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## Understanding the impact of secondhand smoke exposure on clinical outcomes in participants with COPD in the SPIROMICS cohort

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### Abstract

**Background**—Secondhand smoke (SHS) exposure has been linked to the development of and morbidity from lung disease. We sought to advance understanding of the impact of SHS on health-related outcomes in individuals with COPD.

**Methods**—Among COPD participants in SPIROMICS, recent SHS exposure was quantified as, 1) as hours of reported exposure in the past week or 2) reported living with a smoker. We performed adjusted regression for SHS with outcomes, testing for interactions with gender, race, smoking and obesity.

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#### COMPETING INTERESTS

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**Results**—Of 1,580 COPD participants, 20% reported living with a smoker and 27% reported exposure in the last week. Living with a smoker was associated with worse St George's Respiratory Questionnaire score (SGRQ,  $\beta$  3.10; 95% CI 0.99, 5.21), COPD Assessment Test score ( $\beta$  1.43; 95% CI 0.52, 2.35) and increased risk for severe exacerbations (OR 1.51, 95% CI 1.04, 2.17). SHS exposure in the past week was associated with worse SGRQ ( $\beta$  2.52; 95% CI 0.47, 4.58), nocturnal symptoms (OR 1.58; 95% CI 1.19, 2.10), wheezing (OR 1.34; 95% CI 1.02, 1.77), chronic productive cough (OR 1.77; 95% CI 1.33, 2.35), and difficulty with cough and sputum (Ease of Cough and sputum scale,  $\beta$  0.84; 95% CI 0.42, 1.25). SHS was associated with increased airways wall thickness on CT but not emphysema. Active smokers, obese individuals and individuals with less severe airflow obstruction also had higher susceptibility to SHS for some outcomes.

**Conclusions**—Individuals with COPD, including active smokers, have significant SHS exposure, associated with worse outcomes and airways wall thickness. Active smokers and obese individuals may have worse outcomes associated with SHS.

### Keywords

COPD epidemiology; secondhand smoke; tobacco and the lung

## INTRODUCTION

Since the Surgeon General's report in 1964 linking tobacco smoke to lung cancer, the recognition of tobacco's impact on health has grown.[1] There is increasing awareness of the role of secondhand smoke (SHS) exposure in contributing to adverse health outcomes,[1 2] including development of Chronic Obstructive Pulmonary Disease (COPD).[3–6] Moreover, the chemistry of SHS differs from that of primary smoke, creating the possibility of SHS being an additional risk factor even for active smokers.[7] Among those with COPD, a few studies suggest that SHS exposure adversely impacts quality of life, dyspnea and risk for COPD exacerbation, but these studies are limited to former smokers.[8–10] It is not fully known whether SHS is detrimental to health outcomes in COPD, and specifically it has not been shown whether SHS is detrimental in active smokers with COPD. Further highlighting the lack of evidence in this realm, the GOLD consensus report, though noting the possible contribution of SHS to COPD incidence, do not mention SHS as a contributor to COPD morbidity.[11] Additionally, whether there are subgroups of COPD at heightened susceptibility to SHS has not been elucidated, particularly in current smokers with heavy smoke exposure history.

We sought to determine the independent contribution of SHS to clinical characteristics using validated exposure instruments, CT measures, and validated COPD outcomes in a large study of former and current smokers with COPD having a high personal level of primary smoking history. We analyzed the large, well-characterized COPD cohort in SPIROMICS[12] in order to understand if important subgroups of individuals with COPD could be identified who might have heightened susceptibility to the negative impacts of SHS exposure, such as race and gender, given evidence in the literature of heightened susceptibility of African Americans and women[13 14] to the effects of smoking, as well as obesity, given evidence of heightened susceptibility of obese individuals to indoor air

pollution.[15] Additionally, of interest was the potential heightened susceptibility of former smokers (compared to current active smokers) to the adverse effects of SHS.

## METHODS

SPIROMICS[12] is a multicenter study of current and former smokers (  $\geq 20$  pack-years) with and without COPD and non-smokers without COPD age 40–80 years. The original goals of the study were to determine intermediate outcomes and endpoints in the population with COPD in order to identify subgroups of individuals with COPD who could be targeted for future specific therapeutic strategies and treatments. Current and former smokers with (strata 3–4) and without COPD (stratum 2) were recruited, as were healthy, lifelong nonsmokers (stratum 1). We studied all individuals with COPD (post-bronchodilator FEV<sub>1</sub>/FVC of  $<70\%$ ) including subjects in strata 3 (FEV<sub>1</sub>  $\geq 50\%$  predicted) and 4 (FEV<sub>1</sub> $<50\%$  predicted) in primary analysis [11]. Secondary analyses incorporated individuals from strata 1–2. Further details on the study population can be found in the online Supplement.

### SHS characterization

Participants were asked about smokers in the household. SHS exposure over the past week was quantified in hours using a validated questionnaire for the assessment of exposure in multiple locations including within and outside of the home (including other person's home, workplace, car or other location while traveling, place of entertainment, or other location).[9–16] Additional questions quantified lifetime SHS exposure in the home in years, as previously utilized by Eisner et al.[4]

### CT measures

Participants underwent whole-lung multidetector helical CT at full inspiration and expiration. Measurements of interest included percent emphysema, percent gas-trapping, Pi10 (a measure of airway wall thickness), and airway dimensions including area and diameter of walls and lumens of airways in generations 1–6. Details are provided in the online supplement.

