Self-reported alcohol intake and risk of acute exacerbations of chronic obstructive pulmonary disease: a prospective cohort study

Objective: To evaluate the relationship between alcohol consumption and the risk of acute exacerbation of COPD (AECOPD).

Methods and measurements: We conducted a secondary analysis of data previously collected in a large, multicenter trial of daily azithromycin in COPD. To analyze the relationship between amount of baseline self-reported alcohol consumption in the past 12 months and subsequent AECOPD, we categorized the subjects as minimal (<1 drink/month), light-to-moderate (1–60 drinks/month), or heavy alcohol users (>60 drinks/month). The primary outcome was time to first AECOPD and the secondary outcome was AECOPD rate during the 1-year study period.

Results: Of the 1,142 enrolled participants, 1,082 completed baseline alcohol questionnaires and were included in this analysis. Six hundred and forty-five participants reported minimal alcohol intake, 363 reported light-to-moderate intake, and 74 reported heavy intake. There were no statistically significant differences in median time to first AECOPD among minimal (195 days), light-to-moderate (241 days), and heavy drinkers (288 days) (P=0.11). The mean crude rate of AECOPD did not significantly differ between minimal (1.62 events per year) and light-to-moderate (1.44 events per year) (P=0.095), or heavy drinkers (1.68 events per year) (P=0.796). There were no significant differences in hazard ratios for AECOPD after adjustment for multiple covariates.

Conclusion: Among persons with COPD at high risk of exacerbation, we found no significant relationship between self-reported baseline alcohol intake and subsequent exacerbations. The number of patients reporting heavy alcohol intake was small and further study is needed to determine the effect of heavy alcohol intake on AECOPD risk.

Keywords: pulmonary disease, chronic obstructive, ethanol, alcohol, alcoholism

Introduction

COPD is a leading cause of death and disability both in the US and worldwide. Recent studies indicate that in the US alone, COPD is responsible for over 3.5 million hospital days, 15 million physician office visits, and $38.8 billion in direct and indirect costs, annually. Acute exacerbation of COPD (AECOPD) not only accounts for the majority of COPD-related costs, but has also been associated both with disease progression and increased mortality among those with COPD. Greater understanding of factors that affect AECOPD risk could have a significant public health impact.

While heavy alcohol intake has long been associated with adverse health effects including increased risk of respiratory infection, observational studies have shown that moderate alcohol intake may confer health benefits ranging from decreased...
risk of diabetes and cardiovascular events to a reduction in all-cause mortality.13–15 These benefits have been, in part, attributed to an alcohol-related reduction in inflammatory mediators.

Little is known about the effects of alcohol consumption on susceptibility to AECOPD. Using previously collected data from a large randomized controlled trial of patients with COPD, we performed a secondary analysis to evaluate the relationship between alcohol consumption and the risk of AECOPD.

Methods
We conducted a nested prospective cohort study using data collected in a randomized trial that tested the effect of daily azithromycin on reducing AECOPD risk (ClinicalTrials.gov; NCT00325897). The detailed protocol methods and main results of the trial have been previously published.16

Study participants
Inclusion criteria were as follows: age 40 years or older, a ratio of forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) <70%, FEV1 <80% of predicted, ≥10 pack-year smoking history, and an increased risk of AECOPD (defined as requiring oxygen, having received systemic corticosteroids or having an emergency department visit or hospitalization for COPD within 1 year of study entry). Exclusion criteria included a diagnosis of asthma or a disease resulting in the patient being either medically unstable or having a predicted life expectancy <3 years, macrolide hypersensitivity, taking medications with azithromycin interactions, electrocardiographic QTc interval >450 ms, resting heart rate >120 beats/minute, hepatic or renal insufficiency (creatinine >1.5 mg/dL and estimated creatinine clearance <20 mL/min), bronchiectasis, or hearing impairment. Participants were required to be free of AECOPD for ≥4 weeks prior to enrollment. Patients were not excluded on the basis of their alcohol consumption.

