

TITLE PAGE

Title: Albuminuria, lung function decline, and risk of incident COPD: the NHLBI Pooled Cohorts Study

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At a Glance Commentary

Scientific Knowledge on the Subject

Albuminuria is a commonly used biomarker of endothelial damage in the kidneys and correlates with microvascular dysfunction throughout the body, including in the pulmonary circulation. Cross-sectional studies suggest albuminuria is increased in COPD patients, among whom it is adversely associated with lung function, gas exchange, and hypoxia. Co-occurrence of pulmonary and renal endothelial cell injury was recently demonstrated on pathological samples in COPD patients and cigarette smoke-exposed mice, among whom extent of angiopathy in both organs was correlated cross-sectionally with albuminuria. Nonetheless, no large-scale, prospective study has tested whether albuminuria is associated with the development of COPD.

What This Study Adds to the Field

This study, using six population-based observational cohort studies, demonstrates associations between greater albuminuria and accelerated decline in the FEV1 and FEV1/FVC ratio; incident spirometry-defined COPD; and, increased rates of incident clinical chronic lower respiratory disease events, especially COPD events. These associations were identified in adults without prevalent clinical lung disease, and were independent of smoking, diabetes, hypertension, renal function, and cardiovascular disease. This work adds to mounting evidence supporting a role for pulmonary endothelial dysfunction in COPD pathogenesis, suggesting that microvascular mechanisms may be promising targets for COPD prevention and treatment.

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ABSTRACT

Rationale: Chronic lower respiratory diseases (CLRD), including COPD and asthma, are the fourth leading cause-of-death. Prior studies suggest that albuminuria, a biomarker of endothelial injury, is increased in COPD patients.

Objectives: To test if albuminuria was associated with lung function decline and incident CLRD.

Methods: Six US population-based cohorts were harmonized and pooled. Participants with prevalent clinical lung disease were excluded. Albuminuria (urine albumin-to-creatinine ratio) was measured in spot samples. Lung function was assessed by spirometry. Incident CLRD-related hospitalizations and deaths were classified via adjudication and/or administrative criteria. Mixed and proportional-hazards models were used to test individual-level associations adjusted for age, height, weight, sex, race/ethnicity, education, birth-year, cohort, smoking status, pack-years, renal function, hypertension, diabetes, and medications.

Measurements and Main Results: Among 10,961 participants with preserved lung function, mean age at albuminuria measurement was 60 years, 51% were never-smokers, median albuminuria was 5.6mg/g, and mean FEV1 decline was 31.5mL/year. For each standard deviation increase in ln-albuminuria, there was 2.81% greater FEV1 decline (95% confidence interval [CI], 0.86-4.76%; P=0.0047), 11.02% greater FEV1/FVC decline (95% CI, 4.43-17.62%; P=0.0011), and 15% increased hazard of incident spirometry-defined moderate-to-severe COPD (95% CI, 2-31%, P=0.0021). Each standard deviation ln-albuminuria increased

hazards of incident COPD-related hospitalization/mortality by 26% (95% CI, 18-34%, $P<0.0001$) among 14,213 participants followed for events. Asthma events were not significantly associated. Associations persisted in participants without current smoking, diabetes, hypertension, or cardiovascular disease.

Conclusions: Albuminuria was associated with greater lung function decline, incident spirometry-defined COPD, and incident COPD-related events in a US population-based sample.

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Introduction

Chronic lower respiratory diseases (CLRD) are the fourth leading cause-of-death and a major source of health care costs (1-4). The CDC defines CLRD to include chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, and asthma – conditions that share smoking as a cause or contributor, airflow limitation as a physiologic correlate, and acute exacerbations as the major clinical manifestation. No medical therapies have been proven to prevent CLRD or CLRD-related mortality, which has been rising (5). Identifying biomarkers to predict individuals who are at high CLRD risk would be useful to target prevention strategies (6).

Pulmonary microvascular dysfunction has been directly linked to CLRD pathogenesis. Failure of pulmonary endothelial cell survival causes lung alveolar septal cell apoptosis and emphysema in rats (7, 8). Ceramides, which are mediators of endothelial function, have been implicated in the development of airflow obstruction, airway inflammation, and lung hyperinflation in mouse models and humans (9-11). Imaging-based microvascular biomarkers such as retinal vein caliber, myocardial blood flow, and pulmonary microvascular blood flow have been correlated with adult lung function and COPD severity (12-14), although conflicting results have been obtained (15,16). No large-scale, prospective study has tested whether a biomarker of endothelial dysfunction is associated with CLRD development.

Albuminuria is a commonly used biomarker of endothelial damage in the kidneys (17-19) and correlates with microvascular dysfunction throughout the body (20,21), including the pulmonary circulation (22). Prior literature has shown correlations between albuminuria and COPD: greater

albuminuria was observed in COPD patients, and, in cross-sectional analyses, albuminuria has been adversely associated with COPD severity, lung function, gas exchange, and hypoxia (12,22-28). Nonetheless, the biological and clinical significance of this work has remained uncertain due to relatively small samples, often using case-control designs; the possibility of reverse causation; and, potential confounding effects of aging, smoking and comorbid disease. We therefore tested whether albuminuria was associated with development of CLRD in a large, multi-ethnic, population-based sample of US adults.

