



# Ambient Air Pollution Exposure and Incident Adult Asthma in a Nationwide Cohort of U.S. Women

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## Abstract

**Rationale:** Limited prior data suggest an association between traffic-related air pollution and incident asthma in adults. No published studies assess the effect of long-term exposures to particulate matter less than 2.5  $\mu\text{m}$  in diameter ( $\text{PM}_{2.5}$ ) on adult incident asthma.

**Objectives:** To estimate the association between ambient air pollution exposures ( $\text{PM}_{2.5}$  and nitrogen dioxide,  $\text{NO}_2$ ) and development of asthma and incident respiratory symptoms.

**Methods:** The Sister Study is a U.S. cohort study of risk factors for breast cancer and other health outcomes ( $n = 50,884$ ) in sisters of women with breast cancer (enrollment, 2003–2009). Annual average (2006) ambient  $\text{PM}_{2.5}$  and  $\text{NO}_2$  concentrations were estimated at participants' addresses, using a national land-use/kriging model incorporating roadway information. Outcomes at follow-up (2008–2012) included incident self-reported wheeze, chronic cough, and doctor-diagnosed asthma in women without baseline symptoms.

**Measurements and Main Results:** Adjusted analyses included 254 incident cases of asthma, 1,023 of wheeze, and 1,559 of chronic cough. For an interquartile range (IQR) difference ( $3.6 \mu\text{g}/\text{m}^3$ ) in estimated  $\text{PM}_{2.5}$  exposure, the adjusted odds ratio (aOR) was 1.20 (95% confidence interval [CI] = 0.99–1.46,  $P = 0.063$ ) for incident asthma and 1.14 (95% CI = 1.04–1.26,  $P = 0.008$ ) for incident wheeze. For  $\text{NO}_2$ , there was evidence for an association with incident wheeze (aOR = 1.08, 95% CI = 1.00–1.17,  $P = 0.048$  per IQR of 5.8 ppb). Neither pollutant was significantly associated with incident cough ( $\text{PM}_{2.5}$ : aOR = 0.95, 95% CI = 0.88–1.03,  $P = 0.194$ ;  $\text{NO}_2$ : aOR = 1.00, 95% CI = 0.93–1.07,  $P = 0.939$ ).

**Conclusions:** Results suggest that  $\text{PM}_{2.5}$  exposure increases the risk of developing asthma and that  $\text{PM}_{2.5}$  and  $\text{NO}_2$  increase the risk of developing wheeze, the cardinal symptom of asthma, in adult women.

**Keywords:** asthma incidence; particulate matter;  $\text{PM}_{2.5}$ ; nitrogen dioxide;  $\text{NO}_2$

The causes of asthma are not well understood, and research on the etiology of adult-onset asthma, outside of specific occupational settings, is limited. There is increasing literature suggesting a role for

ambient air pollution in the development of asthma in children, but there are few studies in adults (1). Two reviews have cited the need for more research on the role of air pollution in the development of asthma in

adults (1, 2) and specifically for large cohorts with improved exposure assessment (1). Although nitrogen dioxide ( $\text{NO}_2$ ) is typically used as a marker for traffic-related air pollution, both particulate

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## At a Glance Commentary

### Scientific Knowledge on the

**Subject:** Previous research, primarily in children, has demonstrated an association between air pollution and asthma exacerbation, and some evidence suggests a role in asthma incidence in children. The few studies on incident asthma in adults have had less precise exposure measurements and modest sample sizes, and none has directly examined exposure to particulate matter less than 2.5  $\mu\text{m}$  in diameter ( $\text{PM}_{2.5}$ ).

### What This Study Adds to the

**Field:** The results of this large nationwide cohort study suggest that ambient  $\text{PM}_{2.5}$  exposure or other related exposures may be involved in the development of respiratory symptoms, particularly wheeze, and incident asthma in women.

matter and  $\text{NO}_2$  are created by combustion sources such as vehicle exhaust and both are potentially harmful pollutants. Notably, although there have been studies of  $\text{PM}_{10}$  (particulate matter less than 10  $\mu\text{m}$  in diameter) exposure and adult-onset asthma (3, 4), there are no published studies on the association between adult-onset asthma and exposure to  $\text{PM}_{2.5}$ . Particles of various sizes may act differently with respect to potential asthmagenic characteristics such as lung penetration (5) and oxidative potential (6), and  $\text{PM}_{2.5}$  is often not closely correlated with  $\text{PM}_{10}$  (7). Therefore, analyses of  $\text{PM}_{2.5}$  as a possible cause of adult-onset asthma represent an important contribution to existing literature.

