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Clinical Markers Associated With Risk of Suicide or Drug Overdose Among Individuals With Smoking Exposure

A Longitudinal Follow-up Study of the COPDGene Cohort

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BACKGROUND: Studies have shown that COPD and smoking are associated with increased suicide risk. To date, there are no prospective studies examining suicide risk among individuals with smoking exposure along a spectrum of pulmonary diseases ranging from normal spirometry to severe COPD.

RESEARCH QUESTION: Which clinical variables predict death by suicide or overdose of indeterminate intent in a large cohort of individuals with smoking exposure within the Genetic Epidemiology of COPD (COPDGene) study?

STUDY DESIGN AND METHODS: We studied data from 9,930 participants involved in COPDGene, a multisite, prospective cohort study of individuals with smoking exposure. Primary cause of adjudicated deaths was identified by using death certificates, family reports, and medical records. Time to death by suicide/overdose was examined as the primary outcome in Cox regression models including age, sex, race, BMI, pack-years, current smoking status, airflow limitation (FEV_1 % predicted), dyspnea (modified Medical Research Council scale score $\geq$ 2), 6-min walk distance, supplemental oxygen use, and severe exacerbations in the prior year with time-varying covariates and other causes of death as a competing risk.

RESULTS: The cohort was 47% female and 33% Black (67% White); they had a mean $\pm$ SD age of 59.6 $\pm$ 9.0 years and a mean FEV_1 % predicted of 76.1 $\pm$ 25.5. Sixty-three individuals died by suicide/overdose. Factors associated with risk of suicide/overdose were current smoking (hazard ratio [HR], 6.44; 95% CI, 2.64-15.67), use of sedative/hypnotics (HR, 2.33; 95% CI, 1.24-4.38), and dyspnea (HR, 2.23; 95% CI, 1.34-3.70). Lower risk was associated with older age (per-decade HR, 0.45; 95% CI, 0.31-0.67), higher BMI (HR, 0.95; 95% CI, 0.91-0.99), and African-American race (HR, 0.41; 95% CI, 0.23-0.74). Severity of airflow limitation (FEV % predicted) was not associated with suicide risk.

INTERPRETATION: In this well-characterized cohort of individuals with smoking exposure with and without COPD, risk factors for suicide/overdose were identified that emphasize the subjective experience of illness over objective assessments of lung function.

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KEY WORDS: COPD; overdose; prospective cohort study; suicide deaths; tobacco smoking

FOR EDITORIAL COMMENT, SEE PAGE 259

ABBREVIATIONS: GOLD = Global Initiative for Chronic Obstructive Lung Disease; HADS = Hospital Anxiety and Depression Scale; mMRC = modified Medical Research Council scale

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Take-home Points

Study Question: Which clinical variables predict death by suicide or overdose of indeterminate intent in individuals with smoking exposure over an approximately 8-year follow-up?

Results: Current smoking (HR, 6.44; 95% CI, 2.64-15.67), use of sedative/hypnotics (HR, 2.33; 95% CI, 1.24-4.38), and dyspnea (HR, 2.23; 95% CI, 1.34-3.70) were associated with increased risk of suicide/overdose, whereas older age (per-decade HR, 0.45; 95% CI, 0.31-0.67), higher BMI (HR, 0.95; 95% CI, 0.91-0.99), and African-American race (HR, 0.41; 95% CI, 0.23-0.74) were associated with lower risk.

Interpretation: Health care practitioners across disciplines should evaluate suicide risk in patients with COPD, paying particular attention to smoking status, use of sedative/hypnotic medications, and their subjective experience of dyspnea.

Smoking and smoking-related diseases, particularly COPD, are independent risk factors for suicide,[1-5] as well as suicidal ideation and attempts.[6-8] COPD is classically defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report as marked airflow limitation ($FEV_1/FVC < 0.70$ and GOLD stages 1-4 based on the FEV_1 % predicted). Our group has recommended expanding diagnostic criteria for COPD to include exposure, pulmonary symptoms, spirometry, and lung CT scan imaging, as growing evidence shows that some at-risk individuals with smoking exposure experience symptoms, morbidity, and mortality prior to meeting criteria for COPD.[9] Individuals with smoking exposure with preserved spirometry findings can also present with lung CT scan abnormalities and respiratory symptoms, and are therefore important to study.