Participants were randomly assigned in a 1:1 ratio to either daily azithromycin or placebo for 1 year given in addition to their usual treatment. Participants were seen in clinic or contacted by phone on alternate months and detailed exacerbation information was collected over 1 year. AECOPDs were defined as a complex of respiratory symptoms (increased or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least 3 days and requiring treatment with an antibiotic or systemic corticosteroid.

All participants provided written informed consent to participate in the study. Each participating institution’s institutional review board approved the protocol.

At the time of enrollment, study participants were administered an alcohol intake questionnaire quantifying self-reported alcohol consumption in the preceding 12-month period (Figure 1).17 Mean monthly alcohol consumption was calculated based on responses to the following questions: “In the past 12 months, how many days of the year did you drink any alcoholic beverage?” and “On the average, on the days that you drank alcohol, how many drinks did you have a day? (By a drink, I mean a 12 oz [355 mL] beer, a 4 oz [128 mL] glass of wine, or an oz [30 mL] of liquor)”.

Categories of alcohol intake were determined using cut points based on previously published population data demonstrating decreased COPD mortality in those with alcohol intake equaling 1–60 14 g drinks per month.18,19 We categorized subjects’ alcohol use as “minimal to none”, “light-to-moderate”, and “heavy” according to the following criteria: “minimal” if reported <12 drinks in a lifetime or <12 drinks in the past 12 months; “light-to-moderate” if reported 1–60 drinks per month; “heavy” if reported >60 drinks per month.

Participants also completed a St George’s Respiratory Questionnaire (SGRQ), which is a self-completed, validated questionnaire to assess respiratory health status.20 SGRQ scores range from 0 to 100, with lower scores indicating better respiratory health status; the minimal clinically important difference in SGRQ scores is 4 points.21 Good reliability has been demonstrated with SGRQ.22 Participants also completed a Hospital Anxiety and Depression Scale (HADS) questionnaire, performed post-bronchodilator spirometry, and had their medication use recorded. HADS has been validated in general populations of medical patients as well as COPD populations, and good reliability has been established.23,24

We hypothesized that light-to-moderate alcohol use would be associated with a lower risk of AECOPD compared to minimal or no use; secondarily, we hypothesized that heavy alcohol use would be associated with a higher risk of AECOPD. The primary outcome was time to first AECOPD and the secondary outcome was exacerbation rate during the 1-year study period.

Statistical methods
Univariate analysis of continuous and categorical data utilized Student’s t-tests and chi-square tests, respectively. Time to first AECOPD was analyzed by comparing alcohol-use groups using log-rank testing, as well as by use
of a multivariate Cox proportional hazard model to adjust for factors that might influence exacerbations. Covariates forced
into the regression model included study treatment group
(azithromycin or placebo control) and known predictors of
AECOPD, age, and sex. Candidate variables for stepwise
regression covariates included those with potential effect
on subsequent AECOPD including smoking status, chronic
bronchitis, oxygen use, gastroesophageal reflux, FEV\textsubscript{1}/FVC
ratio, COPD medications, SGRQ score, HADS anxiety score,
and HADS depression score. Previous AECOPD is another
established AECOPD risk factor, and was assessed by two
ways in this trial: 1) use of antibiotics or steroids for COPD
in the previous year, or 2) hospitalization or unscheduled
emergency visit for COPD in the previous year. These were
combined into one variable (exacerbation in past year at
baseline) and also included as a candidate covariate in step-
wise Cox regression. Stepwise covariates were included in
the final model if they were significant at $P<0.05$.

Rate of AECOPD was determined by dividing the number
of AECOPDs by person-years of follow-up, allowing use
of data from patients with multiple exacerbations during
follow-up. The relationship between alcohol consumption
and rate of AECOPD was analyzed using zero-inflated nega-
tive binomial regression.