### Outcomes (e-Table 1)

Outcomes of interest were respiratory-specific quality of life (St. George's Respiratory Questionnaire, SGRQ),[17] general quality of life (short-form 12 item questionnaire, SF12), [18] exercise capacity (six minute walk distance in meters, 6MWD),[19] dyspnea (modified Medical Research Council questionnaire, mMRC),[20] and COPD health status (COPD assessment test, CAT).[21] Cough and phlegm over the past day were measured using the total score from the Ease of Cough and Sputum questionnaire.[22] Respiratory Symptoms (cough, phlegm, bronchitis, wheezing and nocturnal symptoms) were measured using the American Thoracic Society Division of Lung Diseases of the National Heart and Lung Institute Questionnaire (ATS/DLD-78-adult).[23] Chronic cough and phlegm status was determined as an affirmative response to the question "Do you usually..." for the individual symptom and chronic productive cough was determined as an affirmative response to both questions, as described previously.[24] Participants were asked about medication changes or

dose adjustments, unscheduled doctor visits, emergency room visits, days hospitalized, and intensive care unit admissions for COPD exacerbations and frequency of these instances over the past year. Severe exacerbations were defined as events requiring emergency room visit or hospitalization. All information was collected at baseline, however additionally we analyzed available data regarding exacerbations noted by participants from the time of study enrollment to most recent follow-up contact.

## Statistical methods

Recent SHS exposure was determined by two exposure metrics including i) report of living with a smoker (yes/no), referred to as “living with a smoker”, and ii) SHS exposure reported in any location over the past week, dichotomized as 0–1 hour of exposure (non-exposed) or 2 or more hours of exposure (exposed) as in previous publications[25], referred to as “recent SHS exposure.” Years of lifetime SHS exposure were also studied and modeled as quartiles of exposure, to evaluate possible dose response.[4] Participant characteristics were compared based upon SHS exposure using t-tests and  $\chi^2$  tests.

We analyzed the relationship between SHS exposures and outcomes using linear and logistic regressions, adjusting for age, gender, race (African American vs. other), education (high school education or less vs. more than high school), current smoking and pack-years smoked. Cross-sectional data were analyzed using linear or logistic regression models (in which coefficients and log odds were the modeled effects) with the exception of analyses of longitudinal exacerbations over follow-up, which were analyzed as count data using adjusted Poisson regression (in which relative risk was the modeled effect) and analysis of mean differences in airway wall and lumen area and diameter as well as wall area percent for generation 1 to 6, for which we used generalized estimating equations (GEE). [26] Further detail on statistical methods can be found in online supplement.

Of interest was possible effect modification of current smoking, such that non-smokers might have relatively higher susceptibility to SHS. In sensitivity analyses, we additionally adjusted these models for the daily number of cigarettes actively smoked to further isolate the effects of SHS over active smoking. We also tested for interactions between SHS exposure and race, gender, severity of airflow obstruction (GOLD 1,2 as less severe vs. GOLD 3,4 as more severe) and obesity (defined dichotomously as BMI>30 kg/m<sup>2</sup>), as noted above.

All analyses were conducted with Stata 12.[27] 0.05 was the threshold for significance for main effects and 0.10 for interactions.[15 28 29] SPIROMICS was approved by Institutional Review Boards at each center and all participants provided written informed consent (clinicaltrials.gov: NCT01969344).

## RESULTS

At the time of analysis, 1,580 participants had spirometric evidence of COPD. Of these, 20% (n=313) reported living with a smoker, 54 % (n=170) of whom were current smokers and 46% (n=143) were former smokers. 428 participants (27%) with COPD reported recent SHS exposure (i.e. 2 or more hours of exposure within the past week), while 1,152 (73%)

reported 0–1 hours of exposure. Participants reporting recent SHS exposure had a median of 7 hours of SHS exposure (25<sup>th</sup> percentile 3, 75<sup>th</sup> percentile 21, e-Figure 1). Participants reporting recent SHS exposure were younger (mean age 61.9 vs. 66.8 years), more likely to be African American (23% vs. 12%), had less education, and lower household income (Table 1). Although there were minimal differences in pack-years smoked, there were more current smokers in the recent SHS exposure group (64% vs. 20%). Individuals reporting recent SHS had significantly better lung function (FEV<sub>1</sub> percent predicted 63.5 vs. 60.2) and less emphysema and gas-trapping on CT (4.8% vs. 8.1%, and 63.5% vs. 66.9%, respectively). SHS exposure data was missing in only 38 of 1,580 participants, who were excluded from analyses. There were strong correlations between metrics of recent SHS exposure (e-Table 2), such that individuals with more reported hours of SHS exposure in the past 7 days were more likely to live with a smoker. Additionally, mean years of SHS exposure reported before and after the age of 18 were significantly higher in the groups reporting more hours of SHS exposure in the past week and living with a smoker. Median follow-up time for exacerbation data was 594 days (25<sup>th</sup> pctl 292, 75<sup>th</sup> pctl 995) in the cohort with COPD (stratum 3–4).

### Association of living with a smoker and outcomes

After adjustment, living with a smoker was associated with worse outcomes (Table 2) including SGRQ, SF12, CAT and higher ease of cough and sputum scores (i.e. more impaired). Living with a smoker was also associated with severe exacerbations in the past year and chronic productive cough. Additionally, living with a smoker was associated with increased airways wall thickness measured by Pi10, but not with emphysema or gas trapping.

### Association of recent SHS exposure (2 or more hours of SHS exposure in the past week) and outcomes

Recent SHS exposure was associated with worse short-term outcomes after adjustment. (Table 3, Figure 1) Recent SHS was associated with worse SGRQ score, nocturnal symptoms, wheezing, worse ease of cough and phlegm, and less exercise capacity. To account for possible influences from occupational exposures,[30] models were additionally adjusted for report of exposure to vapors, dusts, gases or fumes in the longest held job, and results were similar. Measures of recent SHS exposure (hours of SHS exposure in the past 7 days and living with a smoker) were associated with differences in airway dimensions (Tables 2 and 3). In generation 5 airways, wall area and lumen area and diameter were smaller in those with SHS exposure compared to those without, the wall area was thicker relative to lumen size, as indicated by significantly higher wall area percent. Results for other airway generations (1–4, 6) did not have significant results (data not shown).