Some results of these studies have been previously reported in the form of abstracts (29,30).

Methods

NHLBI Pooled Cohorts Study

The NHLBI Pooled Cohorts Study (31) harmonized and pooled data from large US epidemiologic cohorts that conducted lung function assessments over the last four decades. The current report is limited to six cohorts with albuminuria measurements and repeated spirometry and/or ascertainment of CLRD events: Atherosclerosis Risk in Communities (ARIC); Coronary Artery Risk Development in Young Adults (CARDIA); Cardiovascular Health Study (CHS); Framingham Offspring Cohort (FHS-O); Health, Aging and Body Composition (Health ABC); and the Multiethnic Study of Atherosclerosis (MESA) (32-39). The timing of recruitment, albuminuria measurement and spirometry, and events follow-up is shown in **Figure E1**.

Participants with albumin-to-creatinine ratio $>2,200\text{mg/g}$ were excluded from all primary analyses (40), as were those with prevalent clinical CLRD, which was defined at time of albuminuria measurement by self-reported prior physician diagnoses of asthma, chronic bronchitis, emphysema and/or COPD, or inhaler use, assessed by medication inventory (31,41).

Only five cohorts (CARDIA, CHS, FHS-O, Health ABC, MESA) that performed spirometry exams both coincident and subsequent to albuminuria measurement were included in lung function analyses. Spirometry exams occurring prior to albuminuria measurement were not analyzed. Participants with prevalent airflow limitation, defined as forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) $<$ lower-limit-of-normal (LLN) (42), were excluded. Furthermore, since the disease of interest is characterized by an obstructive spirometric pattern, we excluded participants demonstrating a potentially confounding restrictive pattern, defined as $\text{FEV1/FVC} \geq \text{LLN}$ and $\text{FVC} < \text{LLN}$ (42). Of note, spirometric exclusion criteria were not applied in primary events analyses since baseline spirometry was only available in a subset of the participants with events follow-up.

All studies were approved by Institutional Review Boards at participating institutions and all participants provided written informed consent.

Albuminuria

Urine collection was performed via standardized protocols and processed in central laboratories (**Table E1**). Technologies differed across studies, yet measures were performed similarly: urine

albumin measured by nephelometry or immunoturbidometry (43), and urine creatinine assessed by the Jaffe method (44). These were used to calculate the spot urine albumin-to-creatinine ratio, hereafter called “albuminuria.”

Spirometry

Pre-bronchodilator lung function was measured using water-seal, dry-rolling-seal, or flow-sensing spirometers following American Thoracic Society (ATS) guidelines current at the time of assessment (45-48). To harmonize spirometry data, we applied a standardized quality grading system based upon 2005 ATS/European Respiratory Society guidelines for acceptability and reproducibility (31,45).

Incident moderate-to-severe COPD was defined as $FEV1/FVC < LLN$ and $FEV1 < 80\%$ at the final spirometry exam (49).

CLRD Events

Four cohorts (ARIC, CHS, Health ABC, MESA) prospectively attempted to contact participants every 6-12 months for events surveillance and to collect medical records for all hospitalizations and deaths, and hence provided CLRD events data (**Table E2**).

Clinical events committees adjudicated CLRD-related clinical events in Health ABC (hospitalizations/deaths) and CHS (deaths only). For hospitalizations and deaths in ARIC and

MESA, and non-fatal hospitalizations in CHS, *International Classification of Diseases* (ICD) codes were used to classify events attributable to asthma (ICD-9 493, ICD-10 J45-46), COPD (ICD-9 496, ICD-10 J44), chronic bronchitis (ICD-9 490-491, ICD-10 J40-42), and emphysema (ICD-9 492, ICD-10 J43), following a previously validated protocol (50).

CLRD-related event was defined as first hospitalization or death adjudicated as primarily or secondarily attributable to CLRD, or, if adjudication was lacking, those with CLRD listed in any diagnosis field. In prior work in MESA and a second cohort, 82% of such administratively-defined events were physician-confirmed as evidence of clinical CLRD (51).

A secondary endpoint, severe CLRD event, was defined as first hospitalization or death adjudicated as primarily attributable to CLRD or, if adjudication was lacking, with CLRD coded as the primary discharge diagnosis or underlying cause-of-death. This administrative definition was previously found to have a positive predictive value of 97% for physician-adjudicated CLRD exacerbations (51).

CLRD events were stratified into events attributed to asthma versus COPD, the latter of which was defined to include COPD, chronic bronchitis, and emphysema.

Covariates

Covariates were harmonized systematically prior to pooling (31). Smoking status, pack-years, race/ethnicity, sex, and educational attainment were self-reported. Height, weight, and systolic

and diastolic blood pressure were measured using standard methods. Blood glucose and cholesterol were measured on fasting samples. Medication use was assessed by self-report or validated inventories. Estimated glomerular filtration rate (eGFR) was calculated by CKD-EPI equation using creatinine (52). Diabetes was defined by self-report, fasting blood glucose ≥ 126 mg/dl, or relevant medications. Hypertension was defined by blood pressure $\geq 140/90$ mmHg or relevant medications.