Statistical analyses were conducted using SAS 9.3 (SAS
Institute, Cary, NC, USA).

Results
Among the 1,142 participants enrolled in the trial, 1,082
completed alcohol questionnaires and were included in this
analysis. Follow-up AECOPD data were available for all the
1,082 included patients.

Baseline characteristics of the study population are pre-
sented in Table 1. Of the 1,082 subjects, 645 participants
(59.6%) reported minimal to no alcohol intake, 363 (33.5%)
reported light-to-moderate intake, and 74 (6.8%) reported
heavy intake.

There were small but statistically significant differences
in FEV\textsubscript{1} among the alcohol intake categories. Minimal users
had worse respiratory health status as assessed by SGRQ
scores and more anxiety as assessed by HADS scores. Heavy
users of alcohol had a higher mean smoking pack-year his-
tory. There were no differences in proportions of current
smokers or in use of inhaled COPD medications. Random-
ized allocation (azithromycin vs placebo) was similar in each
alcohol intake category.

A total of 1,593 exacerbations were observed during
the study period. There were no statistically significant

Figure 1 Alcohol use questionnaire.
differences in crude median time to first AECOPD among minimal (195 days; 95% CI, 164–372) and heavy users (288 days; 95% CI, 164–372) (**P=0.111, log-rank test). Compared to minimal alcohol users, the crude hazard ratio for time to first AECOPD among light-to-moderate alcohol users was 0.87 (95% CI, 0.74–1.03) and in heavy alcohol users was 0.78 (95% CI, 0.61–0.97; **P=0.123). Adjustment for treatment group (azithromycin vs control) and multiple known risk factors for AECOPD had little effect on these results (Table 2).

At the completion of the 1-year follow-up period, 44% of heavy alcohol users, the crude hazard ratio for time to first AECOPD among minimal drinkers was 0.87 (95% CI, 0.74–1.03) and in heavy alcohol users was 0.78 (95% CI, 0.61–0.97; **P=0.123). Adjustment for treatment group (azithromycin vs control) and multiple known risk factors for AECOPD had little effect on these results (Table 2).

At the completion of the 1-year follow-up period, 44% of heavy alcohol users, the crude hazard ratio for time to first AECOPD among minimal drinkers was 0.87 (95% CI, 0.74–1.03) and in heavy alcohol users was 0.78 (95% CI, 0.61–0.97; **P=0.123). Adjustment for treatment group (azithromycin vs control) and multiple known risk factors for AECOPD had little effect on these results (Table 2).

At the completion of the 1-year follow-up period, 44% of heavy alcohol users, the crude hazard ratio for time to first AECOPD among minimal drinkers was 0.87 (95% CI, 0.74–1.03) and in heavy alcohol users was 0.78 (95% CI, 0.61–0.97; **P=0.123). Adjustment for treatment group (azithromycin vs control) and multiple known risk factors for AECOPD had little effect on these results (Table 2).

At the completion of the 1-year follow-up period, 44% of heavy alcohol users, the crude hazard ratio for time to first AECOPD among minimal drinkers was 0.87 (95% CI, 0.74–1.03) and in heavy alcohol users was 0.78 (95% CI, 0.61–0.97; **P=0.123). Adjustment for treatment group (azithromycin vs control) and multiple known risk factors for AECOPD had little effect on these results (Table 2).

At the completion of the 1-year follow-up period, 44% of heavy alcohol users, the crude hazard ratio for time to first AECOPD among minimal drinkers was 0.87 (95% CI, 0.74–1.03) and in heavy alcohol users was 0.78 (95% CI, 0.61–0.97; **P=0.123). Adjustment for treatment group (azithromycin vs control) and multiple known risk factors for AECOPD had little effect on these results (Table 2).

