

Ambient Air Pollution and Chronic Bronchitis in a Cohort of U.S. Women

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BACKGROUND: Limited evidence links air pollution exposure to chronic cough and sputum production. Few reports have investigated the association between long-term exposure to air pollution and classically defined chronic bronchitis.

OBJECTIVES: Our objective was to estimate the association between long-term exposure to particulate matter (diameter <10 μm, PM₁₀; <2.5 μm, PM_{2.5}), nitrogen dioxide (NO₂), and both incident and prevalent chronic bronchitis.

METHODS: We estimated annual average PM_{2.5}, PM₁₀, and NO₂ concentrations using a national land-use regression model with spatial smoothing at home addresses of participants in a prospective nationwide U.S. cohort study of sisters of women with breast cancer. Incident chronic bronchitis and prevalent chronic bronchitis, cough and phlegm, were assessed by questionnaires.

RESULTS: Among 47,357 individuals with complete data, 1,383 had prevalent chronic bronchitis at baseline, and 647 incident cases occurred over 5.7-y average follow-up. No associations with incident chronic bronchitis were observed. Prevalent chronic bronchitis was associated with PM₁₀ [adjusted odds ratio (aOR) per interquartile range (IQR) difference (5.8 μg/m³) = 1.07; 95% confidence interval (CI): 1.01, 1.13]. In never-smokers, PM_{2.5} was associated with prevalent chronic bronchitis (aOR = 1.18 per IQR difference; 95% CI: 1.04, 1.34), and NO₂ was associated with prevalent chronic bronchitis (aOR = 1.10; 95% CI = 1.01, 1.20), cough (aOR = 1.10; 95% CI: 1.05, 1.16), and phlegm (aOR = 1.07; 95% CI: 1.01, 1.14); interaction *p*-values (nonsmokers vs. smokers) <0.05.

CONCLUSIONS: PM₁₀ exposure was related to chronic bronchitis prevalence. Among never-smokers, PM_{2.5} and NO₂ exposure was associated with chronic bronchitis and component symptoms. Results may have policy ramifications for PM₁₀ regulation by providing evidence for respiratory health effects related to long-term PM₁₀ exposure. <https://doi.org/10.1289/EHP2199>

Introduction

Chronic bronchitis is a common clinical condition defined by chronic cough and sputum production for at least 3 mo in 2 or more consecutive years (American Thoracic Society 1995). Prevalence estimates in the general population of adults range from 3.5 to 27% (Kim et al. 2011; Martinez et al. 2014; Montes De Oca et al. 2012). This wide range may reflect, in part, variability in case definitions. Chronic bronchitis is a phenotype of chronic obstructive pulmonary disease (COPD) (Kim and Criner 2013). Among persons with COPD, chronic bronchitis portends increased frequency and severity of exacerbations (Burgel et al. 2009; Kim et al. 2011). Among persons without COPD, chronic bronchitis symptoms predict an increased risk of developing COPD, lower health-related quality-of-life scores, and increased risk for all-cause mortality (de Marco et al. 2007; Guerra et al. 2009; Lindberg et al. 2005; Martinez et al. 2014).

Smoking is the primary risk factor for chronic bronchitis, but exposure to ambient air pollution may also contribute (Kim and Criner 2013). The relationship between short-term air pollution exposure and acute respiratory symptoms and hospitalizations is well established (Peacock et al. 2011; Peel et al. 2005; Sunyer 2001), but limited data suggest a relationship between long-term ambient pollution exposure and COPD (Schikowski et al. 2014). There is a paucity of data on the possible relationship between classically defined chronic bronchitis and long-term exposure to the criteria pollutants PM_{2.5}, PM₁₀ (particulate matter <2.5 μm and <10 μm in diameter, respectively), and nitrogen dioxide (NO₂). The sparse existing data provide inconsistent support for an association between PM₁₀ and chronic cough and phlegm, and between NO₂ and chronic cough (Bentayeb et al. 2010b; Cai et al. 2014; Schikowski et al. 2005; Zemp et al. 1999).

To address these relationships in a larger study, using specific outcome definitions and advanced exposure assessments, we investigated the association between residential exposure to PM_{2.5}, PM₁₀, and NO₂ and both incident and prevalent chronic bronchitis in a prospective nationwide cohort of more than 50,000 U.S. women participating in the National Institute of Environmental Health Sciences (NIEHS) Sister Study. We estimated exposure at individuals' residential addresses. Taking advantage of the comprehensive survey, we uniformly classified cases of chronic bronchitis using the classical clinical definition.

Methods

Study Population

The NIEHS Sister Study is a longitudinal cohort study of U.S. women with a sister diagnosed with breast cancer, but no personal breast cancer diagnosis at time of baseline interview (*n* = 50,884).

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Women were enrolled between August 2003 and March 2009, and completed a baseline computer-assisted telephone survey. Follow-up telephone surveys were performed every 2 to 3 y. We analyzed data through the second follow-up survey (data release 4, data available through August 2014). Baseline and follow-up surveys queried participants on a wide range of health diagnoses and symptoms.

Of the 50,884 women participating in the NIEHS Sister Study, 1,234 (2.4%) were excluded for missing exposure data due to residential locations outside the modeling region or addresses that could not be geocoded (Figure 1). After excluding those missing baseline data on cough and phlegm, 47,357 individuals remained for analysis of prevalent outcomes. Of the 45,955 participants without chronic bronchitis symptoms at baseline, 6,111 (12.3%) were missing data on cough or phlegm for at least one of the two follow-up questionnaires, leaving 39,844 individuals for analysis of incident outcomes.