Statistical analysis

Baseline characteristics of participants at time-of-albuminuria-measurement were tabulated and compared by albuminuria categories defined to balance statistical and clinical considerations. Symmetric distributional thresholds were set at 2 mg/dl (10th-percentile), 3 mg/dl (25th-percentile), 6 mg/dl (50th-percentile), 12 mg/dl (75th-percentile), and 30 mg/dl (90th-percentile), which is the upper limit for the normal clinical range (40).

Separate models were performed using albuminuria categories and natural log-transformed (ln) albuminuria as categorical and continuous predictors, respectively, and model fit was compared via the Akaike information criterion (AIC).

Linear mixed models predicting lung function from baseline albuminuria, time-since-albuminuria-assessment (years), and their multiplicative interaction term, were used to test associations between albuminuria and lung function. The coefficient for albuminuria was interpreted as the cross-sectional association with initial lung function. The coefficient for

(albuminuria)*(time-since-albuminuria-measurement) was interpreted as the longitudinal association with rate of change in lung function. Longitudinal associations were reported as absolute rate-of-change per year and also as relative rate-of-change, defined as (absolute rate-of-change)/(average model-based rate-of-change per year in the full sample); negative values indicate associations with greater rate-of-decline. Effect estimates were reported per albuminuria category and per standard deviation (SD) of ln-albuminuria.

Cohort-specific unstructured covariance matrices were used to model variability between and within participants, allowing for differences between cohorts. This statistical approach was chosen over random effects modeling (with heterogeneous residual variances across both exams and study cohorts) since the former allows for autocorrelation in repeated measures and non-linear effects of time. *Post hoc* confirmatory analyses demonstrated that our approach achieved better model fit than random effects models (results not shown).

Associations between albuminuria and incident spirometry-defined COPD and CLRD events were tested via proportional-hazards regression. The proportional hazards assumption was checked by residual plots. Time-to-event was treated as age-at-event, with left truncation at age-at-albuminuria-measurement. Non-CLRD mortality was censored. Study was treated as a stratum term, allowing for cohort-specific differences in the underlying survival function. In secondary analyses, the competing risks of COPD events, asthma events, and non-CLRD mortality were analyzed in competing risks regression; and, the time-to-event variable was time-since-albuminuria-measurement.

Models were sequentially adjusted for *a priori* confounders: baseline age (centered), birth-year (centered), height, weight, sex, race/ethnicity, educational attainment, smoking status, pack-years, cohort, eGFR, total cholesterol, hypertension, systolic and diastolic blood pressure, diabetes, and relevant medications. In spirometry models, height, weight, and smoking status were time-varying; for time-invariant terms, both cross-sectional and longitudinal associations were estimated.

Effect modification was examined in stratified models and by three-way multiplicative interaction terms. Sensitivity analyses were conducted in participants with prevalent CLRD and in “low-risk” participants without diabetes, hypertension, cardiovascular disease, eGFR<60ml/min/1.73 m², or current smoking. For comparison with the pooled analysis and evaluation of between-cohort heterogeneity, fixed- and random-effects meta-analysis were performed. Extended events models were additionally adjusted for baseline FEV1/FVC.

Analyses were completed in SAS, v9.4.

Role of funding sources

NHLBI staff routinely monitored the performance of component studies but neither NHLBI nor the US Environmental Protection Agency were involved in analysis, interpretation, or writing of this report, nor the decision to submit the paper for publication.

Results

There were 31,877 participants with albuminuria measures, lung function and/or events (**Figure E2**).

Among 11,911 participants included in lung function analyses, mean age at albuminuria measurement was 60, 55% were female, 64% were non-Hispanic White, 26% were African-American, 6% were Hispanic/Latino-American, and 4% were Asian-American (**Table 1, Table E3**). Fifty-one percent were never-smokers and 11% were current smokers. Among ever-smokers, median pack-years of smoking history was 4. Diabetes and hypertension were present in 11% and 45%, respectively. Median albuminuria was 5.6mg/g, and mean eGFR was 83mL/min/1.73m².

Among 18,900 participants included in analyses of incident CLRD, baseline characteristics were similar, but participants were older and had more comorbidities and smoking history (**Table E4-5**).

Lung function

The mean number of spirometry measures was 1.9 over a mean of 5.7 years. Total follow-up was 87,204 person-years. Twenty-one percent of participants had ≥ 3 spirometry measures, and 56% had follow-up >5 years (**Table E6**). On average, FEV1 was 101% predicted and declined at 31.5mL/year. Average FEV1/FVC was 78%.

Greater albuminuria was associated with lower initial FEV1 and faster declines for FEV1 and FEV1/FVC (**Table 2**). Sequential adjustment resulted in modest attenuation of effect estimates for rates of lung function decline (**Figure E3**), with age having the greatest apparent confounding effect. In adjusted models, for each SD increase in ln-albuminuria, there was 2.81% greater FEV1 decline (95% CI, 0.86-4.76%; P=0.0047), 11.02% greater FEV1/FVC decline (95% CI, 4.43-17.62%; P=0.0011), and 15% increased hazard of incident spirometry-defined moderate-to-severe COPD (N=245, 95% CI, 2%-31%; P=0.0214).