At the completion of the 1-year follow-up period, 44% of heavy alcohol users, the crude hazard ratio for time to first AECOPD among minimal drinkers was 0.87 (95% CI, 0.74–1.03) and in heavy alcohol users was 0.78 (95% CI, 0.61–0.97; **P=0.123). Adjustment for treatment group (azithromycin vs control) and multiple known risk factors for AECOPD had little effect on these results (Table 2).
Discussion

We identified no statistically significant association between self-reported alcohol consumption at baseline and AECOPD risk over the ensuing year.

Existing evidence regarding the effect of alcohol on respiratory health has shown both harm and benefit, depending on the intensity, duration, and frequency of alcohol exposure.\textsuperscript{25,26} At a high level of consumption, alcohol impairs airway clearance and both innate and adaptive immunity,\textsuperscript{10} and observational studies have demonstrated increased risk of pneumonia.\textsuperscript{9,12,27}

The data available in this analysis do not suggest that a self-reported heavy alcohol consumption pattern was associated with increased frequency of AECOPD compared to minimal intake. There was even some suggestion that heavy alcohol users might have had longer time to first exacerbation, although they also had better FEV\textsubscript{1}, less chronic oxygen use, and there was ultimately no statistically significant difference in time to first exacerbation or exacerbation frequency. We note that the subjects reporting heavy alcohol intake were few in number and further study is needed to more closely characterize the relationship between heavy alcohol consumption and AECOPD.

Among the therapies that have been shown to reduce AECOPD risk, inhaled corticosteroids, macrolide antibiotics, and selective phosphodiesterase-4 inhibitors are thought to exert their beneficial effect by reducing or modifying airway inflammation. It is plausible that low-level alcohol consumption could also provide some degree of protective reduction in inflammation.\textsuperscript{28}

Table 2 Time to first AECOPD by alcohol consumption pattern

<table>
<thead>
<tr>
<th>Alcohol intake</th>
<th>Total (n=1,082)</th>
<th>Minimal (n=645)</th>
<th>Light-to-moderate (n=363)</th>
<th>Heavy (n=74)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to first exacerbation, days (95% CI)</td>
<td>216 (190–241)</td>
<td>195 (163–225)</td>
<td>241 (205–302)</td>
<td>288 (164–372)</td>
<td>0.1113</td>
</tr>
<tr>
<td>Crude HR (95% CI)</td>
<td>NA (Referent)</td>
<td>0.87 (0.74–1.03)</td>
<td>0.78 (0.56–1.07)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>NA (Referent)</td>
<td>0.89 (0.75–1.05)</td>
<td>0.93 (0.70–1.29)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Note: \textsuperscript{a}Covariates included in final stepwise model: treatment group, age, sex, smoking status, bronchitis, oxygen, FEV\textsubscript{1}/FVC ratio, exacerbation in past year, SGRQ.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CI, confidence interval; HR, hazard ratio; FEV\textsubscript{1}, forced expiratory volume in 1 second; FVC, forced vital capacity; NA, not applicable; SGRQ, St George’s Respiratory Questionnaire.
While we observed no significant trend of risk reduction for low-level alcohol consumption in this study, multiple population studies analyzing alcohol intake and COPD mortality have reported a U-shaped curve, with the lowest risk of death among men with light-to-moderate alcohol intake, equaling 1–60 drinks per month.\textsuperscript{1,18} A previous prospective cohort study in a US Veteran population identified no association between Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) scores and risk of AECOPD.\textsuperscript{29} Although the AUDIT-C tool is a validated screening tool for alcohol misuse, it does not specifically quantify alcohol consumption patterns, particularly in those without a pattern of abuse such as in light or moderate drinkers. The study was further limited by an inability to capture AECOPD events treated at non-VA facilities, a lack of spirometry data confirming COPD diagnosis, and an overwhelmingly male population.

The strengths of our current study include its large size, use of spirometry to confirm COPD, and its careful collection of prospective AECOPD data, which was the primary outcome of the main trial.