The Institutional Review Boards of the University of Washington and the NIEHS approved this study; all participants provided written informed consent.

Outcome Assessment

Chronic bronchitis was defined according to the classical symptom-based definition of chronic cough productive of phlegm for at least 3 mo out of a year for a minimum of 2 consecutive years (American Thoracic Society 1995). Participants were asked about the presence of cough and phlegm independently, and the duration of each symptom was specified using questions derived from the British Medical Research Council adult respiratory symptom standardized questionnaire. Women with cough and phlegm symptoms, both present for at least 3 mo per year out of the previous 2 y, were considered to have chronic bronchitis. Prevalent chronic bronchitis was determined by meeting symptom-based criteria at the baseline questionnaire. In a sensitivity analysis, we included history of physician diagnosis of chronic bronchitis in the case definition. Incident chronic bronchitis was defined by satisfying the case definition at either the second follow-up survey, or both the first and second follow-ups among participants who did not have chronic bronchitis at baseline. Participants whose symptoms did not persist from first through second follow-up were not considered cases.

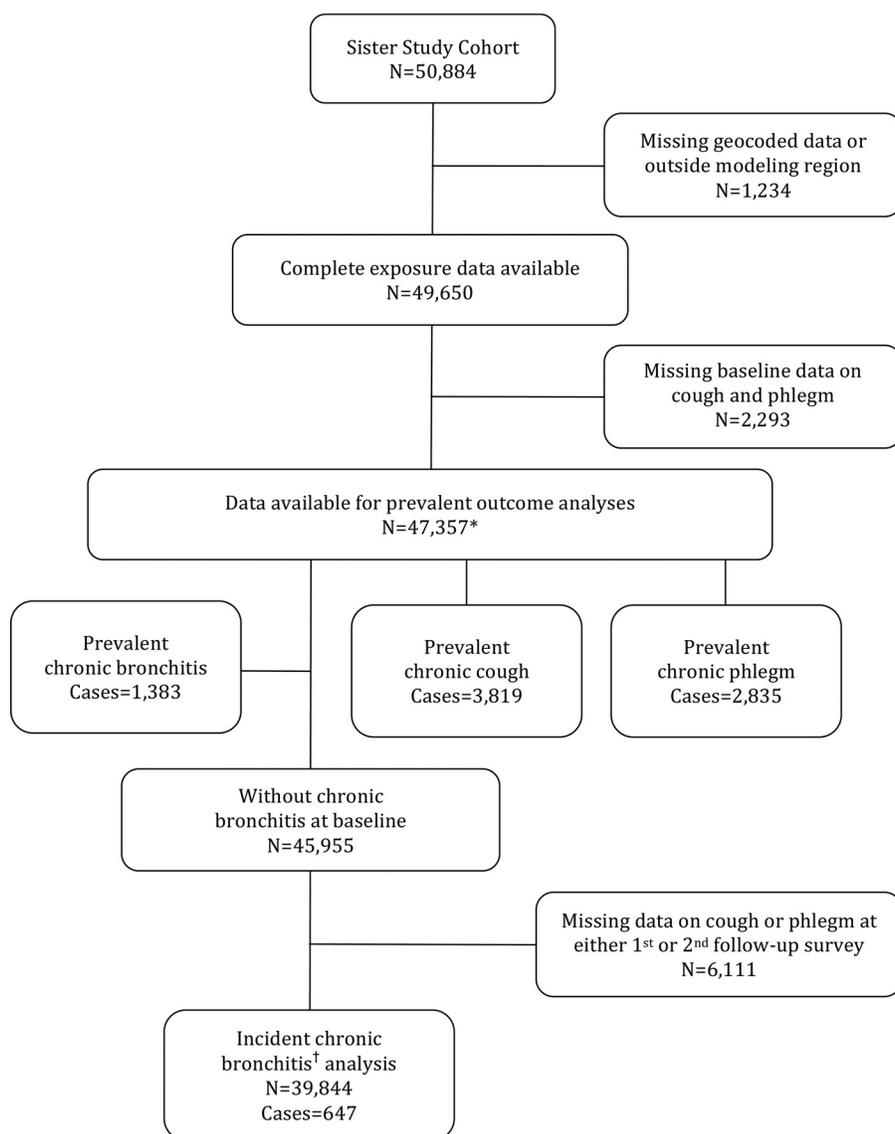


Figure 1. Study population with excluded/missing participants. *Total number of participants with nonmissing covariates for prevalence analyses is 44,158. †Total number of participants with nonmissing covariates for incidence analysis is 38,006.

Secondary outcomes were chronic cough (3 or more months of cough for at least 2 consecutive years, regardless of phlegm production), chronic phlegm (3 or more months of phlegm production for at least 2 consecutive years, regardless of cough), and chronic cough or phlegm. Both prevalent chronic cough and chronic phlegm were defined by being present at baseline.