### Years of SHS exposure and outcomes

Lifetime exposure to SHS was highly prevalent, with 82.1% reporting home exposure before age 18, and 77.8% reporting home exposure after age 18. Participants were divided into quartiles based upon years of home SHS exposure during their lifetime, (median (range): 1<sup>st</sup> quartile 18 years (0–18), 2<sup>nd</sup> quartile 21 years (19–23), 3<sup>rd</sup> quartile 33 years (24–40) and 4<sup>th</sup> quartile 52 years.(41–90) We found minimal contribution of years of cumulative exposure

reported with health outcomes in participants with COPD when testing the associations of quartiles 2–4 compared to the 1<sup>st</sup> quartile using disjoint categories for each quartile (e-Table 3). When we tested the overall contribution of years of SHS exposure using likelihood ratio testing of nested models, only the model of SGRQ reached statistical significance ( $p=0.047$ ) in its overall contribution to the model.

### Subgroups with increased susceptibility to SHS

We found interactions between SHS metrics and smoking status, obesity, and severity of airflow obstruction. Current smoking modified the effect of SHS exposure on several outcomes (Figure 2, Table 4), such that in most cases current smokers appeared to have higher susceptibility to adverse outcomes than former smokers. Living with a smoker was linked to a higher risk of a severe COPD exacerbation in the past year in current smokers compared to former smokers (OR 2.33 vs. 1.12, interaction  $p=0.055$ ). Recent SHS exposure had a greater negative impact on 6MWD in current smokers compared to former smokers ( $-27.41$  vs  $-5.96$ , interaction  $p=0.071$ ); however only general quality of life was worse in former smokers compared to active smokers (SF12  $-2.93$  vs  $0.68$ , interaction  $p=0.006$ ). Models including adjustment for number of daily cigarettes smoked did not appreciably change the effect of SHS among those still smoking (data not shown).

Those with milder airflow limitation and obese individuals had greater adverse effects associated with SHS exposure for some outcomes (Figures 3–4, Table 4). Living with a smoker was associated with worse outcomes among participants with less severe air flow obstruction (GOLD 1–2) compared to those with more severe obstruction (GOLD 3–4), including greater decrement in exercise capacity, worse CAT score, and more wheezing. Among obese individuals, living with a smoker was linked to a higher risk for nocturnal symptoms and chronic cough compared to non-obese individuals. Additionally, recent SHS exposure was associated with worse quality of life among obese individuals compared to non-obese individuals, though no such association was noted for SGRQ. We found no significant interactions with gender or race.

### Impact of SHS exposure on outcomes in nonsmokers and current and former smokers without COPD

Analyses of recent SHS exposure and living with a smoker were also performed similarly in the cohort of healthy nonsmokers (stratum 1,  $n=193$ ) and the cohort of former and current smokers without COPD (stratum 2,  $n=803$ ) and results are displayed in e-Table 4 and e-Table 5. There were fewer statistically significant associations of recent SHS exposure and living with a smoker with outcomes in stratum 1, likely reflecting the small size of the cohort and relative low prevalence of reported SHS exposure (only in 12%), however several significant associations were present within stratum 2, illustrating further the importance of SHS in influencing respiratory symptoms in the general population as well as those with COPD.



## DISCUSSION

Secondhand smoke is an unfortunately common exposure among individuals with COPD. We have shown that SHS is a significant contributor to adverse outcomes in COPD, even among active smokers, in a large, well-characterized cohort of patients with a wide range of COPD severity. Recent SHS exposure and living with a smoker are associated with worse respiratory symptoms, quality of life and relative airway wall thickness in COPD. Living with a smoker is also associated with risk of severe exacerbations. Importantly, SHS is linked to worse outcomes even among active smokers. In addition, obese individuals and individuals with less severe COPD may be more susceptible to the adverse effects of SHS.

Twenty percent reported living with a smoker and 36% of participants with COPD reported 2 or more hours of recent SHS exposure, significantly higher than the CDC's estimates that 5.4% of nonsmoking adults are exposed to SHS at home.[31] Such findings highlight the extraordinary prevalence of SHS exposure in COPD. Recent SHS exposure was associated with higher risk for adverse outcomes in COPD, including lower exercise capacity, worse quality of life, and more respiratory symptoms. Owing to the large size of SPIROMICS, our findings lend substantial weight to the findings of previous studies[8 25] which have shown that higher levels of SHS exposure are associated with worse health status, quality of life, dyspnea, exercise capacity, and healthcare utilization in former smokers with COPD. Further, we were able to test these associations in a well-characterized population with COPD with a high burden of smoke exposure (>20 pack years), and also demonstrated that the associations between SHS and negative health outcomes were also present in former and current smokers without COPD, also lending weight to our findings that SHS is an important risk factor for adverse outcomes.

To our knowledge, our results are the first to show the association of SHS with greater relative airway wall thickness in COPD, a novel finding which correlates with chronic bronchitic symptoms.[32 33]. These findings were shown using two distinct techniques, both Pi10, and also using generation-specific airway lumen and wall data. Though these latter findings were only noted in generation 5 airways, previously, Smith et al. reported significant changes in generation 4–6 airways in the population with COPD when compared to stratum 1–2 individuals. It is likely we were unable to see differences in generations other than 5 because of the smaller sample size studied (COPD participants only) and the limited variability in airway dimensions in the population with COPD when compared to studying the larger cohort. Experimental models of SHS exposure in rats have shown heightened pulmonary inflammation leading ultimately to airway and airspace remodeling.[34] The mechanisms for airways and airspace injury due to SHS have not been clearly established among individuals or in animal models where COPD preexists, and would be the next step in order to better explain the findings of our study. Importantly, our findings are consistent with those of general population studies which have shown a higher risk for chronic bronchitis is nonsmokers exposed to SHS.[1 35]

