Original Research

The Long-Term Effects of Cost-Related Nonadherence on COPD Outcomes and Progression in the COPDGene Study Cohort

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Running Head: **Cost-Related Nonadherence Effects on COPD Outcomes**

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Abbreviations:

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is a progressive disease with a high prevalence and cost burden on the health care system. Overall, adherence to prescribed therapies is low and associated with worse outcomes.

Research Question: Cost-related nonadherence (CRN) is a type of nonadherence that could be addressed through policy. We are evaluating the long-term association of CRN on COPD outcomes in a well-profiled cohort.

Study Design and Methods: We identified 2,521 participants with baseline COPD and having answered the social and economic questionnaire in the COPDGene cohort. Of these, 408 participants endorsed experiencing CRN. Multivariable regression models were utilized to assess the association of experiencing CRN and COPD outcomes including functional status, health status, and progression of disease.

Results: Experiencing CRN is associated with worse functional status by 6MWD, symptom burden by CAT Score and health status by SGRQ. Longitudinal analysis reveals an association of CRN with faster lung function decline and increased risk of COPD exacerbations.

Interpretation: Policy changes to address out-of-pocket medication costs may improve COPD outcomes and potentially lead to long-term cost savings.

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Background

Chronic Obstructive Pulmonary Disease (COPD) has an estimated global prevalence of 10.3%. In the United States alone, COPD is projected to cost over $40 billion per year over the next 20 years.[1] Pharmacologic treatment has the potential to improve symptoms and exercise capacity and reduce exacerbations.[1] Poor adherence to prescribed medication regimen for all diseases results in increased hospitalization, progression of disease, death, and health care costs.[2,3] Non-adherence in COPD due to all causes ranges from 43% to 58.7%, which is associated with increased mortality and hospital admission.[4–6]

Blaschke and Osterberg describe the interactions between patients, providers, and the health care system as areas that can negatively affect medication adherence. This includes an understanding of correct medication delivery, overall disease, and treatment benefits as well as access to physicians and the healthcare system. Additionally, the cost of medications plays an important role and can lead to cost-related non-adherence (CRN). For example, the interaction between patients and the health care system can include frequent switching of formulary, high out-of-pocket medication costs, and poor access to clinics and pharmacies. Additionally, the interaction between providers and the health care system can include poor knowledge of drug costs and of insurance coverage of different formularies.[2]

Up to one third of older adults reduce adherence to all medications to limit the burden of cost.[3] In COPD specifically, national health interview survey data suggests 19% of individuals experience cost-related medication nonadherence.[7] This issue is further exacerbated by a complex health care system where frequent formulary changes due to cost considerations lead to further non-adherence.[8]

This study uses a large longitudinal observational cohort of adults with COPD to better understand the individual level effects on disease progression of non-adherence specifically due to cost. We hypothesize that cost-related nonadherence will be associated with faster lung function decline, increased exacerbation and symptom burden, and worse health status.

Methods

Study Design

The Genetic Epidemiology of COPD (COPDGene) is an observational, multicenter, longitudinal analysis of healthy never-smokers and individuals with ≥ 10 pack year smoking history with and without COPD. Participants were recruited from 20 different sites across the United States and have completed 3 phases of visits, every five years over 15 years. Data collection was conducted in-person and via telephone to complete questionnaires, functional assessment, pulmonary function test, multi-omics assessments and quantitative chest CT evaluation.[9]

This secondary analysis evaluated a subset of individuals within COPDGene with spirometry confirmed COPD GOLD stage I to IV at the baseline visit who completed the social and economic questionnaire at either phase II or III visit. This questionnaire was not administered during phase I visit. This resulted in a total of 2,521 participants.

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An individual was categorized as experiencing CRN if they answered yes to either "in the last year, because of expenses or lack of coverage, have you not filled a prescription" or "in the last year, because of expenses or lack of coverage, have you taken less medication". Answering no to both questions classified an individual as not experiencing CRN. These questions are similar to those administered by the National Health Interview Survey to evaluate cost-related nonadherence.[7] It is important to note that these questions are asking about CRN for any medications and are not specific to COPD directed therapy.