Ambient Air Pollution Exposure Assessment

Air pollution exposure was estimated using annual average PM_{2.5}, PM₁₀, and NO₂ levels at each participant's current primary residence. Home addresses of participants were geocoded using ArcGIS (version 10; Esri). We estimated long-term exposure using year 2000 annual mean concentration levels for all pollutants. Measurements of PM_{2.5}, PM₁₀, and NO₂ concentrations from monitors using federal reference methods were obtained from the U.S. Environmental Protection Agency (EPA) Air Quality System database. After excluding locations with only seasonal coverage or large amounts of missing data, the observations were aggregated into annual averages. The annual averages were used to fit a universal kriging regression model for predicting at points within the contiguous United States. The models for PM_{2.5} (Sampson et al. 2013) and NO₂ (Young et al. 2016) have been previously described in detail, and the model for PM₁₀ was fit in the same manner as the PM_{2.5} model. Partial least squares, a dimension reduction technique, was used to select linear combinations of land use, roadway proximity, and other geographic covariates. The NO₂ prediction model additionally incorporated satellite data (Young et al. 2016). Spatial smoothing was included via an exponential covariance function. This model therefore incorporated land-use regression and spatial smoothing of values observed in the monitoring network. Model performance was evaluated using 10-fold cross-validation and for the year 2000. The cross-validated R² was 0.85 for NO₂, 0.53 for PM₁₀, and 0.77 for PM_{2.5}. Exposure modeling was limited to the continental United States; participants from Alaska, Hawaii, and Puerto Rico were excluded ($n = 1,234$).

Statistical Analysis

To estimate the association between outcomes and pollutant exposures, we used multivariable logistic regression. Covariates were selected *a priori* based on plausible relationships and review of existing literature. Potential confounders, measured at baseline, were age (continuous), ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), body mass index (continuous), education (high school or less, some college, associate or technical degree, bachelor's degree, graduate degree), household income (continuous), occupational exposure to dust (ever/never) or vapors/fumes (ever/never), smoking status (never, former, current), tobacco pack-years (continuous), and years of secondhand smoke exposure since age 19 (continuous). After exclusion of individuals missing any of these covariates, 44,158 individuals were available for the analysis of prevalent outcomes. For incident outcomes, among those without chronic bronchitis at baseline, 38,006 individuals were available after excluding missing covariates.

A model adjusted for age alone was first performed followed by a fully adjusted model including all *a priori* identified covariates. PM_{2.5}, PM₁₀, and NO₂ were modeled separately. Given potential bias by length of follow-up time for the incident chronic bronchitis outcome, adjustment was made for duration of follow-up time (from baseline to second follow-up survey) using restricted cubic splines with four knots (Dinse and Lagakos 1983). We performed analyses stratified by baseline smoking status (ever/never) and tested for interaction using product terms for smoking status and

pollutant exposure. A two-pollutant model was performed by including remaining copollutants in the fully adjusted model. In all instances, a p -value of <0.05 was considered significant.

Sensitivity analyses were prespecified and performed on the following subgroups in independent analyses: *a*) prevalent chronic bronchitis that included either symptom-based criteria or report of physician diagnosis; *b*) excluding baseline asthmatics [defined by history of physician diagnosis, recent (within 12 mo) asthma medication use, and self-reported current asthma], given clinical overlap between asthma and chronic bronchitis; and *c*) participants who lived at least 10 y at their primary residence. In the asthma sensitivity analysis, asthmatics who reported either current smoking or history of ≥ 10 pack-years at baseline were not excluded given possibility of smoking-related symptoms leading to asthma misdiagnosis. Given concern that seasonal variation may affect results, an additional sensitivity analysis was performed by adjusting for season at the time of baseline and follow-up questionnaires.

Statistical analysis was performed using the statistical program Stata (version 11; StataCorp).

Results

Participants were, on average, 55.4 y old at baseline [standard deviation (SD) = 8.9], 84.8% were white, 52.6% had a bachelor's degree or higher level of education, 56.4% had never smoked cigarettes, and only 8% were current smokers. The proportion of black and Hispanic participants increased across tertiles of PM_{2.5}, PM₁₀, and NO₂ (Table 1). The distributions of occupational exposures, smoking history, and cumulative tobacco smoke exposure did not vary materially by ambient air pollution exposure levels (Table 1).

The mean follow-up time was 5.7 y from enrollment to the second follow-up survey. During the follow-up period, there were 638 incident cases of chronic bronchitis, giving an estimated incidence rate of 2.8 cases per 1,000 person-years. At baseline, 1,351 (3.1%) women met symptom-based criteria for chronic bronchitis, whereas 4,698 (10.6%) participants reported ever having had a physician diagnosis of chronic bronchitis. Prevalent chronic cough was reported by 3,749 (8.5%) and chronic phlegm by 2,776 (6.3%) participants at baseline.

The median estimated exposure concentrations were 12.4 $\mu\text{g}/\text{m}^3$ [interquartile range (IQR) = 4.4 $\mu\text{g}/\text{m}^3$] for PM_{2.5}, 2.16 $\mu\text{g}/\text{m}^3$ (5.8 $\mu\text{g}/\text{m}^3$) for PM₁₀, and 11.7 ppb (7.3 ppb) for NO₂. The results of the age-adjusted and fully adjusted regression analyses are presented in Table 2. No statistically significant associations were found between incident chronic bronchitis and any of the air pollution exposures. Limiting the incidence analysis to long-term residents (>10 y) did not appreciably alter the effect estimates (Table S1).

For prevalent chronic bronchitis, a statistically significant positive association was seen with PM₁₀ [odds ratio (OR) per IQR increase in PM₁₀ = 1.07; 95% confidence interval (CI): 1.01, 1.13] (Table 2). Similar magnitudes of association with prevalent chronic bronchitis were seen for NO₂ (OR = 1.05; 95% CI: 0.99, 1.11) and PM_{2.5} (OR = 1.04; 95% CI: 0.96, 1.13), but were not statistically significant. PM₁₀ was also statistically significantly associated with chronic cough (OR = 1.04; 95% CI: 1.00, 1.08), chronic phlegm (OR = 1.07; 95% CI: 1.02, 1.11), and chronic cough or phlegm (OR = 1.05; 95% CI: 1.02, 1.08); coadjustment for PM_{2.5} did not alter these effect estimates (Table S2). Adjustment of the PM₁₀ model for NO₂ resulted in a general attenuation of associations between prevalent symptoms and PM₁₀. This attenuation is likely due in part to the strong correlation between NO₂ and PM₁₀ (Pearson's r : 0.59).