Evidence to inform suicide risk assessment for individuals with smoking exposure with and without COPD is limited. Individuals with smoking exposure have a higher suicide risk. Some have suggested that this increased risk may be due to chronic illness, but studies have not rigorously assessed COPD diagnosis or severity.[10-12] In prior studies, COPD, female sex, multimorbidity, and nicotine dependency were associated with higher risk for suicide[3-5,13] and surrogate outcomes for suicide risk such as suicidal ideation and suicide attempts.[7,14] These previous studies include several case-control studies[2,3,5,14] and three population registry-based cohorts.[4,5,8] Limitations include that COPD diagnosis was based on self-report rather than objective clinical assessment, and individuals with COPD were analyzed as a single group without considering severity. Current smoking is an independent risk factor for suicide,[10,11] but only one study of COPD and suicide considered current smoking in their analysis, finding that the association between COPD and suicidal ideation was no longer significant after adjusting for nicotine dependence, and that the strength of association between COPD and suicide attempts was attenuated after adjusting for nicotine dependence.[7]

In the current analysis, we investigated risk factors for suicide among 9,930 individuals with smoking exposure (≥ 10 pack-year history of smoking) enrolled in the Genetic Epidemiology of COPD (COPDGene) study. This prospective cohort provides the unique opportunity to stratify suicide risk prospectively among individuals who had well-characterized COPD. Individuals were followed up for a mean of 8 years and had death adjudicated at 11 years. The cohort includes individuals with smoking exposure regardless of the presence of airflow limitation, which includes a population that may be at risk for COPD but unrecognized in other studies.[9,15] Although prior literature treats individuals

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DISCLAIMER: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health.

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with smoking exposure and individuals with COPD as separate populations at risk for suicide, our analysis recognizes that these groups have significant overlap. We combined the outcomes of death by suicide and death by overdose of indeterminate intent (overdose) to improve power and mitigate risk for suicide misclassification, which has been shown to be most likely in the case of poisoning or overdose of indeterminate intent.[16-21] We performed a secondary analysis of clinical predictors of death by suicide/overdose of indeterminate intent in individuals with smoking exposure along a spectrum of pulmonary disease ranging from normal spirometry to severe COPD.

Study Design and Methods

COPDGene Study

COPDGene is a 21-center longitudinal cohort study with an original enrollment of 10,371 individuals with smoking exposure (including both people currently smoking and those who had previously quit) who were aged 45 to 80 years, identified as either African American or non-Hispanic White, and who had at least a 10 pack-year smoking history.[15] For this analysis, we included individuals with smoking exposure who completed the Phase 1 visit, and they were censored at last follow-up contact or date of death at the time of death adjudication (January 31, 2018). The values of variables were updated during Phase 2 and Phase 3 visits if available. The Institutional Review Board for each site approved the study (e-Table 1), and all participants provided written informed consent.

Measures

Independent variables in this analysis were collected during Phase 1 (2007-2012), Phase 2 (2012-2017), and Phase 3 (2018-present) visits and modeled as time-varying covariates using data obtained from the most recent site visit. Data obtained during Phase 1 and repeated at Phase 2 and Phase 3 visits included demographic characteristics, medical comorbidities, amount of cigarette use (pack-years), BMI, spirometry, 6-min walk distance, use of supplemental oxygen, number of hospitalizations within the past year, and the modified Medical Research Council Dyspnea Scale (mMRC) score. Use of psychotropic medications was ascertained by coding self-reported medication lists.[22] A description of the original COPDGene design and study variables was previously published.[15]

Spirometry data were used to classify subjects into one of five COPD severity groups: GOLD stage 1 to 4 (defined by FEV_1 % predicted) or preserved ratio impaired spirometry (ie, $FEV_1/FVC \geq 0.70$, FEV_1 % predicted ≤ 80), which was a category previously described by Wan et al.[9] GOLD 0 to normal spirometry findings included those with exposure to smoking who had normal spirometry ($FEV_1/FVC \geq 0.70$, FEV_1 % predicted > 80) results. In our analysis, we combined GOLD stages 1 and 2 (mild to moderate COPD) and GOLD stages 3 to 4 (moderate to severe COPD). Psychotropic medications were categorized as antidepressants, mood stabilizers, sedative/hypnotics, antipsychotics, or stimulants by members of the study team.[22] Comorbidity count was based on a simple, unweighted count of comorbid conditions that has been previously validated in the COPDGene cohort with performance similar to more complicated weighted measures, including: coronary heart disease, diabetes mellitus, congestive heart failure, stroke, osteoarthritis, osteoporosis, hypertension, high cholesterol, gastroesophageal reflux disease, stomach ulcers, obesity, sleep apnea, hay fever, and peripheral vascular disease.[23]