Adult-onset asthma is common and is an important public health problem. It has unique features that differentiate it from childhood-onset asthma. For example, the prevalence of asthma is higher in adult women (8.8%) than men (5.8%) in the United States (8), but before puberty asthma is more common in boys than girls (9). Adult-onset asthma is less likely than childhood asthma to be atopic (10). Ongoing research suggests that childhood-onset and adult-onset asthma represent at least two distinct diseases (11, 12) and thus observed associations between air pollution and development of childhood asthma may

not necessarily extend to the adult phenotype.

To address the paucity of data on the potential role of air pollution in the development of adult-onset asthma, we evaluated the association between  $\text{PM}_{2.5}$  and  $\text{NO}_2$  exposure and incident asthma, incident chronic cough, and incident wheeze in the National Institute of Environmental Health Sciences (NIEHS, Research Triangle Park, NC) Sister Study, a nationwide study of more than 50,000 U.S. women.

Some of the results of these studies have been previously reported in the form of an abstract (13). A previous version of this article exists in the form of an unpublished master's thesis (14).

## Methods

The Sister Study involves a large cohort of women across the United States, who have at least one sister with a diagnosis of breast cancer ( $n = 50,884$ ) but who had not been diagnosed themselves at enrollment (15). Participants were enrolled from August 2003 through March 2009. Each participant underwent a baseline computer-assisted telephone survey at enrollment and completed the first computer-assisted follow-up telephone interview 2–3 years after the baseline survey, depending on enrollment date (March 2008–April 2012).

### Respiratory Outcome Assessment

Both the baseline and follow-up survey included questions about asthma history and symptoms (*see* the online supplement for details). Instead of individualizing follow-up questionnaires to query new diagnoses with respect to each participant's personal baseline date, we asked whether they had been diagnosed since a date that was the earliest they could have completed the baseline questionnaire. Specifically, follow-up questions regarding new symptoms were asked with regard to a reference date, which varied by enrollment period and approximated the date of completion of the baseline survey. Because the first follow-up questionnaire was fielded over several years, the reference date changed each year. The time period since actual completion of the baseline questionnaire and follow-up questionnaires is knowable; this average follow-up time was 2.88 years (minimum, 1.54 yr).

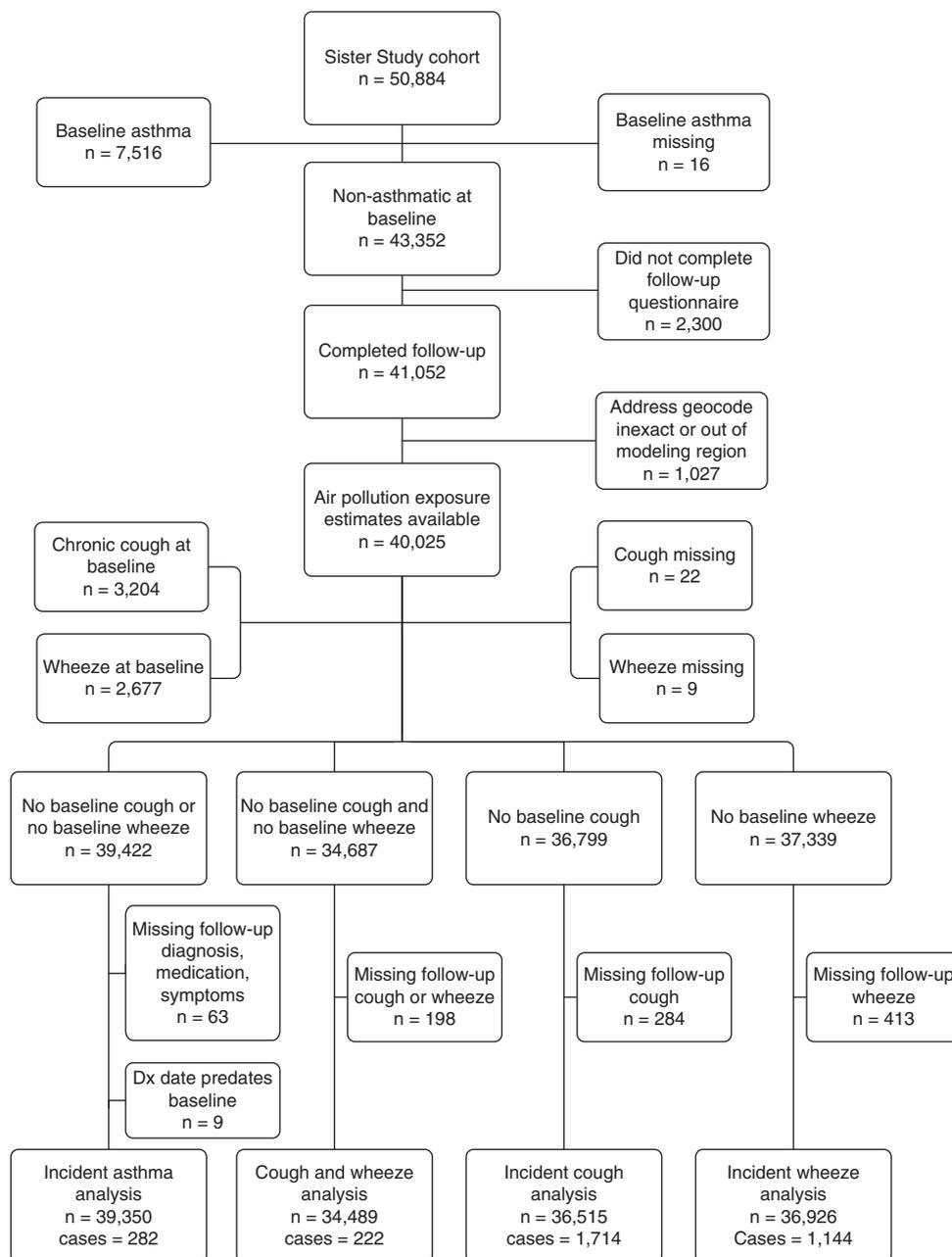
**Adult incident asthma.** Incident asthma was defined on the basis of self-report at follow-up of all three of the following occurring since the reference date: diagnosis of asthma by a doctor, any use of asthma medications, and asthma symptoms. Incident asthma symptoms were defined as self-report of any of the following with onset since the reference date: chronic cough, wheeze, or report of "asthma symptoms" in the 12 months preceding follow-up (additional detail on the survey questions is provided in the online supplement).