Across albuminuria categories, associations were approximately monotonic without clear evidence of a threshold (**Table 2, Figure 1**). Model fit for FEV1 was better for albuminuria categories than for ln-albuminuria; however, for FEV1/FVC modeling, the converse was found.

Results were similar in participants with <10 pack-years (**Table E7**), and even in the subset of 5,580 never-smokers (**Figure 2**), among whom increased albuminuria was associated, per SD, with 2.58% greater rate of FEV1 decline (95% CI, -1.7—5.33%; P=.0664) and 12.20% greater rate of FEV1/FVC decline (95% CI, 1.35—23.05; P=.0276) (**Table E8**).

Associations were comparable among participants with and without prevalent CLRD, diabetes, hypertension, impaired eGFR, obesity, or cardiovascular disease (**Figure 2, Table E9**). Results were consistent across cohorts, although they only attained statistical significance in FHS-Offspring and MESA (**Figure E4**). Fixed and random effects meta-analysis yielded similar results without evidence for substantial between-cohort heterogeneity (P=0.25).

In women, albuminuria was strongly associated with lower initial FEV1 but not with rate of change in FEV1, whereas the opposite was observed in men (**Table E10, Figure E5**). However, the additive effect of albuminuria on initial and decline in FEV1 was similar in both sexes, and there was no evidence of substantial effect modification by sex for FEV1/FVC (P-interaction=0.12, **Figure 2**).

Incident CLRD Events

Median follow-up for incident CLRD events was 15 years, with 95% retention at 10 years. There were 2,269 cases of incident CLRD-related events and 554 incident severe CLRD events over 307,977 person-years. Median years to incident CLRD-related and severe CLRD events were 8 and 9, respectively. Twenty-nine percent of incident CLRD-related events and 25% of incident severe CLRD events occurred within 5 years of albuminuria measurement; 10% and 8%, respectively, occurred within two years.

Incidence rates increased across albuminuria categories (**Table E4**). For participants with albuminuria ≥ 30 mg/dl, the incidence rates per 10,000 person-years for CLRD-related and severe CLRD events were 125 and 26, respectively; the corresponding rates for participants with albuminuria < 2 mg/dl were 68 and 13.

In adjusted models, greater albuminuria was associated with higher rates of incident CLRD-related events (HR 1.11 per SD, 95% CI 1.09—1.14; $P < 0.0001$) and severe CLRD events (HR

1.08 per SD, 95% CI 1.03—1.12; P=0.0008). These associations were mainly due to COPD events, whereas asthma events were not significantly associated (**Table 3**). HRs for COPD-related events increased monotonically across albuminuria categories (**Figure 1**) and were somewhat attenuated but similar after adjusting for baseline FEV1/FVC (**Table E11**).

There was no statistical evidence for effect measure modification by sex, age, obesity, or comorbidities (P>0.05). Results were mainly similar across categories of race/ethnicity and smoking status, and significant associations with COPD-related events were demonstrated in never-smokers (HR 1.45 per SD, 95% CI, 1.13—1.62; P<.0001; **Figure E6**). However, associations were attenuated in low-risk participants (**Figure E6**) and non-significant in the relatively small sample of participants known to be without baseline spirometric abnormalities (**Table E12**). Results were similar in competing risks analysis (**Table E13**) and using time-since-albuminuria-measurement as time-to-event (**Table E14**).

Discussion

Albuminuria was associated with lower lung function, accelerated lung function decline, and incident spirometry-defined COPD and COPD events in a large US population-based sample of adults. Associations were observed across a range of albuminuria values and were independent of smoking, diabetes and hypertension. These results provide large-scale support for the endothelial hypothesis of COPD, suggesting that further investigation is warranted into whether endothelial and microvascular mechanisms may be promising targets for COPD prevention and

treatment.

Associations of albuminuria with cardiovascular and renal outcomes are well established (53,54), yet this is the first study of which we are aware to demonstrate associations between albuminuria and prospective CLRD endpoints in a population-based sample. This suggests that shared biological mechanisms may contribute to the frequent comorbidity of diseases that are associated with prominent vascular pathologies with CLRD, a heterogeneous clinical entity for which most current medical therapies target the airways. We examined associations with all CLRD since they share risk factors, mechanisms, and therapies, and frequently overlap (55). Stronger associations with COPD events versus asthma events could reflect the relatively greater incidence of COPD among older adults, but may also suggest greater biological relevance of endothelial dysfunction to development of COPD – inclusive of emphysema and chronic bronchitis – versus asthma.

Co-occurrence of pulmonary and renal endothelial cell injury was recently demonstrated on pathological samples in COPD patients and cigarette-exposed mice, among whom extent of angiopathy in both organs was correlated cross-sectionally with albuminuria (22). Beyond smoking-related microvascular damage, diabetic microangiopathy has been correlated with thickened alveolar basal laminae (56) and lower transfer coefficients for carbon monoxide, suggesting comorbid pulmonary microangiopathy (57). From a biological standpoint, ceramides, which are known to cause endothelial dysfunction, are associated with increased albuminuria in diabetics and smoking-related lung injury and emphysema (9-11,58-60). In the present work, associations between albuminuria and adverse respiratory outcomes were independent of – and

persisted in the absence of – diabetes and smoking. This suggests that, regardless of its etiology, systemic endothelial injury may be a risk factor for respiratory impairment.