Outcome: Mortality Ascertainment and Cause of Death

Vital status was assessed through January 31, 2018. Deaths were reported from clinical centers, with sources including longitudinal contacts by the longitudinal follow-up program, death certificates, family member reports, obituaries, medical records, and Social Security Death Index searches. The COPDGene Death Adjudication Committee included six physicians who reviewed available information about the cause of death, including death certificates, informant interview, and medical records, and classified cause of death by using Towards a Revolution in COPD-related Health (TORCH) criteria, a methodology that has been previously described.[24] Our primary outcome was time to death by suicide or overdose of indeterminant intent. Deaths by suicide and overdose of indeterminate intent are routinely combined to estimate suicide rates because of frequent suicide misclassification in overdose-related deaths.[16,25-29]

Analysis

Those with and without our primary outcome of interest, suicide/overdose, were contrasted on a variety of sociodemographic and clinical variables at baseline. For our primary analyses, time to primary outcome was modeled in Cox regression models to easily facilitate time-varying covariates and avoid assumptions about the distribution of survival times. As part of the a priori statistical analysis plan, age and sex were included as predictors in all models because they are well-established risk factors for suicide. As a second step to identify covariates, a series of separate models entering each variable individually were run to determine which additional variables were associated with suicide/overdose after adjusting for age and sex (Cox regression analysis). Third, a final multivariable model was run that adjusted for age, sex, and the variables that were significant in step 2 (multivariable Cox regression analysis). This final multivariable model included the following variables (time-varying where appropriate): age, sex, race, BMI, pack-years, current smoking status, airflow limitation (FEV_1 % predicted), dyspnea (mMRC score ≥ 2), 6-min walk distance, supplemental oxygen use, and severe exacerbations in the past year. The analysis censored at loss to follow-up or death due to other causes.

To avoid the assumption that other causes of death were noninformative on risk, we modeled other causes of death as competing risks with a cause-specific relative hazard. This was selected over a cumulative incidence function-based approach to modeling competing risks given our focus on causal mechanisms underlying events rather than estimating prognosis or actual risk.[30,31] The proportional hazards assumption was tested for these variables by modeling interactions with time for each variable in separate, unadjusted models. We then tested whether any of these variables were specific to the presence of an obstructive lung disease by modeling their interaction with a dichotomous variable for obstructive disease. Sensitivity analyses were performed to assess concerns for potential site effects, medication effects (adding medications of each of six psychotropic medication classes individually to models as

indicator variables), and dependence by modeling all subjects with events from other causes of death as either event free or all having the event. Analyses were conducted by using SAS 9.4 (SAS Institute, Inc).

Results

From a total COPDGene Phase 1 sample of 10,371, we excluded those with interstitial lung disease/bronchiectasis (n = 66) and those who never smoked (n = 107) to yield a cohort of 10,198 individuals with smoking exposure. After excluding those who did not consent to nonsmoking-related research, the analytic sample comprised 9,930, 61.7% (n = 6,131) of whom had Phase 2 follow-up and 20.9% (n = 2,078) of whom had Phase 3 follow-up at the time of most recent cause-specific mortality database release. As shown in Table 1, participants had a mean age of 59.6 ± 9.0 years and were mostly non-Hispanic White (67.3%), male (53.4%), currently smoking (52.6%), and overweight (mean BMI, 28.8 ± 6.3 kg/m^2 at intake. Just under one-half (42.5%) of the participants had normal spirometry (GOLD 0) results, 12.4% were classified as having preserved ratio impaired spirometry, 26.8% had mild to moderate COPD (GOLD 1-2), and 17.6% had severe to very severe COPD (GOLD 3-4). The most common psychotropic medications were antidepressants (18.9%; n = 1,862), followed by sedative/hypnotics (10.1%; n = 999), antipsychotics (3.5%; n = 341), mood stabilizers (2.0%; n = 195), and stimulants (0.5%; n = 51). Participants with severe to very severe COPD (GOLD 3-4) had the highest use of sedative/hypnotics (14.0%).