For analyses of incident asthma, we excluded prevalent asthmatics on the basis of their report at baseline of ever having had doctor-diagnosed asthma. To reduce the number of undiagnosed patients with prevalent asthma, we additionally excluded subjects who reported both wheeze and chronic cough at baseline (Figure 1).

**Incident respiratory symptoms.** We identified women who reported, at follow-up, new onset of chronic cough and wheeze, chronic cough, and wheeze since the reference date. For separate analyses of each symptom category, participants were excluded if they reported an asthma diagnosis or the corresponding symptom(s) at baseline.

### Exposure Assessment

We estimated air pollution exposures using year 2006  $\text{PM}_{2.5}$  and  $\text{NO}_2$  concentrations at the participant's reported primary address at study enrollment. Participant home addresses were geocoded using ArcMap version 10 (ESRI, Redlands, CA), and the residential locations (Figure 2) were used for prediction of outdoor pollutant concentrations. Ambient pollutant concentrations were estimated using geographic covariates in a universal kriging regression on annual averages derived from a national network of air pollution-monitoring stations (using U.S. Environmental Protection Agency [EPA] reference methods) in a model described previously (16). The cross-validated  $R^2$  value for the  $\text{PM}_{2.5}$  model in year 2006 was 0.88, the same as the year 2000  $R^2$  value reported previously (16). The cross-validated  $R^2$  value for the  $\text{NO}_2$  model in year 2006 was 0.85. We modeled exposure only for the contiguous United States; participants living in Hawaii, Alaska, and Puerto Rico were excluded.



**Figure 1.** Study populations and exclusions. Additional exclusions due to missing covariates are not shown.

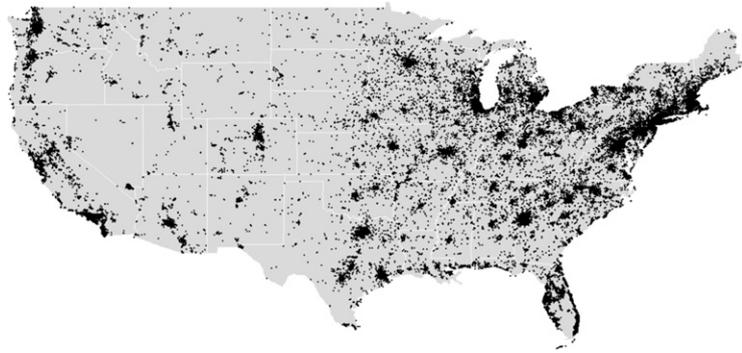
### Data Analysis

Analyses were conducted by multivariable logistic regression. Potential confounders were identified on the basis of *a priori* hypothesized relationships and literature review; the resulting hypothesized causal model is illustrated in Figure 3. The *a priori* identified confounders were age (continuous), body mass index (<25, 25–30, ≥30), race (black, Hispanic, non-Hispanic white, other), education (less than high school; high school or GED; some