Finally, we have shown that there are possibly subgroups of individuals with COPD that experience higher susceptibility to the health effects of SHS exposure. We hypothesized that former smokers would be more sensitive to SHS than current smokers. This was not the



case. For some outcomes such as quality of life, current smokers showed a greater impact of SHS compared to former smokers. One might intuit that SHS exposure would not greatly impact actively smoking individuals given the small burden that SHS represents when compared to the extensive burden of primary smoking. However, our findings suggest that it is possible that current smokers experience worse outcomes related to SHS possibly because they have a longer duration (though no difference in pack-years smoked, there is a possibility of more hours of active and passive smoke exposure in any given day) or concentration of smoke exposure, as opposed to the quantity of exposure. Additionally, it is important to consider that the toxicity of SHS is qualitatively and quantitatively different from direct active smoke exposure and as such has different effects on outcomes in COPD. Though most of the compounds emitted in secondhand smoke are similar to those in mainstream smoke, the quantitative makeup of SHS and mainstream smoke has been shown to differ. In some cases, the concentration of certain compounds in SHS is greater than that of mainstream smoke, i.e. nicotine, ammonia, formaldehyde, and in other cases, i.e. N'-nitrosonornicotine, (methylnitrosamino)-1-(3-pyridyl)-1-butanone(NNK), the opposite is true. Additionally, the makeup of SHS is often greatly impacted by other environmental exposures.[7 36] Such variation in the quantitative burden of certain compounds could potentially explain our paradoxical findings with regards to current and former smokers with COPD. It is also possible that active smokers have heightened airways inflammation and resulting damage to epithelial cells that alters susceptibility to further inflammation and damage due to SHS. It is possible that SHS is a marker for other behaviors such as medication adherence, exercise or other habits which are less favorable to overall health. The mechanism is an important target for further study, but also highlights the clinical and public health importance of minimizing SHS exposure in all individuals regardless of smoking status.

Obese individuals also showed heightened susceptibility to SHS, with a higher risk for nocturnal symptoms, chronic cough and poor quality of life as a result of SHS compared to lean individuals. These findings are consistent with recently published findings showing obesity as a susceptibility factor for adverse health outcomes related to indoor air pollution in both COPD[15] and asthma.[37] To our knowledge this is the first study showing that obesity may be a susceptibility factor for adverse outcomes associated with SHS. The increased inflammation associated with fat, specifically visceral adipose tissue, may lead to higher amounts of systemic and airway inflammation and lead to alterations in immune defenses in the lung leading to worse outcomes as a result of pollutant exposure.[38] Additionally, obesity may be a reflection of more time spent at home (exposed to home SHS), or also a high fat, low antioxidant diet which has been shown to be pro-inflammatory. [39] Whatever the mechanism, our findings lend weight to the necessity for further studies of obesity as a susceptibility factor for pollutant exposure in lung disease. We also found that individuals with less severe airflow limitation (GOLD stage 1–2 participants) had slightly more susceptibility to adverse outcomes due to SHS than participants with more severe airflow limitation (GOLD stage 3–4 participants). Though this finding is seemingly counterintuitive, it is plausible that individuals with worse COPD severity have such negative outcomes that detecting a further negative effect of SHS would be difficult. It is also possible that individuals with more severe COPD adopt avoidance behaviors that would

attenuate the burden of SHS exposure despite having the same amount of exposure as gauged by our metrics of SHS exposure.

Our study is subject to some limitations. Our measures of SHS exposure rely upon self-report, and there is a possibility of measurement error. We utilized a questionnaire that has been previously validated and shown to be associated with health outcomes. Additionally, our findings were consistent across two measures of SHS exposure (living with a smoker and SHS over the past week), further demonstrating their robustness. We were unable to find a signal for health outcomes in COPD being influenced by years of previous exposure to SHS; nor an association between SHS and percentage emphysema or gas-trapping. It is not clear why shorter-term exposures seemed to have more impact than longer-term exposures. It is possible that in the short-term individuals with COPD including active smokers are susceptible to the acute inflammatory effects of SHS, but in the long term, primary smoking outweighs the effect of SHS on progression of COPD. It is also possible that longer term measures are more subject to recall bias. In addition, this study is subject to the limitations of a cross-sectional study design including issues of temporality and causality. For example, perhaps individuals with more symptoms or more severe disease are more likely to live with a smoker or have a higher risk for SHS exposure. We utilized available longitudinal data on exacerbations experienced over follow-up, but found no significant associations at this point. It will be important to reconsider this question once more complete follow-up data is available after the conclusion of the study to better understand the risk for longitudinal exacerbations associated with SHS exposure. Additionally, though we controlled our models for active smoking in multiple ways, we acknowledge the possibility of residual confounding. Finally, as with many observational studies with multiple clinical outcomes of interest, we are limited by the number of statistical comparisons made in that this can increase the possibility of a type I error. Despite this, the consistency of our findings for the comparisons made is notable. Limitations can be addressed as more longitudinal data becomes available in SPIROMICS. Our findings are relatively generalizable to the population with COPD in the US owing to the diversity and broad range of disease in SPIROMICS.