Over a median follow-up of 7.8 years (up to 11.7 years and 69,387 person-years of total follow-up), the composite outcome of suicide/overdose was identified in 63 subjects (90.8 per 100,000 person years). Death with suicidal intent was confirmed in seven subjects (10.1 per 100,000 person years), and death by overdose of indeterminate intent occurred in 56 subjects. There were a total of 1,304 deaths of the 9,930 participants during our observation window (Fig 1). When comparing those who died by suicide/overdose vs those who did not in competing risk Cox regression models adjusting for age and sex (Table 2), we found that those who died by suicide/overdose were more likely to be younger (adjusted across models), be currently smoking (HR, 5.98; 95% CI, 2.46-14.55; $P < .001$), and to use sedative/hypnotics (HR, 2.90; 95% CI, 1.56-5.40; $P < .001$). Subjects who died by suicide/overdose were more likely to report dyspnea (mMRC score ≥ 2) (HR, 2.13; 95% CI, 1.28-3.54; $P = .003$), although there were not significant differences in airflow limitation, 6-min walk distance, supplemental oxygen requirement, or severe exacerbations within the past year. Among subjects who died by suicide/overdose, a nonsignificantly smaller percentage (7.9%) had moderate to severe COPD (GOLD 3-4) compared with those who did not die by suicide/overdose (17.6%).

In the multivariable model (Table 3), we found that younger age, lower BMI, dyspnea (mMRC score ≥ 2), current smoking, and sedative/hypnotic use were independent risk factors for death by suicide/overdose among individuals with smoking exposure enrolled in the study. In the adjusted model, the largest risk factor for death by suicide or overdose was current smoking (HR, 6.44; 95% CI, 2.64-15.67; $P < .001$), followed by sedative hypnotics use (HR, 2.33; 95% CI, 1.24-4.38; $P = .009$), and dyspnea (mMRC ≥ 2) (HR, 2.23; 95% CI, 1.34-3.70; $P = .002$). Sensitivity analyses suggested that models were robust to assumptions regarding site and medication effects and independence between competing risks.

Discussion

In this prospective cohort of approximately 10,000 individuals with smoking exposure, death by suicide/overdose occurred 63 times (90.8 per 100,000 person-years). We observed a higher risk of suicide/overdose with younger age, white race, lower BMI, dyspnea (mMRC score ≥ 2), current smoking, and use of sedative/hypnotics. Airflow limitation was not associated with higher suicide risk. Our study addresses limitations in prior studies of suicide risk in COPD. COPD diagnosis and severity are well characterized using objective parameters, smoking status of participants is known, and suicide risk is based on death adjudication rather than surrogate outcomes for suicide (eg, suicidal ideation or attempts). Of note, participants with and without COPD were primarily recruited from different settings (health care and community, respectively), so caution should be taken when directly comparing COPD and non-COPD groups.

Death by suicide/overdose was rare but still more common than in the general population (13.9 per 100,000 in 2019).[32] Higher rates of suicide were anticipated in this cohort based on prior research showing that COPD is associated with depression,