Potential roles for endothelial dysfunction in COPD pathogenesis is a subject of considerable interest and ongoing investigation. Pulmonary capillary destruction has been well-documented in advanced COPD and emphysema (61,62), as have correlations between endothelial biomarkers, lung function, and emphysema on computed tomography (CT) (63,64). Flow-mediated dilation has not demonstrated consistent associations with lung function, emphysema, or diffusing capacity (15,16). However, magnetic resonance imaging (MRI) studies have shown that pulmonary microvascular blood flow is decreased even in early or mild COPD, and these changes are associated with increases in endothelial microparticles (14,65). Our results using a population-based sample are consistent with endothelial dysfunction being a risk factor for CLRD, particularly COPD, which has both mechanistic and therapeutic implications.

Angiotensin Converting Enzyme Inhibitor (ACEi) and Angiotensin-II Receptor Blocker (ARB) therapies are effective for preventing progression of nephropathy in persons with increased albuminuria. This effect may be mediated via inhibition of transforming growth factor-beta (66), which is implicated in alveolar septation (67). ACEi/ARB use has been associated with attenuation of smoking-induced lung injury in mice (22,68) and slower progression of emphysema on CT in adults (69). ACEi have also been shown to decrease expression of advanced glycation endproducts in pulmonary and renal endothelial cells in cigarette smoke-exposed mice and to abrogate progression of emphysema and small airway remodeling (22). There is currently a phase 4 clinical trial underway to test whether ARBs slow progression of

emphysema on CT among COPD patients (NCT02696564). Our findings support testing microvascular therapies, such as ACEi/ARB, for COPD prevention and treatment.

Strengths of this work include investigation of a biologically-plausible hypothesis using a large, carefully-characterized, population-based sample. This provided power for longitudinal, repeated measures analysis of lung function; adjustment for socio-demographic factors, smoking, and comorbidities; important subgroup analyses; and, classification of incident spirometry-defined COPD and CLRD events over follow-up. There are nonetheless several limitations.

A pooled cohorts approach introduces heterogeneity among participants and measures.

Nevertheless, measurements were frequently accomplished using similar or identical protocols.

Data were systematically harmonized, and we applied current spirometry quality-control

standards (31). We used statistical methods that provided flexibility for cohort-specific

differences, and cohort-stratified analyses and meta-analyses yielded similar results, supporting

the effectiveness of our data harmonization. The fact that cohort-stratified results mainly did not

achieve statistical significance – likely due to imprecision arising out of the limited number of

spirometry exams per individuals, short spirometry follow-up in certain cohorts, and relatively

small magnitude of associations – highlights the value of the pooled cohorts approach.

Post-bronchodilator spirometry, which is required for the current clinical definition of COPD,

was unavailable. Pre-bronchodilator spirometry remains nonetheless highly prognostic of health

outcomes in population-based data, and is highly correlated with post-bronchodilator measures in

the general population (70,71). Furthermore, we corroborated associations between albuminuria and lung function by analyzing validated incident clinical events.

Although an events-based definition of incident CLRD has low sensitivity, since it excludes participants who did not suffer hospitalization or mortality associated with CLRD during the follow-up period, false negative classification would be expected to bias results towards the null (72). This may account for broadly consistent yet slightly attenuated results for the more specific endpoint, incident severe CLRD event, and attenuated results in low-risk participants.

The observed associations between albuminuria and incident COPD events could be confounded by comorbidities. Indeed, associations in low-risk participants, among whom event rates were lower, were weaker and did not attain statistical significance. Nonetheless, associations with lung function were independent of – and apparent in participants both with and without – cardiovascular disease, hypertension, and diabetes.

The prognostic significance of albuminuria for clinical CLRD events, while potentially clinically important, could not be confirmed in this general-population based study. Associations between albuminuria and FEV1 were similar in persons with prevalent CLRD, but imprecise in the context of relatively low power, suggesting that additional studies in COPD cohorts are warranted. That being said, by focusing our analyses on healthy adults without prevalent respiratory conditions, the present work mitigates standard concerns regarding reverse causality and medication-related effects.

Moreover, in demonstrating significant results in never-smokers, we may posit a mechanistic role for endothelial injury in the development of COPD independent of one of the most important causal factors and potential confounders in COPD epidemiology, cigarette exposure. Our work therefore promotes further investigation into other common causes of endothelial dysfunction – such as hypertension, metabolic syndrome, atherosclerotic disease, and physical inactivity – as risk determinants for low lung function and COPD in the general population, including in never-smokers.

Direct clinical applicability of our results may be limited. Nonetheless, albuminuria is a non-invasive measure that could be considered in selection and monitoring of high-risk participants enrolled in clinical trials of COPD prevention, if not risk stratification in the general population. Our findings also highlight clinically important and well-established associations between COPD and well-known causes of albuminuria – chronic kidney disease and diabetes – while suggesting that these comorbidities may share underlying microvascular mechanisms.