Statistical Analysis

Individuals were dichotomized as either experiencing CRN or not experiencing CRN. Baseline characteristics including demographic variables, smoking status and pack years, functional status, symptom burden, and health status were compared using chi-squared tests for categorical variables or Wilcoxon rank sum tests for continuous variables.

Linear regression models were used to assess associations of CRN with six-minute walk distance[10], St George Respiratory Questionnaire (SGRQ) score[11], Body-Mass Index, Airflow Obstruction, Dyspnea and Exercise Capacity (BODE) index[12] at visit I and COPD Assessment Test (CAT)[13] at visit II, which is the first visit in which this questionnaire is used. Exacerbation history was obtained at each of the three visits by asking frequency of exacerbations in the prior 12 months before the visit. To evaluate exacerbation history, a mixed effect negative binomial model was used with the total follow-up time as an offset.

Longitudinal analyses were performed using a mixed effects linear regression model with site and participant random intercept and FEV_1 random slope to evaluate the association of experiencing CRN with FEV_1 both in liters and calculated as percent predicted. Additional longitudinal analyses were conducted evaluating association of experiencing CRN with six-minute walk distance, SGRQ score, bode index, and CAT Score.

Covariate Selection

The models controlled for age, gender, race, smoking status defined as current and former smokers, pack year smoking history, baseline FEV_1, and prior history of asthma. Complete case analysis was used for all models. The national area deprivation index (ADI) is a neighborhood ranking based on education, employment, housing quality, and income.[14,15] Due to significant missing ADI data in 190 participants, this was not included in the primary analysis. A sensitivity analysis was performed with ADI as a covariate to evaluate for any change in association.

Stata version 18 software (StataCorp, College Station, TX) was used for the analysis. COPDGene was approved by the institutional review board at each site and all participants provided written informed consent.

Results:

Baseline Characteristics:

There were 2,740 participants who had baseline COPD and returned for a subsequent visit. Of those, 2,523 participants completed the social and economic questionnaire at either visit

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2 or 3. Differences between the groups having completed the questionnaire are shown in e-Table 1. The group who did not complete the questionnaire was older, had lower FEV_1, and experienced worse overall health status as defined by SGRQ. Of the remaining 2,523, two additional participants had missing data and were omitted from the analysis. Of the remaining 2,521 participants, 408 (16.2%) had reported experiencing CRN. At the time of reporting CRN, 93.5% of participants endorsed having health insurance. Of those with insurance, 86% had Medicare or private insurance, 11% had Medicaid, 2% had military insurance and 1% were unsure of what insurance type.

Individuals experiencing CRN were younger, more likely to be female and had worse lung function on spirometry. They had lower income but no significant difference with regards to race, baseline smoking status, pack year history, education level, ADI, or comorbidities. Individuals experiencing CRN had a shorter 6-minute walk distance and worse SGRQ, CAT Score, and BODE index (Table 1).

After controlling for relevant confounders in a multivariable analysis, experiencing CRN was associated with a reduced FEV_1 of -133mL (95% Confidence Interval (CI): -202 to -63 mL) and shorter 6-minute walk distance by a mean of 65 feet (95% CI: 30 to 100 feet). CRN was also associated with increased reported symptom burden as evidenced by a higher CAT Score by 2.6 points (95% CI: 1.8 to 3.5) and worse health status by SGRQ (+8 points (95% CI: 6 to 10)), which is higher than the minimum clinically important difference for CAT Score and SGRQ of 2 and 4 respectively.[16,17] Additionally, there was an association of increased BODE Index by 0.3 (95% CI: 0.2 to 0.5) (Table 2). There was no difference in magnitude of effect or significance level when controlling for ADI in the models (e-Table 1).

