

Traffic-Related Air Pollution Exposure and Adult Asthma in the Sister Study

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Abstract

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Background: Previous epidemiologic research has suggested an association between air pollution exposure and adult incident asthma. However, there exists limited research specifically focusing on the effect of PM_{2.5} on asthma in adults.

Aims: A prospective analysis was performed to estimate the association between ambient air pollution exposures (NO₂, PM_{2.5}) and incident asthma and incident onset of respiratory symptoms.

Methods: The Sister Study is a national population-based cohort (n=50,884) of sisters of women with diagnosed breast cancer. Participants were asked questions about medical conditions at enrollment and again at follow-up, an average of 2.9 years later. Participant exposures were year 2006 annual average ambient PM_{2.5} and NO₂ concentrations estimated at participant baseline addresses using a national land-use regression kriging model. The primary outcome was incident self-reported doctor-diagnosed asthma at follow-up in individuals who were

asthma-free at baseline. Secondary outcomes were new onset of wheeze or cough in individuals who did not report asthma, wheeze or cough at baseline. Logistic regression was used to assess the relationship between participant exposure and outcomes at follow-up. Models were adjusted for the following covariates based on a directed acyclic graph: age at baseline, race/ethnicity, educational attainment, BMI, occupational dust exposure, occupational vapor exposure, baseline smoking status, age first smoked, packs/day at baseline, smoking status between baseline and follow-up, childhood environmental tobacco smoke exposure, healthcare coverage, and dietary fiber consumption.

Results: The Sister Study cohort interquartile ranges (IQR) of estimated PM_{2.5} and NO₂ were 3.5 µg/m³ and 5.8 ppb respectively. The adjusted OR of incident asthma for PM_{2.5} was 1.20 (95% CI: 0.99-1.45, p=0.069) for an IQR difference in estimated PM_{2.5} exposure. The adjusted OR of onset wheeze for PM_{2.5} was 1.13 (95% CI: 1.02-1.25, p=0.015) for an IQR difference in PM_{2.5} exposure. PM_{2.5} was not significantly associated with cough or the combined outcome of cough and wheeze. NO₂ was not significantly associated with the either incident asthma or onset of wheeze and/or cough.

Conclusions: PM_{2.5} exposure may be a risk factor in the development of incident asthma or wheeze, the cardinal symptom of asthma, in adult women.

Background

Adult onset asthma is a chronic debilitating condition. Compared to childhood asthma, there is less research into risk factors adult onset than childhood onset asthma, outside of the occupational setting. The prevalence of adult asthma is high; 8.8% of females and 5.8% of males in the US have current asthma, and recent evidence suggests prevalence has continued to increase in recent decades (McHugh et al. 2009). Worldwide, the disability-adjusted life years (DALYs) lost due to asthma have been estimated to account for 1% of all DALYs lost, indicating asthma causes a substantial global health burden (Masoli et al. 2004). While the incidence of asthma is typically higher in children, adult onset asthma may represent a distinct disease (Bel 2004). Unlike in childhood, adult women have a higher incidence of asthma than adult men (De Marco et al. 2000).

The relationship between air pollution and asthma has been studied in a number of previous studies. One meta-analysis estimated increased risk of incident asthma for NO₂ (OR: 1.07 per 10 µg/m³, 95% CI: 1.02-1.13) and for PM_{2.5} (OR:1.16 per 10 µg/m³, 95% CI: 0.98-1.37) (Anderson et al. 2011). However, much of the previous research in this area has focused on childhood asthma or exacerbations of existing asthma. Air pollution as a risk factor for adult onset asthma has not been as thoroughly investigated. A review paper identified seven studies of air pollution and adult onset asthma in five independent populations (Jacquemin et al. 2012), but these studies have been non-definitive in their conclusions regarding the association between adult onset asthma and air pollution. Furthermore, no previous studies have assessed PM_{2.5} specifically as a risk factor for adult onset asthma, and there have been no studies estimating the association between air pollution and adult recurrence of latent childhood asthma.

There are several hypothesized biologic mechanisms that could explain an association between air pollution exposure and asthma. Animal studies have demonstrated atopic sensitization by air pollution as a mechanism for development of asthma (Osebold et al. 1988), and atopy is a strong risk factor for asthma in humans (K. Torén and B.A. Hermansson 1999). Air pollution has also been demonstrated to have pro-inflammatory effects in the human lung (Devlin et al. 1991), providing an alternate biologically plausible mechanism for asthma onset.