In conclusion, in a US population-based sample of adults, albuminuria was associated with accelerated lung function decline and incident spirometry-defined COPD and COPD events. This suggests that endothelial and microvascular mechanisms are promising targets for COPD prevention and treatment.

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FIGURE LEGENDS

Figure 1. Associations between albuminuria category, longitudinal lung function, and incident COPD events, the NHLBI Pooled Cohorts Study.

COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; Q1 = albuminuria < 2 mg/dl; Q2 = albuminuria 2-3 mg/dl; Q3 = albuminuria 3-6 mg/dl; Q4 = albuminuria 6-12 mg/dl; Q5 = albuminuria 12-30 mg/dl; Q6 = albuminuria \geq 30 mg/dl.

Point estimates and 95% confidence intervals plotted for each albuminuria category (grouped quantile). Estimates for relative rate of change are calculated as the absolute rate of change per year per albuminuria category divided by the model-based average rate of decline in the total sample; negative values represent greater loss of lung function. Models adjusted for baseline age, birth-year, height, weight, sex, race/ethnicity, educational attainment, smoking status, pack-years of smoking, hypertension status, hypertension medications, systolic blood pressure, diastolic blood pressure, total cholesterol, ACEi/ARB medication, diabetes status, diabetes medication, and eGFR.

Figure 2. Sensitivity analyses for associations between albuminuria and relative rate of change in lung function, the NHLBI Pooled Cohorts Study.

eGFR = estimated glomerular filtration rate; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity. Low risk individuals = participants without current smoking, hypertension, diabetes, cardiovascular disease, or eGFR < 60 at time of albuminuria measurement.

Point estimates and 95% confidence intervals plotted for each stratum. Estimates for relative rate of change are calculated as the absolute rate of change per year per albuminuria category divided by the model-based average rate of decline in the total sample; negative values represent greater rate of loss of lung function.

Models adjusted for baseline age, birth-year, height, weight, sex, race/ethnicity, educational attainment, smoking status, pack-years of smoking, hypertension status, hypertension medications, systolic blood pressure, diastolic blood pressure, total cholesterol, ACEi/ARB medication, diabetes status, diabetes medication, and eGFR. Three-way multiplicative interaction terms attained statistical significance at $<.05$ (*) or $<.001$ (**) in the FEV1 analysis for gender**, race ethnicity*, and smoking status**, and, in the FEV1/FVC analysis, for smoking status**, BMI**, and low-risk status.**

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Table 1. Baseline characteristics of participants included in analyses of longitudinal lung function, by category of albuminuria, the NHLBI Pooled Cohorts Study.

	Albuminuria Categories					
	<2 mg/dl	2-3 mg/dl	3-6 mg/dl	6-12 mg/dl	12-30 mg/dl	≥30 mg/dl
Total sample, no.	988	1,311	3,945	2,706	1,823	1,138
No. spirometry exams, mean (SD)	2.3 (1.0)	1.9 (0.9)	1.9 (0.9)	1.9 (1.0)	2.0 (1.0)	1.8 (1.0)
Years of spirometry follow-up, mean (SD)	8.2 (5.7)	6.5 (5.0)	5.7 (5.0)	5.4 (5.0)	5.5 (5.2)	4.2 (4.8)
Cohort, no. (%)						
CARDIA	258 (26.1)	528 (40.3)	1,185 (30.0)	458 (16.9)	200 (11.0)	103 (9.1)
CHS	41 (4.2)	114 (8.7)	537 (13.6)	497 (18.4)	357 (19.6)	254 (22.3)
FHS Offspring	436 (44.1)	223 (17.0)	599 (15.2)	507 (18.7)	446 (24.5)	217 (19.1)
Health ABC	118 (11.9)	133 (10.1)	405 (10.3)	466 (17.2)	358 (19.6)	289 (25.4)
MESA	135 (13.7)	313 (23.9)	1,219 (30.9)	778 (28.8)	462 (25.3)	275 (24.2)
Age, mean (SD), years	54.6 (14.8)	53.0 (17.0)	56.9 (16.9)	62.9 (15.6)	65.9 (14.5)	68.4 (13.9)
Female sex – no. (%)	416 (42.1)	560 (42.7)	2,116 (53.6)	1,657 (61.2)	1,151 (63.1)	563 (49.5)
Body mass index, mean (SD), kg/m ²	27.7 (4.7)	27.4 (5.1)	27.5 (5.3)	27.5 (5.4)	27.5 (5.3)	28.0 (5.4)
Race/ethnicity, no. (%)						
European-American	740 (74.9)	787 (60.0)	2,426 (61.5)	1,751 (64.7)	1,179 (64.7)	686 (60.3)
African-American	213 (21.6)	427 (32.6)	1,078 (27.3)	639 (23.6)	447 (24.5)	324 (28.5)
Asian-American	12 (1.2)	37 (2.8)	180 (4.6)	145 (5.4)	93 (5.1)	51 (4.5)
Hispanic/Latino	23 (2.3)	60 (4.6)	261 (6.6)	171 (6.3)	104 (5.7)	77 (6.8)
Education status, no. (%)						
Less than high school	52 (5.3)	79 (6.0)	306 (7.8)	251 (9.3)	157 (8.6)	119 (10.5)