Longitudinal Analysis:

In longitudinal analysis using mixed effects models and controlling for relevant confounders, experiencing CRN was associated with a faster lung function decline. Specifically, individuals without CRN had a lung function decline of 38 mL per year while those with CRN had a decline of 45 mL per year, equating to a faster decline of 7mL per year (95% CI: 3mL to 10mL) in those with CRN (Table 3).

Similarly, individuals without CRN had a decline of FEV_1/FVC of 0.3% per year while experiencing CRN was associated with a decline of 0.5%, an additional 0.2% per year (95% CI: 0.1 to 0.3%). Additionally, CRN was associated with increased rates of exacerbation with an incidence rate ratio (IRR) of 1.43 (1.26 to 1.63).

Despite these differences in longitudinal outcomes, there was no difference observed in rate of change in 6-minute walk distance, SGRQ, CAT score, or BODE Index. Importantly, there was no difference in magnitude or significance when controlling for ADI in any of the models (e-Tables 2 & 3).

Discussion:

Prior literature has focused on all-cause medication non-adherence and associations with COPD related outcomes. [4–6] Our analysis is novel and significantly adds to the discussion by

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focusing on an important type of non-adherence due to medication cost, in a large well-profiled cohort of adults with COPD, therefore highlighting a potential targetable policy to improve compliance and COPD outcomes.

This analysis provides several significant findings. In this cohort, over 90% of individuals experiencing CRN had health insurance, suggesting the problem goes beyond simply insurance status. Experiencing CRN is associated with worse lung function by spirometry, higher symptom burden, worse health status, and higher mortality risk by BODE Index. The magnitude of mean difference in these associations is especially notable and clinically significant with SGRQ of +8, CAT of +2.6, and FEV_1 of -133 mL. Longitudinal analysis in this well-profiled cohort further highlights the relationship of CRN and COPD outcomes by demonstrating an association of an increased rate of FEV_1 decline and higher IRR for experiencing a COPD exacerbation.

There are many factors that contribute to CRN. The pharmaceutical industry in the United States functions outside of the free market, which requires a fully informed consumer with an understanding of cost and benefit and free market entry for sellers.[18] The consumer, in this case the patient, is not fully informed as they rely on recommendations from physicians, who may not be aware of out-of-pocket costs incurred by each patient.[2,18] Insurance formulary and pharmacy benefit managers also influence the prescribed medication.[8] Additionally, the market itself allows for temporary monopoly through patents.[19] As a result of these factors, drug prices in the United States are higher than other countries.[18]

According to prior claims data analysis, respiratory medications experience high price elasticity compared to other classes of medications. Increases in out-of-pocket cost for respiratory medications associates with a significant reduction in utilization.[20] In a real-world experiment performed in a Medicare Advantage population, reducing out of pocket co-pay increased proportion of days covered by approximately 15%, which equated to a 55% relative increase compared to the control group. In this study, individuals in the deductible phase saw co-pay reduction from over $400 to $10 or less.[21]

Cost sharing models, with the intent of reducing health care over-utilization, is a tool designed to reign in overall costs. Specifically, pharmaceutical expenditures are significantly reduced with even small increases in co-payment.[22] However, these tools are indiscriminatory in that there is an inability to differentiate between restricting over-utilization versus restricting necessary medical treatment.

As our study highlights, CRN is associated with faster lung function decline and higher rates of COPD exacerbation, which may in turn increase total health care expenditures. COPD exacerbations have previously been shown to be a significant contributor to the total cost of COPD care.[1] The cost-sharing model may not be appropriate or cost-effective for a disease with significant prevalence and high mortality rate such as COPD.

Cost-sharing for airway diseases is further complicated by limited generic options, which are typically cheaper. Patent regulations have allowed for prolonged exclusive rights through techniques such as patents on the device and device hopping without having a medication with a new mechanism of action.[19] Higher costs of brand name drugs combined with high price-

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elasticity for respiratory medications and cost sharing payment models can significantly contribute to CRN.