In order to better characterize the complex relationship between adult asthma phenotypes and air pollution, we estimated the association between PM_{2.5} and NO₂ exposure and adult incident asthma, incident cough, incident wheeze, and adult recurrence of childhood asthma.

Methods

Study Design and Questionnaires

The NIEHS Sister Study is a large national cohort of women who have sisters with diagnosed with breast cancer (n=50,884) but who had not been diagnosed themselves at enrollment. The study was designed to determine genetic and environmental risk factors for incident breast cancer in study participants. Study design has been detailed elsewhere (D'Aloisio et al. 2010). Participants were enrolled over a period of 7 years (August 2003 through March 2009) and were grouped into six recruitment waves according to enrollment date. Each wave underwent a baseline computer assisted telephone survey at enrollment. Two to three years after the baseline survey, depending on enrollment wave, subjects participated in a follow-up computer assisted telephone survey.

The baseline survey included questions about asthma history (“Have you ever had asthma?”), whether the asthma was doctor-diagnosed, age at diagnosis, presence of wheeze (“Have you had wheezing or whistling in your chest at any time in the past 12 months?”), presence of chronic cough (“During the past 12 months, have you had this cough on most days

for three months or more”), and current asthma medication use. At follow-up, participants were asked whether they developed new diagnoses or symptoms since a *reference date* (reference dates were constant within enrollment wave and approximated typical baseline questionnaire dates within each wave) including questions on new diagnoses of asthma (“Has a doctor or other health professional ever told you that you had asthma”), new wheeze, new chronic cough, and new use of asthma medications (“have you used any prescription medicines to treat or prevent asthma”). The follow-up questionnaire also asked about date of asthma diagnosis, and asthma symptoms at follow-up (“Have you experienced any symptoms in the past 12 months”).

Exposure

Exposure variables are outdoor year 2006 PM_{2.5} and NO₂ concentrations estimated at the participant’s reported primary address at study enrollment. Ambient air pollutant exposures were predicted using geographic covariates in a universal kriging regression on annual averages derived from a national network of air pollution monitoring stations in a model described previously (Sampson et al. 2012). Briefly, a dimension reduction technique (partial least squares) was used to select a subset of orthogonal components of the predictor space (i.e., the geographic covariates such as land use characteristics and proximity to roadways). Components were then used as covariates in a universal kriging model. This model therefore incorporated land-use regression and spatial smoothing of values observed in the monitoring network. Predictions from this model were estimated at participant home locations, reported at baseline (Figure 1). Exposure was not estimated for participants whose baseline residence is outside of the modeling area (i.e., Hawaii, Puerto Rico, Alaska, and out of country residences) or for those whose reported addresses could not be adequately geocoded to the intersection or exact location. Individuals missing exposure data were excluded from all analyses.

Outcomes

The primary outcome was adult incident asthma. Participants were excluded from this analysis as prevalent asthmatics if they reported ever having asthma at baseline or if they reported both wheeze and chronic cough at baseline. Cases of incident asthma were participants who reported all three of the following criteria at follow-up: self-reported doctor diagnosed asthma, self-reported use of asthma medications since the reference date, and self-report of asthma symptoms. Presence of incident asthma symptoms was defined as self-report of any of the following: chronic cough since the reference data, wheeze since the reference date, or asthma symptoms in the 12 months preceding follow-up.

Secondary outcomes were incident respiratory symptoms: incident cough and wheeze, incident cough, and incident wheeze reported at follow-up. For all three analyses, participants were excluded if they reported asthma at baseline. Additionally, for each analysis, participants were excluded if they reported the corresponding symptom(s) at baseline. Cases for the three separate analyses were individuals who reported at follow-up cough and wheeze, cough, and wheeze respectively.

An additional secondary analysis was adult recurrence of childhood asthma. This analysis was restricted to participants that reported childhood asthma (age of diagnosis less than or equal to age 13) which stopped by age 21. Additionally, participants reporting chronic cough, wheeze, or use of asthma medications in the 12 months prior to baseline were excluded. Cases for this outcome were participants who reported new cough, wheeze, or asthma symptoms at follow-up.