High school	262 (26.5)	303 (23.1)	965 (24.5)	674 (24.9)	492 (27.0)	299 (26.3)
Some college	243 (24.6)	353 (26.9)	1,010 (25.6)	630 (23.3)	419 (23.0)	263 (23.1)
College or more	364 (36.8)	545 (41.6)	1,561 (39.6)	1,070 (39.5)	677 (37.1)	427 (37.5)
Smoking status, no. (%)						
Never	497 (50.3)	696 (53.1)	2,023 (51.3)	1,399 (51.7)	933 (51.2)	542 (47.6)
Former	366 (37.0)	451 (34.4)	1,442 (36.6)	1,015 (37.5)	704 (38.6)	481 (42.3)
Current	122 (12.4)	162 (12.4)	471 (11.9)	278 (10.3)	171 (9.4)	106 (9.3)
Median pack-years (IQR) in ever-smokers, years	10.0 (28.5)	5.0 (18.8)	9.0 (23.1)	13.9 (27.7)	16.0 (29.3)	18 (33.0)
Medical history						
Diabetes*, no. (%)	57 (5.8)	65 (5.0)	259 (6.6)	299 (11.1)	265 (14.5)	360 (31.6)
Hypertension†, no. (%)	300 (30.4)	390 (30.0)	1,450 (36.8)	1,339 (49.5)	1,042 (57.2)	835 (73.4)
Estimated GFR, mean (SD), mL/min/1.73m ²	85.8 (20.5)	88.0 (21.1)	86.1 (22.6)	81.5 (29.6)	78.7 (21.2)	70.9 (24.8)
Lung function						
Baseline FEV1 percent-predicted, mean (SD), %	100.0 (13.4)	100.6 (15.6)	100.6 (13.8)	100.8 (14.9)	101.0 (15.2)	99.3 (15.9)
Baseline FEV1, mean (SD), L	3.1 (0.8)	3.1 (0.9)	2.8 (0.9)	2.6 (0.8)	2.4 (0.7)	2.4 (0.7)
Baseline FVC, mean (SD), L	4.0 (1.1)	3.9 (1.1)	3.6 (1.1)	3.3 (1.0)	3.2 (0.9)	3.1 (0.9)
Baseline FEV1/FVC, mean (SD), %	77.2 (5.4)	78.6 (5.6)	78.1 (5.6)	77.7 (5.7)	77.5 (5.9)	77.0 (6.0)

ARIC = Atherosclerosis Risk in Communities Study; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular

Health Study; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in one second; FHS = Framingham Heart Study;

FVC = forced vital capacity; Health ABC = Health Aging and Body Composition; MESA = Multi-Ethnic Study of Atherosclerosis.

* Self-reported diabetes or fasting blood sugar levels ≥ 126 mg/dl or use of oral hypoglycemic agents or insulin

† Self-reported hypertension or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or use of anti-hypertensive medications

Lung function analyses restricted to cohorts with longitudinal lung function following measurement of albuminuria and participants without airflow limitation ($FEV_1/FVC < \text{lower-limit-of-normal [LLN]}$) or restrictive pattern ($FEV_1/FVC > \text{LLN}$ and $FVC < 80\%$) on spirometry. In MESA, for the lung function analyses, albuminuria measured concurrently with spirometry at Exams 3 and 4 was treated as baseline.

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Table 2. Associations between albuminuria, initial lung function, and absolute and relative rates of change in lung function in adults without prevalent chronic lower respiratory diseases.

		Albuminuria Categories					Ln-Albuminuria	P-value
		<2 mg/dl N=891	2-3 mg/dl N=1,226	3-6 mg/dl N=3,648	6-12 mg/dl N=2,497	12-30 mg/dl N=1,644	≥30 mg/dl N=1,055	
Initial								
FEV1, mL	Ref	.65	-1.39	-16.80	-25.15	-63.47*	-22.64 (-29.86, -15.42)	<.0001
FEV1/FVC, %	Ref	.47*	.12	.41*	.48*	.16	.06 (-.04, .15)	.27
Absolute rate of change								
FEV1, mL/year	Ref	-.24	-1.61	-1.92	-2.51*	-2.98*	-0.89 (-1.50, -0.27)	.0047
FEV1/FVC, % year	Ref	.01	-.02	-.04*	-.06*	-.03	-.02 (-0.3, -.01)	.0011
Relative rate of change[†]								
FEV1, % average rate (-31.5 mL/year)	Ref	-.77	-5.12	-6.10	-7.94*	-9.43*	-2.81 (-4.76, -.86)	.0047
FEV1/FVC, % average rate (-0.2 %/year)	Ref	5.59	-10.57	-22.09*	-38.42*	-21.21	-11.02 (-17.62, -4.43)	.0011

CI = confidence interval; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; ln = natural log; SD = standard deviation.

*Statistically significant at P <.05.