college; bachelor's degree; associate, tech, or nursing degree; master's or doctoral degree), occupational exposure to either vapor or fumes (ever/never), occupational exposure to dust (ever/never), baseline smoking status (current smokers, current social smokers, former smokers, never-smokers), age started smoking among ever-smokers (age < 20 yr, age ≥ 20 yr), packs per day at baseline (<0.5, 0.5–1, ≥1), smoked since baseline (yes/no), childhood second-hand smoke from primary caregiver

(yes/no), any health care coverage (yes/no), dietary fiber consumption per day (continuous in grams).

To assess the possibility for residual confounding, modeling was performed by a three-stage approach. Minimally adjusted models included age alone. Fully adjusted models included all *a priori* hypothesized confounders. We additionally adjusted for adult second-hand smoke exposure in a model presented in the online supplement; this adjustment did not



**Figure 2.** Sister Study baseline home address locations (data for Alaska, Hawaii, and Puerto Rico are not shown).

appreciably affect the results. In all models, effects of  $\text{NO}_2$  and  $\text{PM}_{2.5}$  were estimated using separate models for the main results.

We performed a limited number of prespecified sensitivity analyses. To assess the effect of varying follow-up times on effect estimates, Cox proportional hazards modeling was performed for the primary outcome of incident asthma. Participants who developed asthma reported the month and year of doctor diagnosis of asthma, and the time between baseline and Day 15 of the diagnosis month was used as the time to failure (see the online supplement for additional details).

In addition, a limited set of potential effect modifiers was specified *a priori*. Interactions between air pollution

exposures and smoking status (current smokers vs. both former and never-smokers) were tested.

This study was approved by the University of Washington (Seattle, WA) Institutional Review Board and the NIEHS Institutional Review Board.

## Results

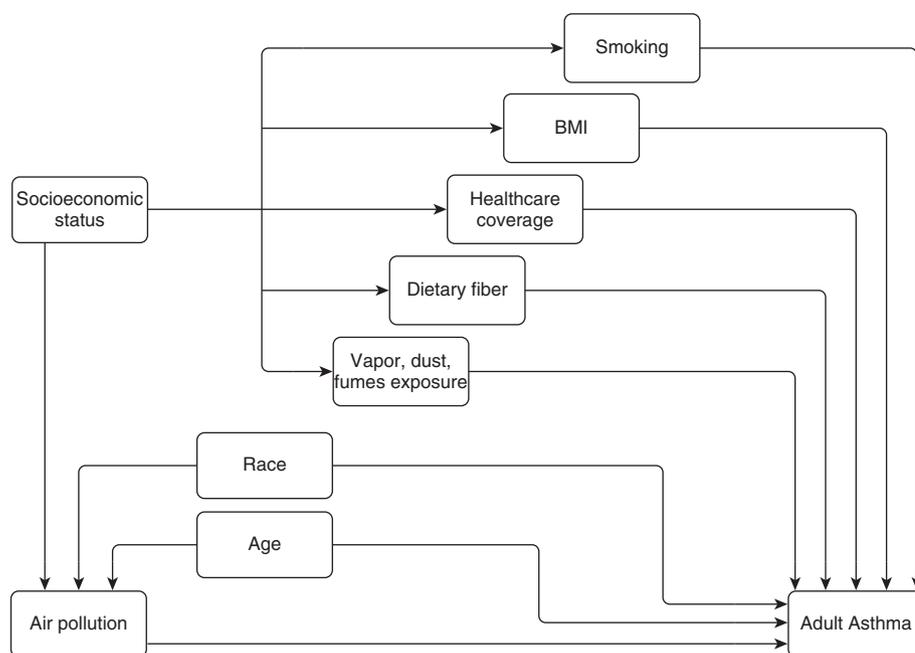
Out of the 50,884 women enrolled in the Sister Study, we excluded the 7,013 reporting asthma at baseline. Of the remaining 43,352 participants eligible for analysis, 2,300 (5.3%) did not complete the follow-up questionnaire. An additional 1,027 (2.4%) participants were missing

exposure data because the locations were outside of the modeling region or could not be geocoded. Additional exclusions were made for each outcome according to the corresponding case definition (Figure 1). The observed incidence rate of adult asthma was approximately 2.5 cases per 1,000 person-years.