TABLE 1] Sociodemographic and Clinical Characteristics of Sample

Variable	Total Sample (N = 9,930)	Outcome		*P* Value
		Suicide/Overdose (n = 63)	No Suicide/Overdose (n = 9,867)	
Age, y[a]	59.6 ± 9.0	53.8 ± 6.1	59.7 ± 9.0	< .0001
BMI (kg/m^2)[b]	28.8 ± 6.3	27.0 ± 5.2	28.8 ± 6.3	.02
Pack-years of tobacco (n = 9,926)	44.4 ± 25.0	44.6 ± 26.5	44.4 ± 25.0	.94
FEV_1 % predicted (n = 9,865)	76.1 ± 25.5	80.9 ± 22.6	76.0 ± 25.6	.13
6-Min walk distance, m (n = 9,789)	411 ± 122	416 ± 89	411 ± 122	.73
COPD	9,865 (99.3%)	63 (100%)	9,802 (99.3%)	.32
GOLD 0: normal spirometry	4,225 (42.5%)	29 (46.0%)	4,196 (42.5%)	
PRISm	1,230 (12.4%)	9 (14.3%)	1,221 (12.4%)	
GOLD 1 and 2	2,666 (26.8%)	20 (31.7%)	2,646 (26.8%)	
GOLD 3 and 4	1,744 (17.6%)	5 (7.9%)	1,739 (17.6%)	
Dyspnea (mMRC score ≥ 2)	4,167 (42.0%)	33 (52.4%)	4,134 (41.9%)	.09
Female	4,627 (46.6%)	24 (38.1%)	4,603 (46.6%)	.17
Race				.49
Black	3,244 (32.7%)	18 (28.6%)	3,226 (32.7%)	
White	6,686 (67.3%)	45 (71.4%)	6,641 (67.3%)	
Currently smoking[a]	5,222 (52.6%)	58 (92.1%)	5,164 (52.3%)	< .0001
Supplemental oxygen	1,165 (11.7%)	7 (11.1%)	1,158 (11.7%)	.88
Severe exacerbation, past year	1,187 (12.0%)	8 (12.7%)	1,179 (11.9%)	.86
Psychotropic medication use (n = 9,862)				
Antidepressants	1,862 (18.9%)	16 (25.8%)	1,846 (18.8%)	.16
Mood stabilizers[b]	195 (2.0%)	4 (6.5%)	191 (1.9%)	.01
Sedative/hypnotics[b]	999 (10.1%)	12 (19.4%)	987 (10.1%)	.02
Antipsychotics	341 (3.5%)	3 (4.8%)	338 (3.4%)	.55
Stimulants	51 (0.5%)	0 (0.0%)	51 (0.5%)	.57
Comorbidity count[a]	2.5 (1.9)	1.8 (1.4)	2.5 (1.9)	.006
Coronary heart disease	651 (6.6%)	1 (1.6%)	650 (6.6%)	.11
Diabetes mellitus	1,296 (13.1%)	7 (11.1%)	1,289 (13.1%)	.65
Congestive heart failure	316 (3.2%)	2 (3.2%)	314 (3.2%)	> .99
Stroke	259 (2.6%)	0 (0%)	259 (2.6%)	.19
Osteoarthritis	1,894 (19.1%)	13 (20.6%)	1,881 (19.1%)	.75
Osteoporosis	897 (9.0%)	3 (4.8%)	894 (9.1%)	.24
Hypertension[a]	4,295 (43.3%)	13 (20.6%)	4,282 (43.4%)	.0003
High cholesterol[a]	3,813 (38.6%)	12 (19.0%)	3,825 (38.5%)	.001
Gastroesophageal reflux disease	2,500 (25.2%)	13 (20.6%)	2,487 (25.2%)	.40
Stomach ulcers[a]	822 (8.3%)	11 (17.5%)	811 (8.2%)	.008
Sleep apnea	1,465 (14.8%)	6 (9.5%)	1,459 (14.8%)	.43
Hay fever	2,898 (29.2%)	16 (25.4%)	2,882 (29.2%)	.73
Peripheral vascular disease	231 (2.3%)	0 (0%)	231 (2.3%)	.21
Obesity	3,660 (36.9)	16 (25.4%)	3,644 (36.9%)	.06

Data are presented as mean ± SD unless otherwise indicated. This table summarizes the clinical and sociodemographic characteristics of the sample for continuous and categorical variables for the total sample and according to outcome (death by suicide or drug). GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council scale; PRISm = preserved ratio impaired spirometry.

[a] $P < .01$.

[b] $P < .05$.