There remain notable limitations. Capturing accurate clinical information about alcohol behavior, particularly for those with large intake, is challenging and study participants may have misrepresented alcohol intake. Self-reporting of alcohol intake, as in the National Health and Nutrition Examination Survey (NHANES) alcohol questionnaire, has been validated by surrogate reporting and by biomarker studies. Therefore, self-report is generally accepted as a valid and reasonably accurate way to quantify alcohol intake for population research studies.\textsuperscript{30} The retrospective nature of the alcohol intake questionnaire is also subject to recall bias. We only administered the alcohol questionnaire at baseline, so although subsequent changes in alcohol consumption behavior seem unlikely, we cannot exclude the possibility that baseline data may not reflect prospective alcohol intake during the follow-up period. We also note that we had a very limited number of heavy alcohol users, so we have limited ability to draw conclusions about that particular group. Recruitment of such subjects is challenging, particularly in the context of a longitudinal trial such as the trial within which the present study was nested.

### Table 3 AECOPD event rates by alcohol consumption pattern

<table>
<thead>
<tr>
<th>Alcohol intake</th>
<th>Total (n=1,082)</th>
<th>Minimal (n=645)</th>
<th>Light-to-moderate (n=363)</th>
<th>Heavy (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean exacerbation rate, exacerbations per year (% CI)</td>
<td>1.66 (1.51–1.80)</td>
<td>1.62 (1.53–1.94)</td>
<td>1.44 (1.31–1.71)</td>
<td>1.68 (1.17–2.19)</td>
</tr>
<tr>
<td>P-value</td>
<td>P=0.095</td>
<td>P=0.964</td>
<td>P=0.796</td>
<td></td>
</tr>
</tbody>
</table>

Note: P-values comparing to referent group of minimal alcohol intake.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CI, confidence interval.

### Conclusion

Among persons with COPD at high risk of exacerbation, we found no significant relationship between self-reported baseline alcohol intake and subsequent exacerbations. The number of patients reporting heavy alcohol intake was small and further study is needed to determine the effect of heavy alcohol intake on AECOPD risk.

### Acknowledgments

The COPD Clinical Research Network is supported by a Cooperative Agreement from the Division of Lung Diseases of the National Heart, Lung, and Blood Institute. Members of this network are: Brigham and Women’s Hospital (affiliated sites: Fallon Clinic, West Roxbury Veterans Hospital) – JJ Reilly Jr (principal investigator [PI]), GR Washko (co-PI), R Rosiello, ML Moy (investigators), Grant HL074428; Denver Health Medical Center (affiliated sites: National Jewish Medical and Research Center, University of Colorado) – RK Albert (PI), B Make (co-PI), M Schwarz, C Welch (investigators), Grant HL074409; Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center – R Casaburi (PI), J Porszasz (investigator), Grant HL074407; Minnesota Veterans Research Institute, Minneapolis (affiliated sites: HealthPartners Research Foundation, Mayo Clinic) – DE Niewoehner (PI), C McEvoy, KR Rice, PD Scanlon (co-PIs), Grant HL074416; Temple University – GJ Criner (PI), W Chatila, N Marchetti, V Kim, G D’Alonzo, S Krachman, F Cordova, K Brennan, N Patel, J Mamary (investigators), Grant HL074408; University of Alabama at Birmingham – WC Bailey, JAD Cooper (co-PIs), MT Dransfield, LB Gerald, P O’Reilly (investigators), Grant HL074418; University of California, San Francisco – SC Lazarus (PI), HA Boushey, PG Woodruff (investigators), Grant HL074431; University of Maryland, Baltimore – SM Scharf (PI), M Alattar, P Amelung, M Cowan, J Hanson, J Hasday, A Iacono, C Shanholz, N Todd, A Verceles (investigators), Grant HL074441; University of Michigan, Ann Arbor – FJ Martinez (PI), JL Curtis, MK Han, KR Flaherty, SE Gay, TE Sisson (investigators), Grant HL074422; University of Pittsburgh, Pittsburgh – F Sciurba (PI), J Bon


References