Data Analysis

All primary and secondary analyses were conducted using multivariable logistic regression. Potential confounders were identified based on *a priori* hypothesized relationships and literature review, and the resulting hypothesized causal model is illustrated in a directed acyclic graph (DAG) (Figure 2). The *a priori* identified confounders were age (continuous), BMI

(continuous), 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; Masters or Doctoral degree), occupational exposure to vapor or fumes (binary), occupational exposure to dust (binary), baseline smoking status (current, former, never, social), age started smoking (never or less than age 20 years, greater than or equal to age 20), packs per day per day at baseline (less than 0.5, 0.5-1, 1 or more), smoked since baseline (yes/no), childhood second-hand smoke from primary caregiver (yes/no), any healthcare coverage (yes/no), dietary fiber consumption per day (continuous, grams). To assess the possibility for residual confounding, modeling was performed using a 3-stage approach: Minimally adjusted estimates were adjusted for age alone. Fully adjusted estimates were adjusted for all *a priori* hypothesized confounders. Additionally, data-driven model estimates were adjusted for age and any hypothesized confounder which, when added to the minimally adjusted model, led to a change of 10% or more in the odds ratio adjusted for age alone. The fully adjusted model was pre-specified to be the primary adjustment model.

To assess the effect of varying follow-up times on effect estimates, a Cox proportional hazards model was additionally performed for the primary outcome of incident asthma. Study entry time was defined to be the maximum of the baseline survey and the reference date used on the follow-up exam. Self-reported month and year of doctor diagnosis of asthma was defined to be the failure time (imputed to the 15th day). If no event occurred, participants were censored at the date of their follow-up questionnaire.

A limited set of potential effect modifiers were specified *a priori*. Interactions between air pollution exposures and the following variables were tested: smoking status (current/not current), BMI (continuous), family history of asthma (one or more parents or siblings/no parents or siblings). Interactions were tested for the incident asthma, cough and wheeze, cough, and wheeze outcomes but not for the adult recurrence of asthma outcome (due to limited sample size). Current smoking, for this analysis alone, was defined as baseline self-report of "current"

or “social” smoker or self-report of any smoking between the reference date and follow-up. For the test for effect modification by smoking, all other smoking variables were removed from the model to avoid issues regarding the estimation of more than one characteristic of exposure (Mcknight et al. 1999). Results are only reported for interactions with statistically significant interaction P values.

A cross-sectional baseline analysis was also performed as a sensitivity analysis. Cases were individuals reporting baseline asthma and either wheeze or frequent cough and use of asthma medications within the last year. Individuals reporting onset of asthma greater than 5 years before baseline were excluded. Smoking since baseline was not included as an adjustment variable for these analyses; otherwise, the same adjustment variables were used as in the prospective analysis.

Results

Racial makeup of the population differed substantially by quartiles of $PM_{2.5}$ (Table 1a) and NO_2 (Table 1b), with higher exposure in African Americans and Hispanics and lower exposures in whites. BMI had a slight positive association with $PM_{2.5}$ but not with NO_2 . The proportion of individuals with masters or doctoral degrees was higher in increasing quartiles of NO_2 , and a similar but weaker association was present with $PM_{2.5}$. Age, smoking status, second-hand smoke exposure, healthcare coverage, occupational dust and fumes exposures, had weak or inconsistent associations with exposures. Missingness of covariates was typically higher in individuals missing exposure. Descriptive statistics by quartiles of exposures are presented in Table 1a and 1b.

Before excluding individuals missing exposure, there were 40,364 individuals eligible for the incident asthma analysis and 291 cases. Total follow-up time for the incident asthma analysis was 116,245 years with an average follow-up time of 2.88 years. The observed incidence rate of adult asthma was therefore 0.0025 cases per person-year.

There were 2,806 participants missing follow-up data and an additional 1,298 participants excluded due to missing exposure data (Figure 3). Participants otherwise eligible for the incident asthma analysis reporting at follow-up a new diagnosis of asthma dated before baseline were excluded (n=9). Final analytic sample sizes differed due to differences in baseline exclusion criteria. After excluding individuals missing exposure, there were 282 cases of adult incident asthma, 222 cases of incident cough and wheeze, 1,711 incident cases of cough, and 1,143 incident cases of wheeze. The final sample size for the adult recurrence of asthma analysis was 368 and there were 84 cases in this analysis.

The interquartile ranges of PM_{2.5} and NO₂ were PM_{2.5} 3.53 µg/m³ and 5.84 ppb, respectively. The fully-adjusted OR of incident asthma for an IQR increase in PM_{2.5} was 1.20 (95% CI: 0.99-1.45, p=0.069) (Table 2). The fully-adjusted OR for an IQR increase in NO₂ was 1.12 (95% CI: 0.96-1.30, p=0.150). PM_{2.5} was significantly associated with incident wheeze with a fully-adjusted OR of 1.13 (95% CI: 1.02-1.25, p=0.015). No potential confounder changed the age-adjusted effect estimate more than 10% for any outcome, so results from the data-driven model are identical to those of the age-adjusted model. Fully-adjusted estimates were not appreciably different from the age-adjusted model.