In summary, using the well-characterized COPD cohort in SPIROMICS, we have shown that SHS exposure is common, impacting over a quarter of the population with COPD. Such exposure is associated with higher risk for adverse outcomes, not only in former smokers but also in those currently smoking, and also with a distinct pattern on CT indicative of heightened airways inflammation. Finally, we have shown that SHS has important impacts on obese individuals and surprisingly also current active smokers, findings which challenge us to further understand the mechanisms responsible for adverse outcomes in COPD associated with SHS exposure.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**What is the key question?**

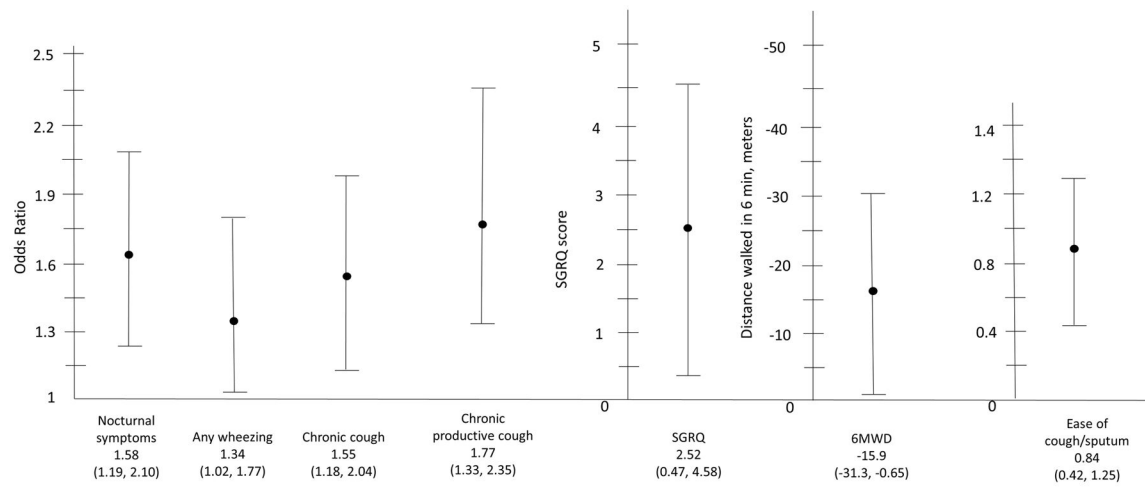
“Do individuals with COPD and exposure to secondhand smoke have worse outcomes compared to individuals with COPD not having exposure to secondhand smoke, and are there subgroups of COPD with higher susceptibility to such adverse outcomes?”

**What is the bottom line?**

Individuals with COPD who are exposed to secondhand smoke have higher risk for worse outcomes including dyspnea, lower exercise capacity and respiratory symptoms, and also have more airways wall thickness on CT.

**Why read on?**

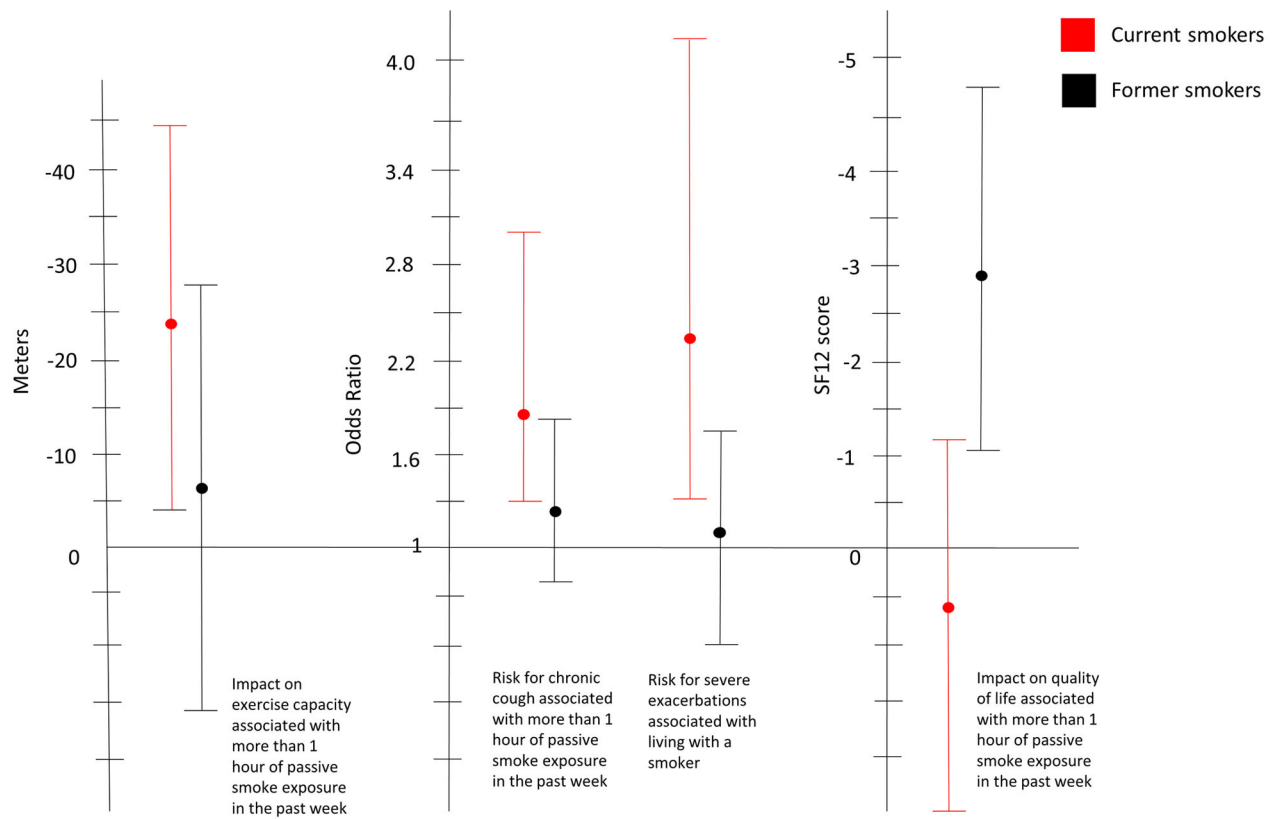
To the best of our knowledge, this is the first study that shows that secondhand smoke exposure is associated with adverse outcomes in current as well as former smokers with COPD, and the first to demonstrate distinct subgroups (current smokers, obese individuals, less severe airflow obstruction) that have a heightened susceptibility to adverse outcomes associated with secondhand smoke.