Table 1. Participant characteristics at baseline by exposure tertiles for particulate matter PM_{2.5}, PM₁₀, and NO₂.

Characteristic	PM _{2.5} (μg/m ³)			NO ₂ (ppb)			PM ₁₀ (μg/m ³)		
	2.1–10.9	10.9–13.9	13.9–25.3	2.16–9.54	9.54–14.1	14.1–39.0	5.68–19.8	19.8–23.4	23.4–56.4
<i>n</i>	14,720	14,719	14,719	14,720	14,719	14,719	14,720	14,719	14,719
Age (years)	55.9 ± 8.9	55.4 ± 9	54.9 ± 8.9	55.7 ± 8.8	55.3 ± 8.9	55.3 ± 9	55.7 ± 8.7	55.3 ± 8.9	55.3 ± 9
BMI	27.5 ± 6	27.9 ± 6.3	28.3 ± 6.5	27.8 ± 6.1	27.8 ± 6.3	27.9 ± 6.5	27.5 ± 6.1	27.9 ± 6.3	28.2 ± 6.5
Race/ethnicity (%)									
White (non-Hispanic)	90.7	85.9	77.7	89.2	85.4	79.7	90.1	85.5	78.6
Black (non-Hispanic)	2.4	8.7	16.8	5.6	9.4	12.9	5.6	9.4	12.9
Hispanic	4.1	2.9	3	2.3	2.9	4.8	1.8	2.7	5.6
Other	2.8	2.5	2.5	2.9	2.3	2.6	2.5	2.3	3
Education (%)									
HS or less	14.7	15.1	14.8	17.6	14.8	12.3	15.1	15.1	14.5
Some college	35.2	33.5	32.1	36.8	33.3	30.8	33.7	32.7	34.3
Bachelor's	27.4	27	26.9	25.7	27.4	28.2	26.6	27.3	27.4
Graduate	22.8	24.4	26.2	20	24.6	28.8	24.6	25	23.8
Household income (USD)	41,218 ± 25,849	43,570 ± 26,914	43,743 ± 28,293	39,995 ± 24,817	43,064 ± 26,339	45,472 ± 29,533	42,473 ± 25,999	43,104 ± 26,892	42,953 ± 28,242
Occupational Exposures (%)									
Vapors/fumes (ever)	24.9	24.3	24	25.7	24.1	23.5	24.4	24.4	24.4
Dust (ever)	22.2	22.7	23.8	23.5	22.4	22.9	22.7	22.6	23.5
Smoking status (%)									
Never	56.2	55.7	57.2	57.2	57.3	54.6	54.4	57.4	57.3
Former	36.6	36.4	33.9	34.8	35	37.1	37.6	34.8	34.5
Current	7.2	8	8.9	8.1	7.7	8.3	7.9	7.8	8.3
Pack-years among ever-smokers	14.5 ± 15.3	14.7 ± 15.2	14.8 ± 15.5	15.1 ± 15.6	14.3 ± 15.1	14.5 ± 15.2	14.8 ± 15.5	14.5 ± 15.2	14.6 ± 15.2
Packs per day among current smokers	0.7 ± 0.4	0.7 ± 0.4	0.7 ± 0.5	0.7 ± 0.5	0.7 ± 0.4	0.6 ± 0.4	0.7 ± 0.5	0.7 ± 0.4	0.7 ± 0.4
Adult secondhand smoke (years)	10.9 ± 12.9	11.3 ± 13.3	11.4 ± 13.2	11.5 ± 13.2	11.1 ± 13.1	11.1 ± 13.1	11.3 ± 13.1	11.1 ± 13.1	11.3 ± 13.3
Number of years at primary residence	12.8 ± 10.9	13.5 ± 11.3	13.6 ± 11.5	12.7 ± 11	12.7 ± 10.7	14.6 ± 11.8	13.4 ± 11	13.2 ± 11.2	13.3 ± 11.5
Lived at primary residence ≥ 10 y (%)	50.7	53.5	53.9	50.1	50.8	57.1	53.6	52.2	52.4
Asthma at baseline (%)	5.7	5.6	5.9	5	6	6.3	5.4	5.9	6
Physician diagnosis of COPD (%)	1.5	1.5	1.5	1.6	1.6	1.4	1.5	1.5	1.5
Physician diagnosis of chronic bronchitis (%)	7.4	8	8.4	8	8.1	7.8	7.5	8	8.4

Note: BMI, body mass index; COPD, chronic obstructive pulmonary disease; HS, high school; PM, particulate matter.

Table 2. Odds ratios per interquartile range (IQR) increase in particulate matter PM_{2.5} (4.4 µg/m³), NO₂ (7.3 ppb), and PM₁₀ (5.8 µg/m³).