A Cox proportional hazard model was used to assess the sensitivity of the incident asthma analysis to differences in follow-up time. Individuals missing date of diagnosis and exposure were excluded, leaving 255 cases for this analysis. The fully-adjusted hazard ratio (HR) for an IQR increase in PM_{2.5} was 1.20 (95% CI: 0.98-1.47, p=0.084). The fully-adjusted HR for an IQR increase in NO₂ was 1.05 (95% CI: 0.90-1.24, p=0.50).

The association between recently diagnosed cases at baseline and air pollution was estimated in a cross-sectional analysis. These models were adjusted for all covariates with the exception of smoking between baseline and follow-up. The adjusted OR of prevalent asthma for an IQR increase in PM_{2.5} was 1.06 (95% CI: 0.93-1.20, p=0.39). Estimated NO₂ exposure

was significantly associated with prevalent asthma. The adjusted OR for an IQR increase in NO₂ was 1.11 (95% CI: 1.01-1.23, p=0.033).

The association between NO₂ and incident wheeze was stronger in nonsmokers (interaction p value =0.020). The OR for wheeze corresponding to an IQR increase in NO₂ was 1.13 (95% CI: 1.04-1.24, p=0.007) in nonsmokers and 0.90 (95% CI: 0.75-1.07, p=0.233) in current smokers. The remaining tests for interaction between the two pollutants and three pre-specified interaction variables (BMI, family history, smoking) on incident asthma, cough and wheeze, cough, and wheeze were all non-significant.

Discussion

We found a statistically significant association between estimated PM_{2.5} exposure and incident wheeze. Additionally, the association between PM_{2.5} exposure and the primary outcome, incident asthma, approached statistical significance. NO₂ was significantly associated with incident wheeze in non-smokers only. NO₂ was also significantly associated with baseline recently-diagnosed asthma. Collectively, these results support the hypothesis that air pollution exposure may be a risk factor for wheeze and asthma diagnosis in previously asymptomatic adult women.

Previous research has demonstrated associations between air pollution and respiratory symptoms in asthmatics. Asthma exacerbations have been shown to be related to PM₁₀ (Lipsett et al. 1997; Samoli et al. 2011), SO₂ (Samoli et al. 2011), and NO₂ (Andersen et al. 2012; Lipsett et al. 1997). A number of studies have also estimated the association between air pollution exposure and incident asthma in children. For example, McConnell et al showed that ozone exposure modified the effect of team sport participation on risk of incident asthma in Southern California where these sports are generally played outdoors (McConnell et al. 2002). Our observed non-significant association between PM_{2.5} and asthma incidence corresponded to a stronger association than that estimated in a meta-analysis of studies where the odds ratios was

1.16 (95% CI: 0.98-1.37) per 10 $\mu\text{g}/\text{m}^3$ (Anderson et al. 2011). By comparison, our adjusted OR was 1.68 (95% CI: 0.97-2.87) per 10 $\mu\text{g}/\text{m}^3$. The 10 $\mu\text{g}/\text{m}^3$ exposure contrast used in the analysis of Anderson et al. is larger than the interquartile range of exposures in our analysis, so the effect size at this scale may be exaggerated. Additionally, their analysis included both children and adults. The hypothesized etiologic differences between childhood and adult onset asthma (Bel 2004) supports analyzing these outcomes separately.

The present study adds to the small but growing body of literature indicating that air pollution may additionally be a risk factor for the development of asthma in adults (Jacquemin et al. 2012). An analysis of the Danish Diet, Cancer and Health cohort of adults aged 50-65 found an association between NO_2 and new hospitalization for asthma (Andersen et al. 2012). A prospective cohort in Swedish cities found a 1.46 (1.07-1.99) increase in NO_2 per 10 $\mu\text{g}/\text{m}^3$ for onset asthma (Modig et al. 2009). An earlier case-control study by the same authors found an elevated but non-significant association with NO_2 (Modig et al. 2006). Previous studies of air pollution and adult incident asthma have not considered $\text{PM}_{2.5}$ as an exposure. McDonnell et al (McDonnell et al. 1999) as well as Künzli et al (Künzli et al. 2009) found associations between incident asthma and PM_{10} .