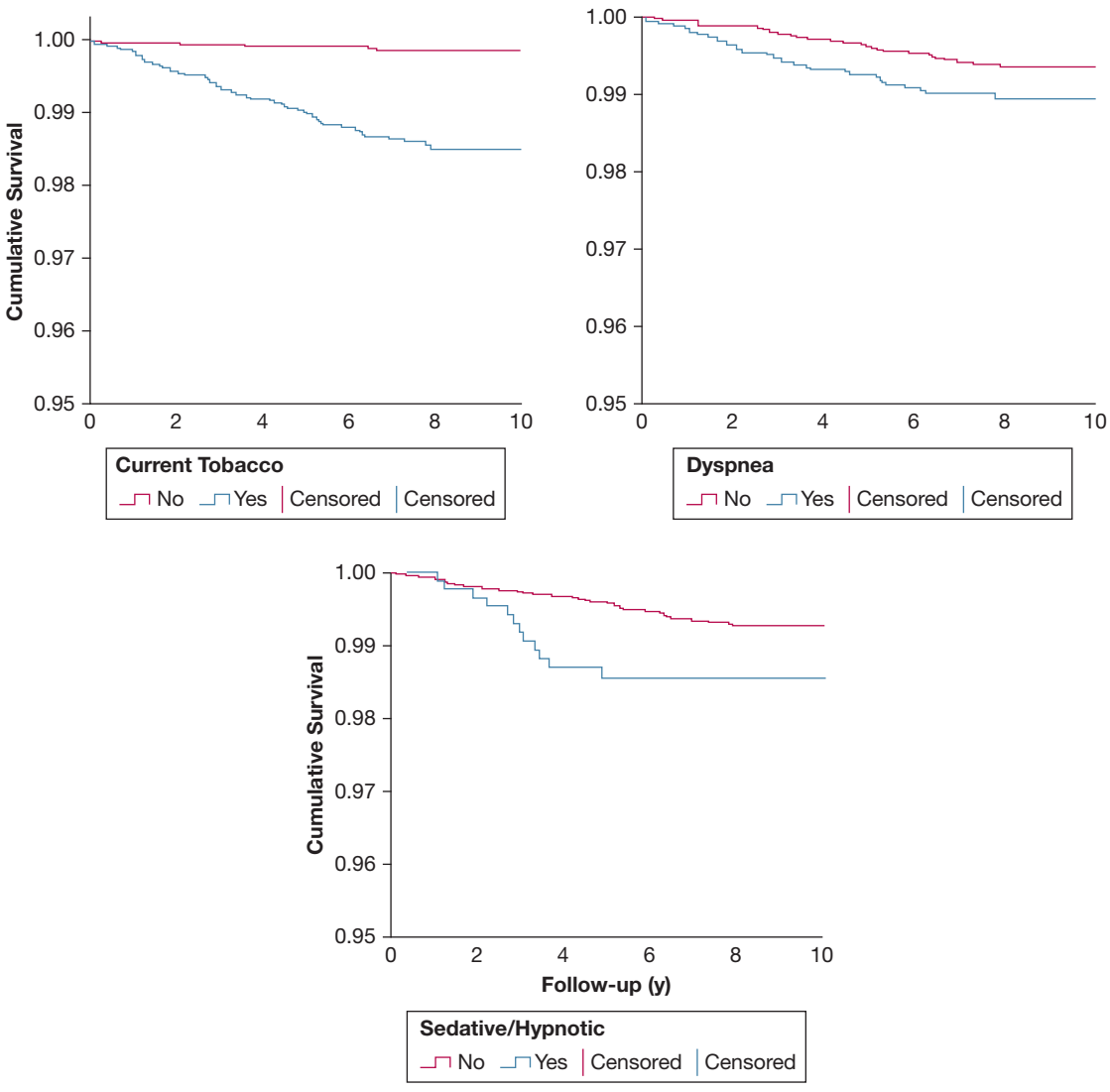

Figure 1 – *Kaplan-Meier survival curves for clinical variables of interest. Figure shows the Kaplan-Meier survival curves for time to death by suicide/overdose for groups stratified according to clinical variables of interest at baseline. These variables included current tobacco use, dyspnea (defined by a modified Medical Research Council Dyspnea scale score ≥ 2) and use of sedative/hypnotic medications. Unlike the primary Cox regression models, which model these variables as time-varying covariates, groups here are based on baseline variables only, and without adjustment, to illustrate differences in risk between groups on these variables of interest at baseline.*

anxiety, and suicide.[1-5,33-35] In the current study, men had a nonsignificantly higher risk of suicide than women. This is contrary to studies by Crump et al[4] and Webb et al,[5] who observed higher suicide risk among women with physical illness, and Strid et al,[2] who found more pronounced suicide risk in women with COPD.

The strongest risk factor for death by suicide/overdose was current smoking, which was associated with a sixfold increase in risk. Inability to quit smoking despite the adverse effects of COPD could be a source of demoralization. Smoking may also be confounded by other risk factors for suicide such as socioeconomic status, financial strain, social isolation, psychological distress, and other substance use disorders.[36,37] The association between smoking and disrupted sleep has been described as a possible cause of psychological distress among individuals with smoking exposure,[36] which may also contribute to the relationship between suicide and sedative/hypnotic use in the current cohort. Large population-based studies and meta-analyses have shown that smoking itself is a risk factor for suicide, with twofold to threefold increase in risk.[10-12,38] Green et al[39] discussed four potential mechanisms to explain the link between smoking and suicide: smoking may directly affect mood by reducing serotonin and dysregulation