Exposure and outcome	Cases	Age adjusted		Fully adjusted	
		OR (95% CI)	p-Value	OR (95% CI)	p-Value
PM_{2.5}					
Incident chronic bronchitis	638	0.94 (0.84, 1.05)	0.256	0.94 (0.83, 1.06)	0.289
Prevalent (at baseline)					
Chronic bronchitis	1,351	1.04 (0.97, 1.13)	0.276	1.04 (0.96, 1.13)	0.318
Chronic cough	3,749	1.03 (0.98, 1.08)	0.213	1.04 (0.99, 1.10)	0.103
Chronic phlegm	2,776	1.07 (1.02, 1.13)	0.010	1.04 (0.98, 1.10)	0.213
Chronic cough or phlegm	5,271	1.05 (1.01, 1.10)	0.015	1.04 (1.00, 1.09)	0.067
NO₂					
Incident chronic bronchitis	638	0.95 (0.87, 1.03)	0.198	1.00 (0.92, 1.09)	0.974
Prevalent (at baseline)					
Chronic bronchitis	1,351	1.00 (0.95, 1.06)	0.923	1.05 (0.99, 1.11)	0.136
Chronic cough	3,749	1.02 (0.99, 1.06)	0.215	1.06 (1.02, 1.10)	0.002
Chronic phlegm	2,776	1.01 (0.97, 1.05)	0.730	1.02 (0.98, 1.07)	0.266
Chronic cough or phlegm	5,271	1.02 (0.99, 1.05)	0.199	1.04 (1.01, 1.08)	0.008
PM₁₀					
Incident chronic bronchitis	638	0.92 (0.85, 1.01)	0.066	0.98 (0.90, 1.08)	0.745
Prevalent (at baseline)					
Chronic bronchitis	1,351	1.06 (1.01, 1.12)	0.027	1.07 (1.01, 1.13)	0.019
Chronic cough	3,749	1.04 (1.00, 1.07)	0.045	1.04 (1.00, 1.08)	0.030
Chronic phlegm	2,776	1.07 (1.03, 1.12)	<0.001	1.07 (1.02, 1.11)	0.002
Chronic cough or phlegm	5,271	1.05 (1.01, 1.08)	0.001	1.05 (1.02, 1.08)	0.003

Note: Each outcome was compared to all participants without that outcome. The total number of participants with nonmissing data on all covariates was 38,006 for the analysis of incident outcomes, 44,158 for prevalent outcomes. Fully adjusted model includes age, race/ethnicity, body mass index, education, household income, occupational exposure to vapors/fumes or dust (ever), smoking status, total pack-years, and environmental tobacco smoke exposure. Primary outcome (incident chronic bronchitis) analysis additionally adjusted for length of follow-up time. CI, confidence interval; IQR, interquartile range; OR, odds ratio; PM, particulate matter.

NO₂ showed a significant positive association with chronic cough (OR = 1.06; 95% CI: 1.02, 1.10) and chronic cough or phlegm (OR = 1.04; 95% CI: 1.01, 1.08). In the NO₂ model, ORs were robust to coadjustment for PM_{2.5} (Table S2). Coadjustment for PM₁₀ in the NO₂ model resulted in a loss of precision for the association between NO₂ and chronic cough or phlegm, and an overall decrease in size of effect estimates across all prevalent outcomes. The significant association with chronic cough was preserved (OR = 1.05; 95% CI: 1.01, 1.10). ORs for all pollutants and outcomes were generally very similar between age-adjusted and fully adjusted models.

For prevalent chronic bronchitis, sensitivity analyses incorporating additional case requirements into the classical symptom-based definition showed comparable effect estimates in association with PM₁₀ (Table 3). For example, PM₁₀ was significantly associated with prevalent chronic bronchitis defined either by

symptoms or including participant-reported physician diagnosis (OR per IQR increase = 1.06; 95% CI: 1.02, 1.09). In an analysis of prevalent chronic bronchitis excluding baseline asthmatics, the effect estimate was similar but less precise, commensurate with the smaller sample size (OR for IQR increase in PM₁₀ = 1.06; 95% CI: 0.99, 1.13). Similarly, exclusion of the 47% of participants who lived at their residence less than 10 y largely preserved the estimated association, but with loss of precision reflecting the smaller sample size (OR per IQR increase in PM₁₀ = 1.07; 95% CI: 0.99, 1.16). Comparable sensitivity analyses involving PM_{2.5} or NO₂ and prevalent chronic bronchitis yielded ORs that were similar in magnitude and direction to the primary models (Table 3). Effect estimates for all three pollutants were essentially unchanged by seasonal adjustment (Table S3).

In smoking-stratified analyses, we found evidence for stronger associations between all three air pollutants and prevalent outcomes

Table 3. Sensitivity analyses evaluating case definitions with additional inclusion or exclusion criteria for association of prevalent (baseline) chronic bronchitis with ambient air pollutants: odds ratios per interquartile range (IQR) increase in particulate matter PM_{2.5} (4.4 µg/m³), NO₂ (7.3 ppb), and PM₁₀ (5.8 µg/m³).

Exposure and case definitions (primary and sensitivity analyses)	n ^a	Cases	Adjusted OR (95% CI)	p-Value
PM_{2.5}				
Prevalent chronic bronchitis (primary case definition)	44,158	1,351	1.04 (0.96, 1.13)	0.318
Including physician diagnosis	44,099	4,698	1.04 (0.99, 1.09)	0.104
Excluding asthma at baseline	41,488	1,104	0.99 (0.90, 1.08)	0.798
Excluding those living at residence <10 y	23,273	720	0.97 (0.87, 1.09)	0.643
NO₂				
Prevalent chronic bronchitis (primary case definition)	44,158	1,351	1.05 (0.99, 1.11)	0.136
Including physician diagnosis	44,099	4,698	1.02 (0.99, 1.06)	0.191
Excluding asthma at baseline	41,488	1,104	1.02 (0.96, 1.09)	0.492
Excluding those living at residence <10 y	23,273	720	1.03 (0.95, 1.11)	0.444
PM₁₀				
Prevalent chronic bronchitis (primary case definition)	44,158	1,351	1.07 (1.01, 1.13)	0.019
Including physician diagnosis	44,099	4,698	1.06 (1.02, 1.09)	0.001
Excluding asthma at baseline	41,488	1,104	1.06 (0.99, 1.13)	0.077
Excluding those living at residence <10 y	23,273	720	1.07 (0.99, 1.16)	0.093