The racial/ethnic makeup of the population differed substantially by tertiles of  $\text{PM}_{2.5}$  and  $\text{NO}_2$  (Table 1), with higher exposure in black subjects than in non-Hispanic white subjects. Body mass index had a slight positive association with  $\text{PM}_{2.5}$  but not with  $\text{NO}_2$ . The proportion of women with master's or doctoral degrees was higher in increasing quartiles of  $\text{NO}_2$ ; a similar but weaker association was present with  $\text{PM}_{2.5}$ . Age, smoking status, second-hand smoke exposure, health care coverage, and occupational exposure to dust and fumes had only weak or inconsistent associations with the air pollutants. Final analytic sample sizes differed because of differences in baseline exclusion criteria for the different outcomes. After excluding individuals missing exposure and covariate data in the fully adjusted model, there were 254 cases of adult incident asthma out of 35,862 at risk; 194 cases with incident chronic cough and wheeze out of 31,545 at risk; 1,559 cases with incident chronic cough only out of 33,316 at risk; and 1,023 cases with incident wheeze only out of 33,747 at risk.

The medians (and interquartile ranges) for estimated exposures at participant locations were  $10.8 \mu\text{g}/\text{m}^3$  ( $3.6 \mu\text{g}/\text{m}^3$ ) for  $\text{PM}_{2.5}$  and 9.3 ppb (5.8 ppb) for  $\text{NO}_2$ . The fully adjusted odds ratio (OR) for incident asthma was 1.20 (95% confidence interval [CI] = 0.99–1.46,  $P = 0.063$ ) for an interquartile range (IQR) increase in  $\text{PM}_{2.5}$  and 1.12 (95% CI = 0.96–1.30,  $P = 0.141$ ) for an IQR increase in  $\text{NO}_2$  (Table 2).  $\text{PM}_{2.5}$  was significantly associated with incident wheeze (fully adjusted OR = 1.14, 95% CI = 1.04–1.26,  $P = 0.008$ ). The association of  $\text{NO}_2$  with incident wheeze was slightly weaker (fully adjusted OR = 1.08, 95% CI = 1.00–1.17,  $P = 0.048$ ). Fully adjusted estimates were not appreciably different from the age-adjusted estimates with the exception of the  $\text{NO}_2$  and wheeze result, which was nonsignificant in the age-adjusted model.

The Cox proportional hazard model, assessing the sensitivity of the analysis to



**Figure 3.** Causal model of air pollution and asthma demonstrating potential confounders. BMI = body mass index.

**Table 1.** Population Characteristics by Tertiles of PM<sub>2.5</sub> Exposure (μg/m<sup>3</sup>) and NO<sub>2</sub> Exposure (ppb)

	PM <sub>2.5</sub>			NO <sub>2</sub>		
	[1.89, 9.45]	(9.45, 11.9]	(11.9, 18]	[0.729, 7.59]	(7.59, 11.4]	(11.4, 31.5]
n	16,490	16,489	16,489	16,490	16,489	16,489
Age, yr	55.7 ± 8.9	55.1 ± 9.1	54.6 ± 8.9	55.5 ± 8.9	54.9 ± 9.0	55.0 ± 9.1
BMI	27.1 ± 5.8	27.5 ± 6.0	28.0 ± 6.3	27.5 ± 5.9	27.5 ± 6.0	27.6 ± 6.3
Daily fiber consumption	17.3 ± 8.4	17.0 ± 8.5	16.8 ± 8.5	16.9 ± 8.3	16.9 ± 8.4	17.3 ± 8.8
Baseline smoking status, %						
Current smoker	7.6	8.2	8.9	8.5	7.6	8.6
Never smoked	52.8	53.1	54.6	54.0	54.6	51.9
Past smoker	37.4	36.3	34.3	35.4	35.6	37.0
Social smoker	2.2	2.4	2.3	2.2	2.2	2.5
Education, %						
Less than high school	0.8	1.1	1.1	1.1	0.9	1.1
High school or GED	13.8	15.2	13.3	16.6	14.1	11.6
Some college	20.3	19.7	19.2	20.9	19.3	19.0
Bachelor's	27.5	25.8	27.3	25.2	27.4	28.1
Associate, tech, or nursing	15.0	14.4	12.9	16.1	14.2	12.0
Master's/doctoral	22.4	23.8	26.2	20.1	24.1	28.2
Race, %						
Black	2.5	7.0	17.8	5.0	9.3	13.0
Hispanic	3.4	3.1	3.1	2.2	2.7	4.7
Non-Hispanic white	91.4	87.3	76.7	90.0	85.7	79.7
Other	2.7	2.6	2.4	2.8	2.3	2.7
Childhood secondhand smoke, %	47.0	47.9	47.6	46.5	47.3	48.6
Health care coverage, %	96.3	96.2	95.9	96.1	96.3	96.1
Occupational dust exposure, %	21.2	22.1	23.4	22.7	21.6	22.4
Occupational fumes exposure, %	23.9	23.3	23.7	24.7	23.2	23.1

*Definition of abbreviations:* BMI = body mass index; GED = general educational development; NO<sub>2</sub> = nitrogen dioxide; PM<sub>2.5</sub> = particulate matter less than 2.5 μm in diameter.