TABLE 2] Survival Analyses on Time to Suicide/Drug Overdose

Variable	Hazard Ratio	95% CI	*P* Value
BMI (kg/m^2)[a,b]	0.95	0.90-0.99	.01
Pack-years of tobacco[a]	1.01	0.999-1.02	.07
FEV_1 % predicted[a]	1.00	0.99-1.01	.59
6-Min walk test distance (≤ 400 ft)[a]	0.86	0.67-1.11	.25
Comorbidity count[a]	0.88	0.75-1.03	.12
COPD group[a]			
GOLD 0: normal spirometry	REF		
PRISm	1.30	0.61-2.76	.50
GOLD 1 and 2	1.79	0.995-3.23	.052
GOLD 3 and 4	0.99	0.38-2.67	> .99
Dyspnea (mMRC score ≥ 2)[a,b]	2.13	1.28-3.54	.003
Black race[b]	0.48	0.27-0.86	.01
Currently smoking[a,b]	5.98	2.46-14.55	< .001
Supplemental oxygen[a,b]	2.04	0.90-4.59	.09
Severe, exacerbation in the past year[a]	1.43	0.71-2.91	.32
Psychotropic medication use (baseline)			
Antidepressants[a]	1.67	0.93-2.98	.08
Mood stabilizers[a]	2.16	0.78-6.01	.14
Sedative/hypnotics[a,b]	2.90	1.56-5.40	< .001
Antipsychotics[a]	1.13	0.35-3.61	.84
Stimulants[a]	…	…	…

Impact of selected variables on risk of suicide and accidents as time-varying covariates (where applicable) in separate Cox regression models adjusting for age and sex. Other causes of death were modeled as a competing risk in cause-specific models. PRISm = preserved ratio impaired spirometry.
[a]Time-varying covariate.
[b]$P < .05$.

hypothalamic-pituitary-adrenal axis; individuals with smoking exposure are more likely to have mental health conditions and concurrent substance use disorders; smoking is associated with multiple debilitating health conditions; and smoking is more common in structurally disadvantaged populations that are also more vulnerable to mental health disorders.

One strength of the current study was the well-characterized pulmonary phenotyping of the cohort. It is noteworthy that objective measures of COPD severity (eg, FEV_1 % predicted, 6-min walk distance, supplemental oxygen requirement, severe exacerbations in the past year) were not associated with suicide/overdose. Rather, the experience of feeling dyspneic as

TABLE 3] Survival Analyses on Time to Suicide/Drug

Variable	Hazard Ratio	95% CI	*P* Value
Age (decades)[b]	0.45	0.31-0.67	< .001
BMI (kg/m^2)[a,b]	0.95	0.91-0.995	.03
Male	1.68	0.996-2.83	.051
Race (Black)[b]	0.41	0.23-0.74	.003
Dyspnea (mMRC score ≥ 2)[a,b]	2.23	1.34-3.70	.002
Currently smoking[a,b]	6.44	2.64-15.67	< .001
Sedative/hypnotics[a,b]	2.33	1.24-4.38	.009

Multivariable Cox regression model including age, sex, and variables significant in univariable models (from Table 2).
[a]Time-varying covariate.
[b]$P < .05$.

measured by using mMRC scoring was associated with a twofold increased risk of suicide/overdose. The mMRC dyspnea scale assesses the experience of dyspnea with varying levels of activity, with a score of 2 given for "walking slower than people of the same age because of dyspnea or having to stop for breath when walking at own pace" and a maximum score of 4 given for being "too dyspneic to leave the house or breathless when dressing." These findings emphasize that the subjective experience of physical illness contributes most to suffering, and experience of illness is not always captured by objective parameters. This has been observed in other chronic medical conditions; for example, there is not a strong correlation between esophageal pH and heartburn.[40]

Another explanation for the stronger association between dyspnea and suicide/overdose is that the experience of dyspnea is more severe among those with untreated symptoms of depression or anxiety. Iyer et al[22] performed a cross-sectional analysis of Phase 2 data from COPDGene when depression and anxiety were first assessed in the cohort. The highest frequency of depressive symptoms as measured by using the Hospital Anxiety and Depression Scale (HADS)-Depression score was in individuals with severe to very severe COPD; this group was also most likely to have unmedicated symptoms. In contrast, anxiety symptoms as measured according to HADS-Anxiety scores were evenly distributed across COPD stages. Depression and anxiety symptoms were not assessed during Phase 1 of the COPDGene study and therefore not included in this analysis. It is possible that dyspnea reflects, in part, more severe or untreated depression or anxiety.