Note: For each case definition, the comparison group was all individuals without that outcome. Each analysis was performed independently for each case definition. Adjusted for age, race/ethnicity, body mass index, education, household income, occupational exposure to vapors/fumes or dust (ever), smoking status, total pack-years, and secondhand smoke exposure. CI, confidence interval; OR, odds ratio; PM, particulate matter.

^aTotal number of individuals with nonmissing data on all covariates for analysis.

in never-smokers (Table 4). PM_{2.5} was strongly associated with prevalent chronic bronchitis among never-smokers (OR per IQR difference = 1.18; 95% CI: 1.04, 1.34), and the difference by smoking status was statistically significant ($p_{\text{interaction}} = 0.013$). Similarly with NO₂, in never-smokers, significant associations were seen for all four prevalent outcomes: chronic bronchitis (OR = 1.10; 95% CI: 1.01, 1.20), chronic cough (OR = 1.10; 95% CI: 1.05, 1.16), chronic phlegm (OR = 1.07; 95% CI: 1.01, 1.14), and chronic cough or phlegm (OR = 1.09; 95% CI: 1.04, 1.13), and the differences by smoking status were statistically significant for both cough ($p_{\text{interaction}} = 0.020$), phlegm ($p_{\text{interaction}} = 0.017$), and cough or phlegm ($p_{\text{interaction}} = 0.004$). Corresponding ORs for PM_{2.5} and NO₂ were close to null for ever-smokers. For PM₁₀, results did not differ significantly by smoking status, although the same pattern of stronger associations in never-smokers was seen (Table 4).

Discussion

To our knowledge, this is the largest study to investigate the association between classically defined chronic bronchitis and long-term ambient air pollution exposure using a validated national exposure model. We did not find an association between incident chronic bronchitis and any of the three air pollution measures. However, exposure to higher concentrations of PM₁₀ was significantly associated with all prevalent outcomes: chronic bronchitis, chronic cough, chronic phlegm, and chronic cough or phlegm. These findings were robust to coadjustment for PM_{2.5} in a two-pollutant model (Table S2). We also found NO₂ exposure was significantly associated with chronic cough and chronic cough or phlegm. To the best of our knowledge, no other study has shown an association between PM₁₀ and classically defined chronic bronchitis. These findings provide evidence that long-term ambient air pollution exposure, particularly PM₁₀, is a risk factor for chronic bronchitis and the chronic respiratory symptoms of cough and phlegm that define it.

Incident chronic bronchitis should be superior to prevalent chronic bronchitis for making causal inference regarding observed associations with air pollution. However, the relatively short

follow-up duration (mean: 5.7 y) limited our power to detect an association between ambient air pollutants and incident chronic bronchitis. With the much larger number of cases of prevalent conditions, we had substantially higher power than for the incident analyses. One smaller study of nonsmoking Seventh Day Adventists in California has shown an association between incident chronic bronchitis and long-term exposure to PM_{2.5}; however, levels were in excess of 20 µg/m³, a concentration almost double that observed in our study (Abbey et al. 1995).

Comparison to previous studies is limited due to substantial variability in defining chronic bronchitis and exposure estimation methods. The observed incidence rate of 2.5 cases per 1,000 person-years and prevalence of 2.9% are at the low end of the range reported in the literature (Cai et al. 2014; Cerveri et al. 2001; Huchon et al. 2002; Kim et al. 2011; Sobradillo et al. 1999). However, our study population was more than half non-smoking women, and our estimates are in agreement with study populations with similar demographics (Montes De Oca et al. 2012; Sunyer et al. 2006). National prevalence and incidence figures for chronic bronchitis are lacking because they rely on physician diagnosis rather than the classical symptom-based diagnostic criteria (American Lung Association 2013). Including participant-reported physician diagnosis greatly increases the prevalence of chronic bronchitis in this study and likely elsewhere (Schikowski et al. 2005).

Our study provides evidence that PM₁₀ exposure is a risk factor for chronic bronchitis, while the existing literature suggests associations between PM₁₀ and various respiratory symptoms. A large cross-sectional study in Switzerland found an association between increased prevalence of chronic cough and phlegm with PM₁₀ exposure among never-smokers (Zemp et al. 1999). The European Study of Cohorts for Air Pollution Effects (ESCAPE) meta-analysis of five European cohorts similarly showed an association between PM₁₀ and prevalent chronic phlegm, but not chronic bronchitis, in never-smokers (Cai et al. 2014). A French study of elderly adults demonstrated increased prevalence of chronic cough associated with PM₁₀ exposure (Bentayeb et al.

Table 4. Chronic bronchitis in relation to air pollutants [particulate matter PM_{2.5}, NO₂, and PM₁₀] by smoking status (never/ever): odds ratios per interquartile range (IQR) increase in PM_{2.5} (4.4 µg/m³), NO₂ (7.3 ppb), and PM₁₀ (5.8 µg/m³).