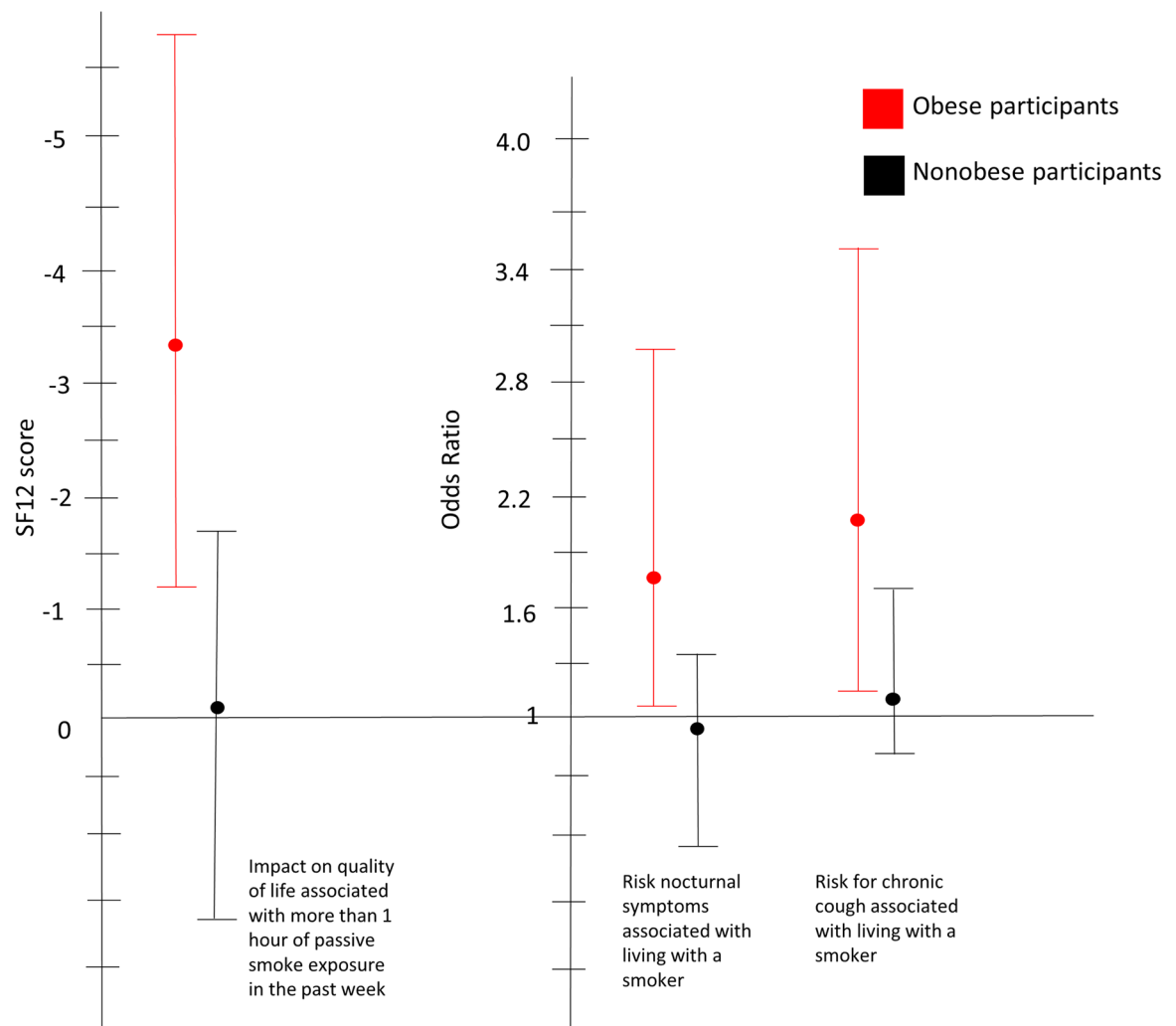
**Figure 1.**

Impact of hours of secondhand smoke exposure in the past week on health outcomes in all participants with COPD. Modeled estimates shown are for 2 or more hours of recent SHS exposure compared to participants with 0–1 hours of exposure.