Continuous variables are expressed as means ± standard deviation. Percentages are expressed as a percentage of nonmissing column totals.

differences in follow-up time, gave comparable results. Individuals missing date of diagnosis were excluded, leaving 231 cases of incident asthma after excluding individuals missing exposure or covariate data. The fully adjusted hazard ratio (HR) for an IQR increase in PM<sub>2.5</sub> was 1.20 (95% CI = 0.98–1.47, *P* = 0.079). The fully

adjusted HR for an IQR increase in NO<sub>2</sub> was 1.06 (95% CI = 0.90–1.25, *P* = 0.486).

An association between NO<sub>2</sub> and incident wheeze was evident among never-smokers or former smokers but not in the smaller group of current smokers (interaction *P* = 0.012). The OR for wheeze for an IQR increase in NO<sub>2</sub> was 1.14 (95%

CI = 1.04–1.24, *P* = 0.003) in former/never-smokers (792 cases) and 0.89 (95% CI = 0.74–1.06, *P* = 0.179) in current smokers (232 cases). For wheeze plus cough, the OR for an IQR increase in NO<sub>2</sub> was 1.12 (95% CI = 0.92–1.37, *P* = 0.272) in never-smokers or former smokers (144 cases) and 0.71 (95% CI = 0.48–1.07, *P* = 0.102) in

**Table 2.** Effect Estimates for PM<sub>2.5</sub> and NO<sub>2</sub> in Relation to Incident Asthma, Cough, and Wheezing

Exposure (IQR)	Outcome	Age-adjusted*		Fully Adjusted†	
		OR (95% CI)	<i>P</i> Value	OR (95% CI)	<i>P</i> Value
PM <sub>2.5</sub> (3.6 μg/m <sup>3</sup> )	Incident asthma	1.19 (0.99–1.42)	0.059	1.20 (0.99–1.46)	0.063
	Cough and wheeze	0.98 (0.81–1.19)	0.855	0.94 (0.75–1.16)	0.555
	Cough	0.98 (0.91–1.06)	0.621	0.95 (0.88–1.03)	0.194
	Wheeze	1.17 (1.07–1.28)	<b>0.001</b>	1.14 (1.04–1.26)	<b>0.008</b>
NO <sub>2</sub> (5.8 ppb)	Incident asthma	1.12 (0.97–1.28)	0.123	1.12 (0.96–1.30)	0.141
	Cough and wheeze	1.00 (0.85–1.18)	0.977	1.01 (0.84–1.21)	0.913
	Cough	0.99 (0.93–1.05)	0.680	1.00 (0.93–1.07)	0.939
	Wheeze	1.05 (0.98–1.13)	0.151	1.08 (1.00–1.17)	<b>0.048</b>

*Definition of abbreviations:* CI = confidence interval; IQR = interquartile range; OR = odds ratio; NO<sub>2</sub> = nitrogen dioxide; PM<sub>2.5</sub> = particulate matter less than 2.5 μm in diameter.

Entries in boldface indicate statistical significance (*P* < 0.05).

\*Adjusted for age.

†Adjusted for age, body mass index, race, education, occupational exposure to vapor or fumes, occupational exposure to dust, baseline smoking status, age started smoking, packs per day at baseline, smoked since baseline, childhood second-hand smoke exposure, any health care coverage, and dietary fiber consumption per day.

current smokers (50 cases) (interaction  $P = 0.049$ ).

## Discussion

This is the first study of  $PM_{2.5}$  and adult-onset asthma. Higher  $PM_{2.5}$  concentrations were associated with incident wheeze and asthma in a large national cohort of women, with a prospective study design, strict definition of incident asthma, and the use of hybrid partial least squares regression universal kriging models. Our results were also consistent with an association between higher  $NO_2$  and current wheeze, especially in women who did not currently smoke. Collectively, these results support the hypothesis that air pollution exposure may be a risk factor for new-onset wheeze and diagnosis of asthma in previously asymptomatic adults. Neither incident cough alone nor cough and wheeze combined was significantly associated with either pollutant. Although cough is not specific to asthma, cough may represent other pathologies potentially relevant to air pollution and thus we included this analysis.