Exposure and outcome	Never-smoker			Ever-smoker			$p_{\text{Interaction}}$
	Cases	OR (95% CI)	p -Value	Cases	OR (95% CI)	p -Value	
PM _{2.5}							
Incident chronic bronchitis	271	0.92 (0.77, 1.10)	0.382	367	0.95 (0.81, 1.11)	0.516	0.815
Prevalent (at baseline)							
Chronic bronchitis	580	1.18 (1.04, 1.34)	0.011	771	0.96 (0.86, 1.07)	0.427	0.013
Chronic cough	1,802	1.07 (1.00, 1.15)	0.053	1,947	1.02 (0.95, 1.10)	0.545	0.345
Chronic phlegm	1,362	1.08 (1.00, 1.17)	0.059	1,414	1.00 (0.92, 1.09)	0.956	0.189
Chronic cough or phlegm	2,632	1.06 (0.99, 1.12)	0.077	2,639	1.03 (0.97, 1.10)	0.292	0.638
NO ₂							
Incident chronic bronchitis	271	1.03 (0.91, 1.17)	0.609	367	0.97 (0.86, 1.10)	0.660	0.498
Prevalent (at baseline)							
Chronic bronchitis	580	1.10 (1.01, 1.20)	0.029	771	1.00 (0.92, 1.08)	0.955	0.097
Chronic cough	1,802	1.10 (1.05, 1.16)	<0.001	1,947	1.01 (0.96, 1.06)	0.642	0.020
Chronic phlegm	1,362	1.07 (1.01, 1.14)	0.014	1,414	0.97 (0.92, 1.03)	0.359	0.017
Chronic cough or phlegm	2,632	1.09 (1.04, 1.13)	<0.001	2,639	0.99 (0.95, 1.04)	0.806	0.004
PM ₁₀							
Incident chronic bronchitis	271	1.04 (0.91, 1.18)	0.587	367	0.95 (0.83, 1.08)	0.458	0.359
Prevalent (at baseline)							
Chronic bronchitis	580	1.09 (1.00, 1.20)	0.055	771	1.06 (0.98, 1.14)	0.131	0.597
Chronic cough	1,802	1.07 (1.01, 1.12)	0.015	1,947	1.02 (0.97, 1.08)	0.391	0.260
Chronic phlegm	1,362	1.10 (1.04, 1.17)	0.002	1,414	1.04 (0.98, 1.10)	0.179	0.189
Chronic cough or phlegm	2,632	1.08 (1.03, 1.13)	<0.001	2,639	1.02 (0.98, 1.07)	0.352	0.081

Note: For each case definition, the comparison group was all individuals without that outcome. The total number of participants with nonmissing data on all covariates was 38,006 (21,527 never-smokers and 16,479 ever-smokers) for the analysis of incident outcomes and 44,158 (24,894 never-smokers and 19,264 ever-smokers) for prevalent outcomes. Adjusted for age, race/ethnicity, body mass index, education, household income, occupational exposure to vapors/fumes or dust (ever), total pack-years, and environmental tobacco smoke exposure. Incident analysis additionally adjusted for length of follow-up time. CI, confidence interval; IQR, interquartile range; OR, odds ratio; PM, particulate matter.

2010a). Furthermore, in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) cohort, decline in PM₁₀ over time was associated with a reduction in chronic cough and phlegm (Schindler et al. 2009). Our study suggests long-term PM₁₀ exposure is associated with prevalent chronic bronchitis, the distinct clinical entity, as well as the associated symptoms that define it.

In contrast to PM_{2.5}, which deposits within the distal alveoli, the preferential deposition of coarse particles within the conducting airways of the tracheobronchial tree provides biologic plausibility for the association between PM₁₀ and chronic bronchitis (Carvalho et al. 2011). Chronic airway epithelial inflammation and mucus metaplasia are the pathologic bases of chronic bronchitis (Kim and Criner 2013). Chronic bronchitis is associated with narrowing and mucus plugging of the nonalveolated conducting airways (Matsuba and Thurlbeck 1973). PM has been frequently implicated in triggering pro-inflammatory cascades within airway epithelial cells (Øvrevik et al. 2015). Certain PM₁₀ components, including transition metals and endotoxins, have been shown to drive airway inflammation and mucus hypersecretion via upregulation of transcription factors and generation of reactive oxygen species and oxidative stress (Longpre et al. 2000; Øvrevik et al. 2015).

For NO₂, we saw no associations with prevalent chronic bronchitis or chronic phlegm in the main analyses; however, there were positive associations with both chronic cough and chronic cough or phlegm. These associations were robust to coadjustment for PM_{2.5}. Adjustment for PM₁₀, in an attempt to isolate the effect of NO₂, was limited by the strong correlation between these copollutants. Previous studies have shown inconsistent associations between respiratory symptoms and NO₂. The ESCAPE meta-analysis showed no significant association between NO₂ and chronic bronchitis, cough, or phlegm (Cai et al. 2014). The German Study on the Influence of Air Pollution on Lung, Inflammation and Aging (SALIA) cohort analysis showed association with cough, but not chronic bronchitis, while the Swiss SAPALDIA study showed no association overall (Schikowski et al. 2005; Zemp et al. 1999). In both the SALIA and SAPALDIA studies, conducted in the 1990s, the annual mean NO₂ levels were more than double those in our study.