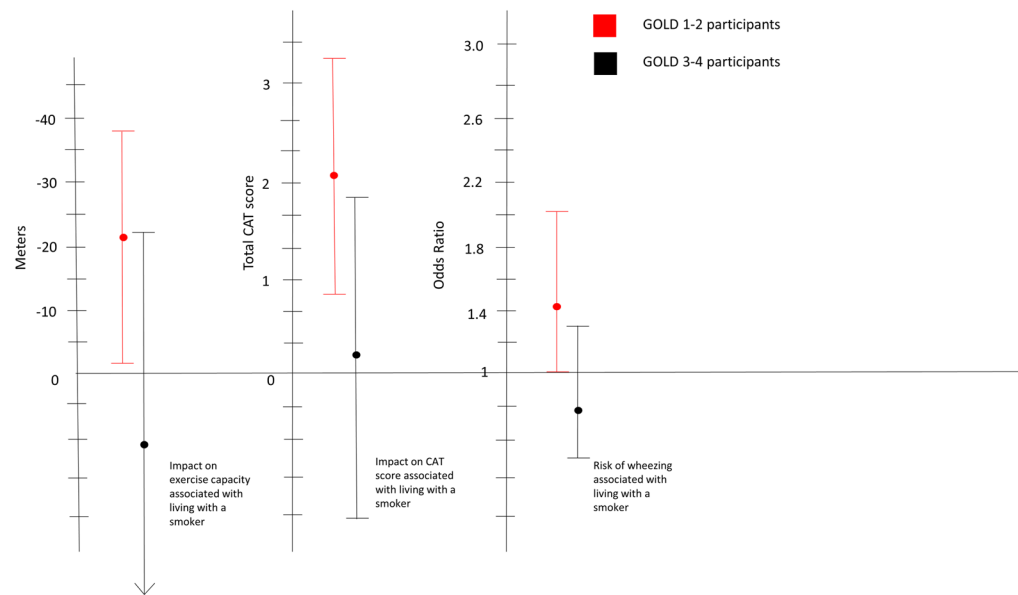




**Figure 2.**  
Interactions between current smoking and secondhand smoke exposure in COPD.



**Figure 3.**  
Interactions between obesity and secondhand smoke exposure in COPD.



**Figure 4.**  
Interactions between severity of COPD and secondhand smoke exposure in COPD.

**Table 1**

Characteristics of GOLD 1–4 participants, by hours of secondhand smoke exposure per week. All values are mean (SD) unless otherwise indicated.

	0–1 hours SHS exposure in a week (N=1,152)	2+ hours SHS exposure per week (N=428)	p-value
Age (years)	66.8 (7.41)	61.9 (8.27)	<0.0001
Female, n(%)	506 (44%)	165 (39%)	0.055
African American, n(%)	136 (12%)	98 (23%)	<0.0001
Hispanic ethnicity, n(%)	42 (4%)	19 (4%)	0.467
FEV1 % predicted	60.19 (23.75)	63.53 (21.66)	0.013
GOLD categories, n (%)			0.016
1	248 (22%)	103 (24%)	
2	491 (43%)	208 (49%)	
3	288 (25%)	84 (20%)	
4	125 (11%)	33 (8%)	
Oxygen use, n(%)	268 (23%)	55 (13%)	<0.0001
Current inhaled steroid use	555 (49%)	192 (45%)	0.237
BMI	27.49 (5.20)	27.17 (5.58)	0.301
Pack-years smoked *	48.5 (36, 66)	48 (37, 64.5)	0.557
Current smoker, n(%)	229 (20%)	276 (64%)	<0.0001
> high school education, n(%)	749 (65%)	219 (51%)	<0.0001
Income \$75K/year or more, n(%)	215 (24%)	55 (15%)	0.001
Obesity, n(%)	358 (31%)	138 (32%)	0.657
% gas trapping	66.93 (13.73)	63.52 (14.43)	<0.0001
% emphysema *	8.07 (2.73, 19.1)	4.82 (1.82, 12.59)	<0.0001
Pi 10 all airways	3.71 (0.08)	3.73 (0.09)	0.011

GOLD- Global initiative for obstructive lung disease

SD- standard deviation

SHS- secondhand smoke

FEV1- Forced expiratory volume in 1 second

SPIROMICS- subpopulations and intermediate outcomes of COPD Study

BMI- body mass index

\* Values displayed are median (25<sup>th</sup> percentile, 75<sup>th</sup> percentile).

**Table 2**

Associations of living with a smoker and COPD outcomes in SPIROMICS

Linear regression models	Absolute difference	95% CI	p-value
6MWD, meters	-7.68	(-23.50, 8.15)	0.341
FEV1 % predicted	-2.13	(-4.87, 0.62)	0.129
<b>SGRQ score</b>	<b>3.10</b>	<b>(0.99, 5.21)</b>	<b>0.004</b>
<b>SF12 GH score</b>	<b>-1.53</b>	<b>(-2.90, -0.16)</b>	<b>0.029</b>
<b>CAT score</b>	<b>1.43</b>	<b>(0.52, 2.35)</b>	<b>0.002</b>
MMRC score	0.07	(-0.05, 0.20)	0.223
<b>Ease of cough and sputum in past day</b>	<b>0.76</b>	<b>(0.34, 1.19)</b>	<b>&lt;0.0001</b>
% emphysema	0.35	(-0.92, 1.55)	0.573
% gas-trapping	0.06	(-1.65, 1.88)	0.946
<b>PI 10 (all airways)</b>	<b>0.16</b>	<b>(0.03, 0.29)</b>	<b>0.020</b>
<b>Airway dimensions (5<sup>th</sup> generation airways)</b>			
<b>Wall area percent</b>	<b>0.431</b>	<b>(0.023, 0.840)</b>	<b>0.039</b>
Wall area	-0.79767	(-1.64367, 0.04832)	0.065
<b>Lumen area</b>	<b>-1.08644</b>	<b>(-2.00936, -0.16352)</b>	<b>0.021</b>
Lumen diameter	-0.0799	(-0.1697, 0.0098)	0.081
Logistic regression models	<b>OR</b>	<b>95% CI</b>	<b>p-value</b>
Nocturnal symptoms	1.17	(0.87, 1.57)	0.295
Any wheezing	1.16	(0.86, 1.54)	0.325
<b>Chronic cough</b>	<b>1.41</b>	<b>(1.06, 1.87)</b>	<b>0.019</b>
<b>Chronic productive cough</b>	<b>1.71</b>	<b>(1.28, 2.30)</b>	<b>&lt;0.0001</b>
Exacerbation risk in past year	1.11	(0.81, 1.51)	0.511
<b>Severe exacerbation risk in past year</b>	<b>1.51</b>	<b>(1.04, 2.17)</b>	<b>0.029</b>
Poisson models	<b>RR</b>	<b>95% CI</b>	<b>p-value</b>
Exacerbations experienced over follow-up	1.04	(0.84, 1.30)	0.696
Severe exacerbations experienced over follow-up	1.11	(0.82, 1.52)	0.497

Adjusted for age, gender, race, FEV1% predicted (except for analysis of FEV1 % predicted), education level, current smoking status, oxygen use, pack-years smoked. Measures of airway dimensions additionally adjusted for total lung volume achieved at CT. Poisson models of exacerbations and severe exacerbations over follow-up additionally adjusted for follow-up time.