The Inflation Reduction Act passed by Congress in 2022 allows for the Secretary of Health and Human Services to negotiate certain drug prices. The first round of 10 medications is estimated to save Medicare $6 billion dollars yearly and save beneficiaries an additional $1.5 billion.[23] This program, in addition to the $2000 out-of-pocket cap, is a significant step in the right direction to reducing overall cost-related nonadherence. The first round of medications selected did not include any respiratory medications targeting COPD. The second round, which would go into effect in 2027 and is currently undergoing negotiation, does include two respiratory inhalers. Including inhaler medications targeting COPD to reduce CRN could be beneficial to individuals with COPD.

This analysis has several limitations. The definition of CRN in this analysis is narrow compared to other definitions in the literature, which also ask about skipping medications or delaying refills due to cost.[7] There were differences in baseline characteristics for those who completed the questionnaire, which may introduce bias, as those who completed the questionnaire were younger and had healthier lung function, indicating we may be underestimating effects of CRN. For those who completed the questionnaire, information regarding cost related nonadherence and exacerbations is subject to recall bias, and was not specific to COPD-related medications. Specifically, one could theorize a potential recall bias, such that individuals with faster lung function decline may be more likely to report cost-related barriers, as greater symptom burden could enhance their awareness and recollection of obstacles to optimal outcomes. Additionally, the questions for nonadherence were only asked at visit 2 and 3 and asked retrospectively for the preceding 12 months. This analysis does not include granular data on participant insurance, co-pay, frequency of missed doses, or other types of nonadherence that are unrelated to cost but may still contribute to outcomes. The cohort study design also does not account for unmeasured confounders and limits the potential for causal inference. An example of an unmeasured confounder is ambient pollution exposure which is associated with worse COPD outcomes and is also associated with individuals experiencing lower socioeconomic status and subsequently CRN.

Despite these limitations, this analysis has significant strengths. COPDGene is a well profiled and relatively large cohort study of Black and White adults with 15 years of longitudinal follow-up that specifically inquired about social determinants of health. Additionally, outcome assessments included not only subjective measurements such as CAT questionnaire but also objective measurements such as 6-minute walk distance, exacerbations, and spirometry.

Conclusion:

Cost-related non-adherence is associated with increased symptom burden, worse health status, faster lung function decline, and increased exacerbations. Policy changes to reduce medication costs may reduce cost-related non-adherence to COPD medications, reduce decline in lung function, and presumably lead to long-term cost-savings for the healthcare system. Future negotiation of drug prices should include medications targeting COPD.

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Authorship contribution: RS: conceptualization, methodology, formal analysis, writing – original draft and review and editing. AN: conceptualization, methodology, writing – review and editing. JB: conceptualization, writing - review and editing; DC: conceptualization, writing – review and editing.

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RS, DC participated in an advisory board for Verona.

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	No Cost Barriers n=2113	Cost Barriers Present n=408	p-value
Age	63 (57-70)	60 (54-65)	<0.01
Gender			
Female	947 (45%)	221 (54%)	<0.01
Race			
White	1637 (77%)	330 (81%)	0.13
Black	476 (23%)	78 (19%)	
Baseline FEV1	1.7 (1.3-2.3)	1.6 (1.2-2.1)	<0.01
Baseline FVC	3.1 (2.5-3.9)	3.0 (2.5-3.7)	0.04
Baseline FEV1/FVC	59 (47-66)	56 (46-63)	<0.01
Pack years	44 (33-62)	45 (33-66)	0.29
Smoking status at baseline			
Former Smoker	1213 (57%)	221 (54%)	0.23
Current Smoker	900 (43%)	187 (46%)	
Asthma	482 (23%)	128 (31%)	<0.01
Income			<0.01
<35k	982 (48%)	269 (69%)	
35k-50k	271 (13%)	52 (13%)	
>50k	441 (22%)	35 (9%)	
No answer	238 (17%)	39 (10%)	
Education			0.16
Less than HS	233 (11%)	56 (14%)	
HS/GED	534 (25%)	89 (22%)	
some college	592 (28%)	126 (31%)	
College or more	754 (36%)	137 (34%)	
6MWD at baseline (feet)	1356 (1126-1600)	1286 (1013-1505)	<0.01
SGRQ Total	27 (11-45)	43 (26-58)	<0.01
CAT Score	13 (7-20)	19 (12-24)	<0.01
ADI Score*	40 (22-64)	44 (24-72)	0.1
Taking Respiratory Medication	1197 (57%)	287 (70%)	<0.01
LABA	704 (33%)	182 (45%)	<0.01
LAMA	553 (26%)	134 (33%)	<0.01
ICS	749 (35%)	190 (47%)	<0.01
Congestive Heart Failure	104 (5%)	23 (6%)	0.57
Coronary Artery Disease	230 (11%)	49 (12%)	0.54
Diabetes	324 (16%)	69 (17%)	0.45