For both  $NO_2$  and  $PM_{2.5}$ , the effect of each pollutant on incident asthma was comparable in size to the effect of  $NO_2$  on incident wheeze (1.12 vs. 1.08 for  $NO_2$  and 1.16 vs. 1.12 for wheeze). Although analyses of incident asthma were not statistically significant, they included fewer cases than the wheeze analyses (254 vs. 1,023) and thus are not as well powered.

Notably, the current EPA National Ambient Air Quality Standard (NAAQS) for annual  $NO_2$  is 53 ppb. By comparison, the maximum estimated participant exposure in this analysis was 31.5 ppb. Our results indicate respiratory effects with long-term exposure may be occurring at levels well below the current national standards.

Associations between acute exposure to air pollution and exacerbation of respiratory symptoms in subjects with asthma are fairly well established, especially in children (2). Symptom exacerbations in subjects with asthma have been shown to be related to  $PM_{2.5}$  (17),  $PM_{10}$  (18),  $SO_2$  (18), and  $NO_2$  (19). There are fewer studies on long-term exposure and incident asthma and most are in children (20, 21). A meta-analysis, including four studies of childhood asthma and one study of adult asthma symptom

scores, found an association between asthma and  $PM_{2.5}$  (22).

The only previous study on  $PM_{2.5}$  and adult incident asthma used visibility data to estimate  $PM_{2.5}$  exposure and symptom scores to define incident asthma (23). We cannot directly compare our effect size with that of Abbey and colleagues (23) because their reported exposure contrast of  $45 \mu\text{g}/\text{m}^3$  is considerably larger than our observed variability; nevertheless, despite substantially reduced exposure variability in the Sister Study population, we find effects at lower levels of exposure. The results are also not directly comparable because of the different outcome classification approaches, greater exposure misclassification due to the indirect estimation method used in the earlier study, or different exposure characteristics given the different periods and locations of observation.

The present study adds to the small, but growing, body of literature indicating that air pollution may be a risk factor for the development of asthma in adults (1). An analysis of the Danish Diet, Cancer and Health cohort of adults aged 50–65 years found an association between  $NO_2$  and new hospitalization for asthma (977 cases) (19). A prospective cohort in Swedish cities found an elevated risk of incident asthma for  $NO_2$  with 55 cases (24). An earlier case-control study in Sweden by the same authors of the Swedish cohort study found an elevated but nonsignificant association with  $NO_2$  (203 cases) (25). Two cohort studies have reported associations between incident asthma and  $PM_{10}$  (3, 4).

We found some evidence that smoking may modify the effect of  $NO_2$  on the development of wheezing. This is consistent with the finding of Künzli and colleagues (3) that the association between  $NO_2$  and wheeze was present only in nonsmokers. Air pollution may be plausibly more asthmagenic in nonsmokers if smoking saturates biologic pathways between air pollution exposure and development of asthma. Alternatively, the observed effect of  $NO_2$  may be masked in smokers who have a higher risk of incident airway obstruction in adulthood.

Whereas the mechanisms by which air pollution might cause asthma are uncertain, the hypothesis that air pollution induces oxidative stress leading to airway inflammation has been proposed by various investigators (1).  $NO_2$  and specific components of particulate matter, possibly

transition metals, increase oxidative stress in lung tissue (26). Lung lining fluid, containing antioxidants such as reduced glutathione, ascorbic acid, uric acid, and  $\alpha$ -tocopherol, can act as defensive barrier against reactive oxygen species, but air pollutant exposure may deplete antioxidative capacity, leading to secondary oxidant species that can cause inflammatory responses (6). In response to secondary oxidants that reach lung tissue, cells may release proinflammatory molecules such as cytokines and chemokines that promote migration of additional inflammatory cells to the lung, and this could initiate an inflammatory cascade resulting in the initiation of asthma or asthma-like conditions (6).

Like any epidemiologic study of air pollution, ours has limitations for drawing causal inference. Although adjusting for well-recognized risk factors resulted in little or no attenuation of our effect estimates, the potential for residual confounding by unmeasured factors remains. We were not able to adjust for mold, dampness, gas cooking, or pets. This could confound our results to the extent that these factors are related to the spatial pattern of air pollution exposure.