SPIROMICS- subpopulations and intermediate outcomes of COPD Study

COPD- Chronic Obstructive Pulmonary Disease

$\beta$ -coefficient for modeled estimate

OR- odds ratio

IRR- incidence rate ratio

CI- confidence interval

6MWD- six-minute walk distance

FEV1- forced expiratory volume in 1 second

SGRQ- St George's Respiratory Questionnaire

SF12 GH- Medical outcomes short form-12 item questionnaire general health score

CAT- COPD assessment test

MMRC- modified medical research council questionnaire

**Table 3**

Associations of 2 or more hours of SHS exposure in past week with COPD outcomes in SPIROMICS

Linear regression models Hours of SHS smoke in the past 7 d 0–1 Hr (REF) 2+ hours	Absolute difference	95% CI	p-value
6MWD, meters	–15.9	(–31.33, –0.65)	<b>0.041</b>
SGRQ score	2.52	(0.47, 4.58)	<b>0.016</b>
SF12 GH score	–1.17	(–2.50, 0.16)	0.084
CAT score	0.82	(–0.06, 1.71)	0.068
MMRC score	0.097	(–0.018, 0.21)	0.098
Ease of cough and sputum total score	<b>0.84</b>	<b>(0.42, 1.25)</b>	<b>&lt;0.0001</b>
Pi10 (all airways)	<b>0.18</b>	<b>(0.05, 0.31)</b>	<b>0.006</b>
Airway dimensions (5 <sup>th</sup> generation airways)			
Wall area percent	<b>0.432</b>	<b>(0.048, 0.816)</b>	<b>0.027</b>
Wall area	–0.67611	(–1.47355, 0.12133)	0.097
Lumen area	–0.89061	(–1.76076, –0.02046)	<b>0.045</b>
Lumen diameter	–0.07514	(–0.1597, 0.00939)	0.081
Logistic regression models	OR	95% CI	p-value
Nocturnal symptoms	<b>1.58</b>	<b>(1.19, 2.10)</b>	<b>0.001</b>
Any wheezing	<b>1.34</b>	<b>(1.02, 1.77)</b>	<b>0.039</b>

Adjusted for age, gender, race, FEV1% predicted (except for analysis of FEV1 % predicted), education level, current smoking status, pack-years smoked, oxygen use. Measures of airway dimensions also adjusted for total lung volume achieved at CT.

REF- reference group

β-coefficient for modeled estimate

OR- odds ratio

CI- confidence interval

SPIROMICS- subpopulations and intermediate outcomes of COPD Study

COPD- Chronic Obstructive Pulmonary Disease

SHS- secondhand smoke

6MWD- six-minute walk distance

FEV1- forced expiratory volume in 1 second

SGRQ- St George's Respiratory Questionnaire

SF12 GH- Medical outcomes short form-12 item questionnaire general health score

CAT- COPD assessment test

MMRC- modified medical research council questionnaire



Table 4

Significant interactions between secondhand smoking exposure and smoking status, obesity, severity of airflow obstruction.

	$\beta$	95% CI	p-value	$\beta$	95% CI	p-value
<b>Interactions with current smoking (correspond to Figure 2)</b>						
	<b>Impact of 2+ hours recent SHS exposure on current smokers</b>			<b>Impact of 2+ hours recent SHS exposure on former smokers</b>		
Six Minute walk distance	-24.41	(-44.81, -4.01)	0.019	-5.96	(-27.90, 15.97)	0.594
SF12 GH quality of life score	0.68	(-1.22, 2.59)	0.481	-2.93	(-4.76, -1.08)	0.002
Chronic cough, OR	2.00	(1.32, 3.02)	<0.0001	1.26	(0.86, 1.85)	0.238
	<b>Impact of living with a smoker on current smokers</b>			<b>Impact of living with a smoker on former smokers</b>		
Severe exacerbation risk past yr, OR	2.33	(1.30, 4.18)	0.004	1.12	(0.67, 1.86)	0.665
SF12GH quality of life score	-3.42	(-5.76, -1.09)	0.004	-0.06	(-1.68, 1.57)	0.945
<b>Interactions with obesity (correspond to Figure 3)</b>						
	<b>Impact of 2+ hours recent SHS exposure on obese participants</b>			<b>Impact of 2+ hours recent SHS exposure on nonobese participants</b>		
SF12GH quality of life score	-3.42	(-5.76, -1.09)	0.004	-0.06	(-1.68, 1.57)	0.945
	<b>Impact of living with a smoker on obese participants</b>			<b>Impact of living with a smoker on nonobese participants</b>		
Nocturnal symptoms, OR	1.78	(1.04, 3.04)	0.036	0.97	(0.68, 1.38)	0.863
Chronic cough, OR	2.10	(1.23, 3.58)	0.007	1.16	(0.83, 1.64)	0.384
<b>Interactions with disease severity (correspond to Figure 4)</b>						
	<b>Impact of living with a smoker on GOLD 1–2 participants</b>			<b>Impact of living with a smoker on GOLD 3–4 participants</b>		
Six Minute walk distance	-20.13	(-38.34, -1.91)	0.030	10.05	(-21.79, 41.89)	0.535
Total CAT score, measure of health status	2.04	(0.86, 3.22)	0.001	0.23	(-1.34, 1.80)	0.774
Any wheezing, OR	1.42	(1.00, 2.02)	0.050	0.84	(0.53, 1.33)	0.457

Adjusted for age, gender, race, FEV1% predicted, education level, current smoking status, oxygen use, pack-years smoked. Refer to Table 2 legend for all abbreviations. P(int) is defined as p-value for interaction term in the models.

SHS- secondhand smoke

FEV1- forced expiratory volume in 1 second

SF12 GH- Medical outcomes short form-12 item questionnaire general health score

CAT- COPD assessment test

OR- Odds ratio