Among never-smokers, associations between prevalent symptoms and exposures were stronger for all pollutants. If we limit our interpretation of the stratified analyses to those with statistically significant interactions, we find stronger evidence for associations between both NO₂ and PM_{2.5} and our prevalent outcomes among never-smokers. The finding of stronger associations with these two pollutants and outcomes in never-smokers is consistent with some previous literature findings. In the Swiss SAPALDIA study, NO₂ was related to chronic bronchitis only among non-smokers. For PM_{2.5}, the ESCAPE meta-analysis found a positive association between chronic cough and PM_{2.5} only among never-smokers (Cai et al. 2014). NO₂ was associated with chronic cough in a study of about 4,700 women in Germany, 74% of whom were never-smokers (Schikowski et al. 2005).

The reason for stronger associations with NO₂ in never-smokers in our study and others is unclear. Perhaps the airways of smokers are more tolerant to the irritant effects of ambient NO₂ than nonsmokers who, as a result, are dissuaded from smoking because of greater sensitivity to these effects. Alternatively, the effects of compounds in cigarette smoke might swamp the effects of ambient NO₂ exposure. Stronger associations with PM_{2.5} in never-smokers could reflect, in part, the high dose of fine particles inhaled by smokers. The biologic effects of cigarette smoke may overwhelm the effects from long-term, low-level ambient air pollution and thus mask any association. For PM₁₀, we saw

clear associations with chronic bronchitis in all subjects, possibly related to PM₁₀ favoring deposition in the conducting airways that are responsible for producing bronchitic symptoms. This association is apparent in the aggregate sample. In contrast, the associations between chronic bronchitis and PM_{2.5} and NO₂ were only apparent in never-smokers. These pollutants have distribution patterns that tend to bypass the conducting airways for deposition and adsorption in the distal alveoli.

Outcome misclassification was reduced by using the symptom-defined definition of chronic bronchitis. However, the symptom-based questionnaire still has limitations; due to recall bias, it likely results in inclusion of cases with recent, but not necessarily chronic, symptoms. Overlap with asthma remains possible given the clinical similarities of these conditions. Sensitivity analyses excluding subjects with a physician diagnosis of asthma and active asthma symptoms at baseline attenuated the association with all pollutants. However, the exclusion of these participants with overlapping chronic bronchitis symptoms may have eliminated true cases of chronic bronchitis and thus reduced power.

The sensitivity analysis including individuals reporting doctor diagnosis of chronic bronchitis showed preserved associations with increased precision. Self-report of doctor diagnosis is likely to include more individuals with symptom duration shorter than the 2-y minimum required for the chronic bronchitis definition (i.e., may include participants who have received a diagnosis of acute bronchitis in the past). Given that chronic bronchitis is defined by duration of symptoms, directly asking subjects questions on cough and phlegm is preferable to asking about physician diagnosis, which requires accurate reporting by both parties. However, the association between PM₁₀ and prevalent chronic bronchitis remains robust, even with the less strict definition, suggesting that presence of symptoms is driving the relationship, rather than the specific duration of symptoms.

The objection has been raised that chronic bronchitis prevalence as reported on questionnaires may reflect recent symptoms and that prevalence and/or severity might then vary by season. Therefore, we undertook a sensitivity analysis adjusting for season of both baseline and follow-up questionnaire (Table S3). No change was observed in the effect estimates for outcomes associated with PM_{2.5} or NO₂. The associations between prevalent chronic bronchitis and chronic cough and PM₁₀ were no longer statistically significant after adjusting for season, but the effect estimates remained largely unchanged and in the anticipated direction. Season of questionnaire administration does not seem to contribute significant bias in reporting of chronic bronchitis.

Our air pollution exposure estimates are based on a validated national model using land-use regression and spatial smoothing to capture within- and between-region air pollution variability and minimize exposure misclassification. This model is a considerable improvement over road proximity, regional fixed-monitor averages, and simple land-use regression models employed in prior chronic bronchitis investigations (Keller et al. 2014; Young et al. 2016). In addition, seasonal bias in the exposure should be mitigated by using annual averages and a chronic outcome whose case definition dictates that symptoms must span a minimum of 2 consecutive years. Air pollution estimates used year 2000 annual averages, predating baseline enrollment for all participants. While concentrations of criteria pollutants are declining nationally, spatial differences of annual average pollution concentrations account for the majority of variability in PM_{2.5} measurement and were relatively stable across the study period (Kim et al. 2017). However, it is acknowledged that variability in the decline in pollution levels may contribute to exposure misclassification, and the resulting biases are difficult to predict. It is plausible that our observed lack of association for incident outcomes and positive effects for

prevalent symptoms could be related to variable change in pollution levels; e.g., if the most polluted regions experienced more dramatic declines in levels than the cleaner areas.

Additional limitations exist. This study is limited to women, and the findings may not be broadly applicable to men. Outdoor ambient pollutant concentrations may not reflect the indoor exposures. Exposure measurement error owing to our use of residential addresses to characterize exposure owing both to subjects' residential mobility, time spent away from home or indoors, and spatiotemporal trends is a limitation both of this study and epidemiological studies of air pollution health effects in general. Exposure measurement of this nature error is generally expected to bias associations toward the null rather than producing false positive associations.

In 2006, the EPA revoked the National Ambient Air Quality Standard for annual PM₁₀ due to insufficient data on health risks associated with long-term exposure to PM₁₀ as opposed to the finer PM_{2.5} fraction (U.S. EPA 2006). The preceding long-term PM₁₀ exposure standard was an annual average of 50 µg/m³, roughly double the mean concentration experienced by participants in this study. This study provides evidence that chronic respiratory health effects occur with long-term exposure to PM₁₀ at levels below the previous national standards. These results add to a limited body of evidence relating morbidity to long-term PM₁₀ exposure and consequently may have policy implications both nationally and globally.

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