Participants were asked to report month and year of asthma diagnosis, which may not have corresponded to actual disease onset. Therefore, the Cox regression analysis, which modeled time to diagnosis, was considered a sensitivity analysis rather than the primary analysis because of concerns regarding uncertainty of time of onset and nonetheless produced similar results. Our study relied on self-report of doctor-diagnosed asthma rather than methacholine challenge or other objective tests of nonspecific bronchial hyperresponsiveness. However, this type of testing is not feasible in national population studies of this size, and a past study of air pollution and asthma with a methacholine challenge component was unable to incorporate the results into the case definition (27). Although relying on self-reported doctor diagnosis to identify incident asthma may lead to outcome misclassification, it remains a frequently used approach for large epidemiological studies. Self-report of symptoms and doctor diagnosis provide useful, if imperfect, information about incident asthma. Consistency between the direction of the effect between these complementary

analyses, despite differences in case counts, strengthens the conclusions of our study. In addition, highly replicable genetic loci have been identified in genome-wide association studies using self-reported doctor diagnosis of incident asthma (28).

The observed incidence of asthma, 2.5 cases per 1,000 person-years, was somewhat lower in our population than reported in other studies. A meta-analysis found an average of 4.6 cases per 1,000 person-years in women (29). However, using a less restrictive definition of asthma, and relying only on doctor diagnosis to exclude baseline prevalent cases and to define incident cases at follow-up, the incidence in the Sister Study cohort was 4.7 cases per 1,000 person-years, indicating that doctor diagnosis alone provides incidence rates consistent with other studies of adult asthma.

The possibility exists that the observed association between air pollution and asthma diagnosis may result from an association between air pollution and subclinical asthma exacerbations (leading to diagnosis during follow-up). Although we cannot completely eliminate this possibility, we addressed it by excluding from the incident asthma analysis women reporting both cough and wheeze in the 12 months before baseline and making similar exclusions in our analysis of incident symptoms. To help reduce outcome misclassification at follow-up, we used a strict definition of asthma requiring cases to have symptoms, medication use, and a doctor diagnosis. This definition therefore excluded individuals whose incident asthma was well controlled by medication. One study has suggested that more severe adult-onset asthma may differ phenotypically from milder adult-onset asthma in that it is less frequently atopic and associated with greater airway inflammation (30), characteristics that are consistent with the proposed action of air pollution on the lung.

We classified subjects as incident asthmatics only if they reported no prior asthma, even in childhood, at baseline. Some proportion of incident asthma in adults may represent recrudescence of childhood-onset asthma that was either never diagnosed or forgotten by the subject. Among all subjects who reported asthma before baseline, there were only 3.6% who reported a diagnosis of childhood asthma before the age of 16 with subsequent disappearance of symptoms for 10 years or greater. Although we cannot eliminate the possibility that air pollution is simply exacerbating occult childhood-onset asthma, a substantial proportion of incident cases is likely to have true adult-onset asthma.

Exposure misclassification is a concern for all air pollution studies that rely on predicted concentrations. Exposure models have several potential sources of misclassification, including ambient outdoor concentrations not fully characterizing indoor exposures. Furthermore, estimation of ambient concentrations at home addresses does not fully capture participant exposure because it cannot account for infiltration into the home or potentially important exposures from commuting or other activities. Nonetheless, our exposure model represents a substantial improvement over the previous generation of nearest monitor (4) and may be more comparable to high-quality dispersion models (3, 24) used in previous publications on incident asthma because our model better captures within-region and between-region contrasts in air pollution, reduces exposure misclassification through spatial smoothing, and has overall excellent model performance. We anticipate that misclassification in exposure, which would not be expected to differ by case status, would tend to attenuate the observed associations rather than lead to spurious positive ones. We also used

annual average exposures, although the true biologically relevant exposure period could be shorter or longer. Misspecification of the exposure period should, at worst, lead to attenuation. Furthermore, although it is possible that seasonal bias in asthma symptom recall exists, exposure was an annual average. Therefore, seasonality in the outcome would not be related to seasonality in the exposure and would, at worse, attenuate the results.

In conclusion, our study, conducted in a nationwide prospective cohort of women and using advanced exposure modeling, provides evidence for an association between air pollution and an increased risk of incident asthma symptoms in nonasthmatic adults. We also found some evidence to support an association with asthma development. PM<sub>2.5</sub> and NO<sub>2</sub> were the only air pollutants analyzed in this study. Air pollution is a complex mixture; therefore, despite suggestive associations, PM<sub>2.5</sub> and NO<sub>2</sub> may not be the underlying etiologic agents but instead may be acting as surrogates for unmeasured pollutants. Further research is needed investigating complex multipollutant mixtures in the context of adult-onset asthma. ■

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