Table 1: Baseline characteristics of participants categorized by experiencing cost-related nonadherence. Descriptive characteristics with median (IQR) and rank sum test for continuous variable or number (percent) and chi^2 test for categorical variables.
*190 participants with missing ADI data.
Abbreviations: FEV1: Forced expiratory volume over 1 second; FVC: Forced vital capacity; HS: High School; GED: General Education Development; 6MWD: 6-minute walk distance; SGRQ:

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St. George's Respiratory Questionnaire; CAT: COPD assessment test; ADI: Area Deprivation Index; LABA: Long-Acting Beta Agonist; LAMA: Long-Acting Muscarinic Antagonist; ICS: Inhaled corticosteroid

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Effect of cost-related nonadherence on COPD outcomes at baseline	Mean Difference (95% CI)	p-value
FEV_1 (mL)	-133 (-202 to -63)	<0.01
6MWD (ft)	-65 (-100 to -30)	<0.01
SGRQ	8 (6 to 10)	<0.01
CAT	2.6 (1.8 to 3.5)	<0.01
BODE Index	0.3 (0.2 to 0.5)	<0.01

Table 2: Mean difference in each outcome associated with CRN at baseline visit using linear regression model controlling for age, gender, race, smoking status, smoking pack years, and asthma. All models except FEV_1 also controlled for baseline FEV_1.

Abbreviation: 6MWD: 6-minute walk distance; SGRQ: St. George's Respiratory Questionnaire; CAT: COPD Assessment Test; BODE: Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity.

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	Adjusted Differences (95% CI)	p-value
Post BD FEV_1 in mL(SD)[1]	-7 (-3 to -10)	<0.01
6MWD in feet (SD)[1]	3.4 (-1.3 to 8.0)	0.16
SGRQ (SD)[1]	-0.1 (-0.3 to 0.1)	0.43
CAT Score (SD)1	0.02 (-0.17 to 0.21)	0.82
BODE (SD)[1]	0.01 (-0.01 to 0.03)	0.48
Exacerbation (IRR)[2]	1.43 (1.26 to 1.63)	<0.01

Table 3: Adjusted differences in outcome comparing individuals with COPD experiencing cost-related nonadherence versus no cost-related nonadherence. All models adjusted for baseline FEV_1, age, gender, race, smoking status, smoking pack years, and asthma.
1. Mixed effects linear regression model with site and participant random intercept and FEV_1 random slope.
2. Mixed effects negative binomial model with total follow up time as an offset.
Abbreviation: BD: bronchodilator; SD: slope difference; FEV_1: Forced expiratory volume in 1 second; 6MWD: 6-minute walk distance; SGRQ: St George's Respiratory Questionnaire; CAT: COPD Assessment Test; BODE: Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity; IRR: Incidence Rate Ratio;