†Estimates for absolute and relative rates of change in lung function are derived from the same model. The estimates for the latter reflect the estimates for the former divided by the model-based average rate of decline in the total sample; negative values indicate greater loss of lung function.

Excludes participants with prevalent clinical chronic lower respiratory disease (CLRD), airflow limitation ($FEV_1/FVC < LLN$), or restriction on spirometry ($FEV_1/FVC > LLN$, $FVC < LLN$) at time of albuminuria measurement.

Linear mixed models predicted lung function from baseline albuminuria, time since albuminuria assessment (years) and their multiplicative interaction term, with cohort-specific unstructured covariance matrix, adjusted for time-varying height, weight, and smoking status; time-invariant age (centered), birth-year (centered), study, sex, race/ethnicity, educational attainment, pack-years of smoking, hypertension status, hypertension medications, systolic blood pressure, diastolic blood pressure, total cholesterol, ACEi/ARB medication, diabetes status, diabetes medication, and eGFR. All time-invariant factors were modeled for both cross-sectional associations and longitudinal associations via inclusion of the covariate as well as its interaction with time since albuminuria assessment.

Separate models were run using categorical (grouped quantile) and continuous (natural log-transformed albuminuria) predictors, and effect estimates were reported per category or per standard deviation, respectively. Model fit was compared by the Akaike information criterion (AIC). For FEV_1 , the AIC for the categorical analysis was lower (better) than for the continuous term (295,296.8 versus 295,509.5). For the FEV_1/FVC , the AIC for the categorical analysis was higher (worse) than for the continuous term (121,725.5 versus 121,715.7).

Table 3. Associations of albuminuria with incident chronic lower respiratory disease events over a median of 15 years of follow up, the NHLBI Pooled Cohorts Study.

	At Risk	Events (cum. inc.)	Albuminuria Categories						Ln-Albuminuria	
			<2 mg/dl <i>N</i> =1,568	2-3 mg/dl <i>N</i> =1,610	3-6 mg/dl <i>N</i> =4,293	6-12 mg/dl <i>N</i> =3,091	12-30 mg/dl <i>N</i> =2,016	≥30 mg/dl <i>N</i> =1,635	Per SD (95% CI)	P-value
CLRD Events										
Severe CLRD event	14,213	379 (2.67)	Ref.	1.09	1.07	0.98	1.34	1.52	1.17 (1.04, 1.30)	0.0074
CLRD-related event	14,069	1,414 (10.05)	Ref.	0.97	1.07	1.00	1.25*	1.76*	1.23 (1.16, 1.30)	<.0001
COPD Events										
Severe COPD event	14,213	298 (2.10)	Ref.	1.22	1.18	1.14	1.66	1.87*	1.23 (1.08, 1.39)	.0013
COPD-related event	14,069	1,114 (7.92)	Ref.	1.00	1.10	1.10	1.34*	1.93*	1.26 (1.18, 1.34)	<.0001
Asthma Events										
Severe asthma event	14,213	84 (0.59)	Ref.	0.68	0.86	0.62	0.73	0.93	1.04 (0.81, 1.35)	.75
Asthma-related event	14,069	319 (2.27)	Ref.	0.95	0.98	0.71	1.02	1.21	1.07 (0.94, 1.22)	.29

CI = confidence interval; CLRD = chronic lower respiratory disease; COPD = chronic obstructive pulmonary disease; Cum. Inc. = cumulative incidence; ln = natural log; SD = standard deviation.

*Statistically significant at P <.05.

Excludes participants with prevalent clinical chronic lower respiratory disease (CLRD) at time of albuminuria measurement.

CLRD-related events were defined as hospitalizations or deaths adjudicated as primarily or secondarily attributable to CLRD, or, if adjudication was lacking, those with CLRD listed in any diagnosis field. Severe CLRD events were defined as hospitalizations or deaths adjudicated as primarily attributable to CLRD or, if adjudication was lacking, with CLRD coded as the primary discharge diagnosis or underlying cause-of-death. COPD and asthma events are subsets of CLRD events; there was co-incidence of COPD and asthma events in certain participants.

Cox proportional hazards models were used. Time-to-event was treated as age-at-event, with left truncation at age-at-albuminuria-measurement.

Non-CLRD mortality was censored. Study was treated as a stratum term, allowing for cohort-specific differences in the underlying survival function.

Models were adjusted for baseline age, birth-year, height, weight, sex, race/ethnicity, educational attainment, smoking status, pack-years of smoking, hypertension status, hypertension medications, systolic blood pressure, diastolic blood pressure, total cholesterol, ACEi/ARB medication, diabetes status, diabetes medication, and eGFR.

Separate models were run using categorical (grouped quantile) and continuous (natural log-transformed albuminuria) predictors, and effect estimates were reported per category or per standard deviation, respectively. Model fit was compared by the Akaike information criterion (AIC). For all endpoints, the AIC for the categorical analysis was higher (worse) than for the continuous term (COPD/Primary cause: 3910.37 versus 3903.88; COPD/Contributing cause: 14978.94 versus 14967.12; Asthma/Primary cause: 1170.38 versus 1164.38; Asthma/Contributing cause: 4519.81 versus 4517.58).