In the current model, sedative/hypnotics, which include benzodiazepines, were most frequently prescribed to participants with moderate to severe COPD (GOLD 3-4), and their use was independently associated with death by suicide/overdose. Donovan et al[41] observed that individuals with COPD and posttraumatic stress disorder who reported long-term benzodiazepine use had higher rates of psychiatric admissions compared with matched control subjects but did not differ in terms of all-cause mortality or COPD-related deaths. These findings suggest that underlying psychiatric illness may drive the suicide risk in those using sedative/hypnotics such as benzodiazepines. Our study builds upon this analysis by also including spirometry data showing that those with the most severe airflow limitation are more likely to be prescribed sedative/hypnotics although they did not have significantly higher suicide/overdose risk in our multivariable analysis.

Sedative/hypnotics are often used to treat insomnia, which is common among patients with COPD, particularly when severe due to nocturnal desaturation events, increased sleep latency, and frequent nighttime awakenings.[42,43] Sleep disturbances are also a diagnostic feature of depression. Therefore, it is possible that use of sedative/hypnotics is a marker of COPD symptom burden or depression.[42] This association was previously shown in a case-control study comparing hospitalized patients with COPD vs those without, in which insomnia was significantly associated with more physical illness and more severe depressive symptoms.[44] Similar to sleep, the association between lower BMI and suicide risk may be explained by lower BMI being a marker of worse overall health (ie, cahexia associated with more severe COPD).

Health care providers treating individuals with smoking exposure should inquire about smoking status, severity of respiratory symptoms, and prescription of sedative/hypnotics, as these factors may indicate the presence of other suicide risk factors such as depression, anxiety, sleep disturbances, and physical disability. In individuals with smoking exposure with heavy symptom burden, clinicians should consider assessing for depression, anxiety, and suicidal ideation. Fleehart et al[35] showed that individuals with COPD and suicidal ideation were dissatisfied that their providers did not address suicidal thoughts during clinical appointments. Therefore, providers should not consider any such screening unwelcomed.

The current study has several limitations. Data on socioeconomic status, substance use disorders, other comorbid mental health conditions, history of inpatient psychiatric hospitalizations, or history of suicidal gestures or attempts were not collected during Phase 1 of the COPDGene study, and therefore we cannot evaluate these exposures of interest. Although HADS-Depression and HADS-Anxiety questionnaires were collected at Phase 2 visits, these scores were not included in our study because it would result in removal of many of the study participants who had enrolled at Phase 1, leaving the analysis underpowered. Our analysis of comorbidities is an imperfect measure that cannot capture the complexity of how comorbidities affect suicide risk in the current cohort. We used comorbidity count rather than adjusting our model for each comorbidity individually to reduce the number of parameters in the multivariable model, given the rarity of our outcome of interest. Comorbidity count has been used previously in the COPDGene cohort.[23] The

COPDGene cohort was from US sites with African-American and non-Hispanic White subjects and may not be generalizable to other populations or racial groups. Conditioning on heavy smoking through the study design may introduce a collider bias for which the magnitude or direction of which for any given variable is difficult to assess. Finally, the COPDGene study was not originally designed to evaluate depression, anxiety, or suicide/overdose. COPDGene used a range of recruitment strategies, and individuals with smoking exposure with COPD were largely recruited from clinical sites, whereas many individuals with smoking exposure without COPD were recruited from the general community. Caution should be exercised in comparing those with and without COPD. The current analysis is not focused on COPD status alone but rather identifying key demographic characteristic and clinical factors associated with suicide/overdose in individuals with smoking exposure.

Interpretation

Among individuals with smoking exposure with and without airway obstruction, current smoking was the strongest risk factor, associated with a sixfold greater risk for suicide/overdose, followed by sedative/hypnotics use and dyspnea (mMRC score $\geq$ 2). Objective measures of COPD severity were not associated with suicide/overdose. One implication of our findings is that the subjective experience of COPD is important in assessing suicide risk among individuals with smoking exposure. Further work is required to determine the generalizability of these results in other health care settings, nonsmoking or lighter smoking populations, and the role of psychological distress.

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