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Online Supplement

	No Questionnaire n=217	Questionnaire n=2523	p-value
Age	66 (60-73)	63 (57-69)	<0.01
Gender			
Female	117 (54%)	1168 (46%)	0.03
Self-reported Race			
White	192 (88%)	1969 (78%)	<0.01
Black	25 (12%)	554 (22%)	
Baseline FEV_1	1.3 (0.9-1.8)	1.7 (1.2-2.3)	<0.01
Baseline FVC	2.7 (2.2-3.4)	3.1 (2.5-3.9)	<0.01
Baseline FEV_1/FVC	49 (36-61)	59 (47-65)	<0.01
Pack years	49 (37-71)	44 (33-62)	<0.01
Smoking status at baseline			
Former Smoker	157 (72%)	1436 (57%)	<0.01
Current Smoker	60 (28%)	1087 (43%)	
Asthma	48 (22%)	612 (24%)	0.48
6MWD at baseline (feet)	1134 (936-1365)	1341 (1100-1586)	<0.01
SGRQ Total	39 (24-57)	29 (13-48)	<0.01
Taking Respiratory Medication			
LABA	110 (51%)	888 (35%)	<0.01
LAMA	108 (50%)	689 (27%)	<0.01
ICS	115 (53%)	940 (37%)	<0.01
Congestive Heart Failure	14 (6%)	81 (3%)	0.01
Coronary Artery Disease	28 (13%)	216 (9%)	0.03
Diabetes	27 (12%)	286 (11%)	0.62

e-Table 1: Baseline characteristics of participants categorized by having completed versus not completed the questionnaire regarding cost-related nonadherence.
Abbreviation: FEV_1: Forced expiratory volume over 1 second; FVC: Forced vital capacity; 6MWD: 6-minute walk distance; SGRQ: St. George's Respiratory Questionnaire; LABA: Long-Acting Beta Agonist; LAMA: Long-Acting Muscarinic Antagonist; ICS: Inhaled corticosteroid

Effect of cost-related nonadherence on COPD outcomes at baseline		
	Mean Difference (95% CI)	p-value
FEV_1 (mL)	-124 (-196 to -53)	<0.01
6MWD (ft.)	-58 (-94 to -23)	<0.01
SGRQ	8 (6 to 10)	<0.01
CAT	2.6 (1.7 to 3.4)	<0.01
BODE Index	0.3 (0.1 to 0.5)	<0.01

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e-Table 2: Mean difference at baseline visit using linear regression model controlling for baseline FEV_1, age, gender, race, smoking status, smoking pack years, asthma, and ADI.
Abbreviation: 6MWD: 6-minute walk distance; SGRQ: St. George's Respiratory Questionnaire; CAT: COPD Assessment Test; BODE: Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity.

Longitudinal Outcomes associated with Cost-related nonadherence		
	Adjusted Differences (95% CI)	p-value
Post BD FEV_1 in mL (SD)[1]	-8 (-4 to -11)	<0.01
6MWD in ft. (SD)[1]	3.0 (-1.7 to 7.80)	0.21
SGRQ (SD)[1]	-0.1 (-0.3 to 0.1)	0.44
CAT Score (SD)1	0.01 (-0.20 to 0.19)	0.95
BODE (SD)[1]	0.01 (-0.02 to 0.03)	0.54
Exacerbation (IRR)[2]	1.47 (1.29 to 1.68)	<0.01

e-Table 3: Adjusted differences in outcome comparing individuals with COPD experiencing cost-related nonadherence versus no cost-related nonadherence. All models adjusted for baseline FEV_1, age, gender, race, smoking status, smoking pack years, asthma, and ADI.
1. Mixed effects linear regression model with site and participant random intercept and FEV1 random slope.
2. Mixed effects negative binomial model with total follow up time as an offset.
Abbreviation: BD: bronchodilator; SD: slope difference; FEV_1: Forced expiratory volume in 1 second; 6MWD: 6-minute walk distance; SGRQ: St George's Respiratory Questionnaire; CAT: COPD Assessment Test; BODE: Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity; IRR: Incidence Rate Ratio;

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