases from selection. Furthermore, our main outcome is categorical and objective, and less prone to bias (25, 26) than reports of diagnoses, though some of the covariates may be more prone to recall bias. In addition, we have used post-bronchodilator measurements, in accordance with international guidelines, and we have a large sample size from a general global population with standardized data collection across sites. Also, we have built regression models based on a priori hypotheses of associations, rather than including all variables that were significant in bi-variable analyses or by an automated stepwise approach.

Some limitations deserve to be mentioned. First of all, the BOLD study is a cross-sectional study, and as such we cannot infer temporality and we have no direct evidence that the CAO was directly responsible for the unemployment. It is not unthinkable that some of the association between CAO and unemployment is a result of unemployed participants being more susceptible to the disease, even if we have adjusted for education, age and smoking habits. Economic hardship in the form of unemployment can worsen individual unhealthy behaviors including smoking (27). Second, the employment question is based on any paid work in the past year, and does not differentiate between full-time and part-time work. In other words, subjects who have needed to reduce their work participation due to CAO from full-time to part-time will still be defined as in paid work in our analysis. This may lead to an underestimation of associations between CAO and employment. Being able to present absolute rates of disease-related unemployment standardized at the site population level would have been an advantage, but as our data did not include census information with age distribution details from each site this was not feasible. Future research could preferably include such data for this purpose. Further, lack of a direct question on retirement means that we may have underestimated the problem of unemployment above the age of 65. Furthermore, our chosen cut-off of 65 years of retirement age may have affected results in both directions. Third, our spirometry-derived variables were calculated from the NHANES III reference equation for Caucasians. This is relatively uncontroversial for measures of FEV1/FVC in the age group 40-65 years as normal values are not strongly associated with ethnicity. Overall, however, prevalence of spirometry-defined CAO (FEV1/FVC<LLN) will be slightly lower with NHANES reference values than with the recently recommended GLI (Global Lung Function Initiative) reference values (28). The difference would not be large enough for us to expect substantial differences in the associations observed in the present study. If anything, a higher CAO prevalence would lead to larger effects of CAO on unemployment – including more persons with less severe obstruction. The use of NHANES may be more controversial for the measures of FVC than for the measures of the ratio. In this case, we have used FVC as a continuous variable so that the “lower limit of normal” is not an issue and, as we have allowed a separate baseline in each centre and as most centres are ethnically homogeneous, this should not present a problem. (29, 30). Since the main focus of the present study was on associations rather than prevalences, we chose to implement the same reference values for the whole study population. This may also allow for possible factors that might have affected the lung function at a national level to become apparent instead of being lost with the use of different reference equations at each site. And fourth, regarding study limitation, the registration of never-smokers may have been somewhat exaggerated if there were participants who started smoking recently before study inclusion, but who had not yet gotten to 20 lifetime packs of cigarettes. The risk of this however, would seem small given that the youngest participants included in this study are 40 years old. Lastly, there might be a bias toward more women responding being unemployed in low-to-middle income sites due to cultural differences where women might not have a formal employment, though they attend work and have an informal income. This information bias might make the gender difference in risk of being unemployed somewhat higher than the actual risk in these sites, but unfortunately it is beyond the potential of our dataset to disentangle this possible female misclassification. E-table 3 shows that the differences between men and women applied to almost all sites.

The association between CAO and unemployment was significant in overall analyses, but in stratified analyses we observed that the association was likely driven by high-income sites. There may be several reasons for this. Firstly, low-to-middle-income countries may have more prevalent diseases than CAO rendering them vulnerable for unemployment. Secondly, there may be more heterogeneity in low-to-middle-income sites than in high-income sites. Our analyses showed consistent results across the high-income sites that seemed to be more homogeneous than the low-to-middle-income sites where CAO was a risk factor for unemployment in some sites and almost a protective factor against unemployment in other sites. The suspicion was further strengthened by crude meta-analysis, showing significant site heterogeneity in the univariate association between CAO and unemployment. However, when other covariates were accounted for, the site heterogeneity lost significance. Thirdly, other factors may be more important than health factors for unemployment risk in low-to-middle-income countries. We observed that female gender was an important risk factor for unemployment in these sites, while age and education were important for the high-income sites. Traditional gender roles in low-to-middle-income countries may affect work-life participation to such a degree that they blur the association between health-related factors and unemployment. Such large gender differences in work participation were illustrated in our e-Table 3 in the present study. And last, but not least, our results may be an indication of how disease burden act differently in high- versus low-to-middle-income sites, due to a strictly economic component. In high-income sites those most severely affected are given the possibility to be economically sustained by the corresponding social security systems, while in low-to-middle income sites such alternatives are few or non-existing. While in high-income sites, the welfare system bears the economic burden of disease; in low-to-middle-income sites the humans affected both bear the personal *and* the economic burden of disease.

In conclusion, we have found that work-life participation of subjects with CAO is overall lower than work-life participation of subjects without CAO, and that CAO is associated with unemployment also after adjusting for gender, age, smoking, education, comorbidities and even FVC. There was no significant heterogeneity between sites, although stratified analyses showed that CAO may be of more importance for unemployment in high-income-sites. Our study shows the risk of unemployment among people with this high-frequent respiratory disease, and illustrates how CAO considerably impacts productivity and social security systems worldwide.

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Data management and quality control: RG, AJ, ME, and WV.

Statistical analyses: RG, AJ, and WV.

Analysis plan: RG, AJ, PB, WV and ME.

Drafting: RG, ME, and AJ.

Revision and approval of drafts: RG, ME, WT, DO, AA, TG, SJ, PK, MS, SS, PB, SB, WV, and AJ.

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Conflicts of interest

All authors have competed the ICMJE uniform disclosure form at [www.icmje.org/coi\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare:

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