The significant interaction between NO_2 and smoking status on the odds of wheeze suggests that smoking may modify the effect of NO_2 on asthma symptoms. However, if NO_2 exposure leads to an absolute increase in the risk of incident wheeze, interaction at the relative odds ratio scale would be expected even in the absence of biological effect modification given the differences in baseline risk of wheeze between smokers and non-smokers. That the association between NO_2 and wheeze was present only in non-smokers was consistent with Künzli et al (Künzli et al. 2009) who found an association between PM_{10} and incident asthma only in never smokers.

Air pollution has been shown to cause respiratory changes at the cellular level in toxicology and animal studies, indicating several biologically plausible pathways through which

particulate and gas exposure might lead to respiratory sensitization. An *in vitro* study of PM_{2.5} found this exposure to cause cytotoxicity, implicating particulate matter as potentially leading to inflammatory sensitization (Monn and Becker 1999). Controlled human exposure to particulate matter has been shown to lead to increased oxidation. Evidence suggests that this effect may be due to transition metals contained in particulate matter and that this oxidation can lead to inflammation and hyperresponsiveness characteristic of asthma (Gavett and Koren 2001).

Limitations and Strengths

We have adjusted for typical risk factors with minimal attenuation of effect estimates. Residual confounding by measured variables is unlikely due to the absence of large changes between the minimal and fully-adjusted effect estimates, but we cannot rule out the possibility of confounding by unknown variables.

Our primary analysis of incident asthma was limited by a relatively crude characterization in the time of onset of asthma, which was measured as month of diagnosis via patient recall. The Cox analysis was therefore chosen as a sensitivity analysis due to concerns regarding uncertainty of time of onset. Conversely, the logistic model is also limited in that it assumes identical follow-up times, which, in actuality, differ by enrollment date (earlier waves had longer follow-up). Differences between exposure estimates by follow-up time or enrollment date could therefore lead to bias in the logistic model. We chose to model exposure as a fixed-year annual average, regardless of enrollment rate, to avoid inducing an association between follow-up time and secular trends in air pollution exposure. Additionally, follow-up time was not empirically observed to be associated with exposure estimates. Therefore, the logistic model is unlikely to be biased by differing follow-up times. Consistency between the Cox model and the logistic model further indicates that respective limitations of each model may be minimal.

Additionally, any study of incident asthma that relies on doctor diagnosis is limited by the possibility of undiagnosed asthma at baseline. The observed association between asthma

diagnosis and air pollution may therefore result in part from air pollution-induced exacerbations leading to diagnosis during follow-up. We addressed this limitation by excluding from the incident asthma analysis individuals reporting both cough and wheeze in the 12 months prior to baseline. However even in a study with regular objective measurements of asthma, it would be difficult to separate out incident cases of asthma resulting from air pollution exposure from exacerbations of subclinical, preexisting asthma. To truly differentiate between air pollution as an etiologic factor versus an asthma trigger, complicated study designs may be necessary which investigate whether incident asthma symptoms resulting from air pollution exposure persist after a substantial reduction in that air pollution.

A final limitation relates to the inaccuracy of exposure estimation. Our exposure model represents a substantial improvement over the previous generation of nearest monitor (McDonnell et al. 1999), or dispersion models (Künzli et al. 2009; Modig et al. 2009) methods used for incident asthma analyses. Even so, exposure models have several potential sources of misclassification including time spent in micro-environments other than the home. We anticipate that our estimates may be attenuated due to non-differential misclassification if this misclassification is not associated with case status. Additionally, our specified exposure period to assess adult onset asthma may not be well characterized due to uncertainty regarding the biologically relevant time period. We assumed a medium-term exposure period of interest (one year of exposure). However, if lifetime exposure were the relevant exposure period, we would be unable to characterize this period (especially childhood exposures) due to limitations in monitoring data. However, because our exposures are well-correlated in time, year 2006 exposure also acts as a proxy for exposures in the following and preceding years, indicating that choosing a slightly shorter or longer exposure period would not substantially alter our results.

Strengths of this study include the use of a large national cohort, prospective study-design, strict definition of incident asthma, and the use of advanced exposure models.

In conclusion, our analysis adds to a growing body of literature suggesting an association between air pollution and incident asthma symptoms in non-asthmatics. To determine whether air pollution is truly an etiologic factor in the development of asthma, further research is needed. Novel studies on this topic would benefit from temporally-resolved air pollution estimates and objective assessments of asthma at multiple time points.

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Tables and Figures

Sister Study Participant Locations (Jittered)

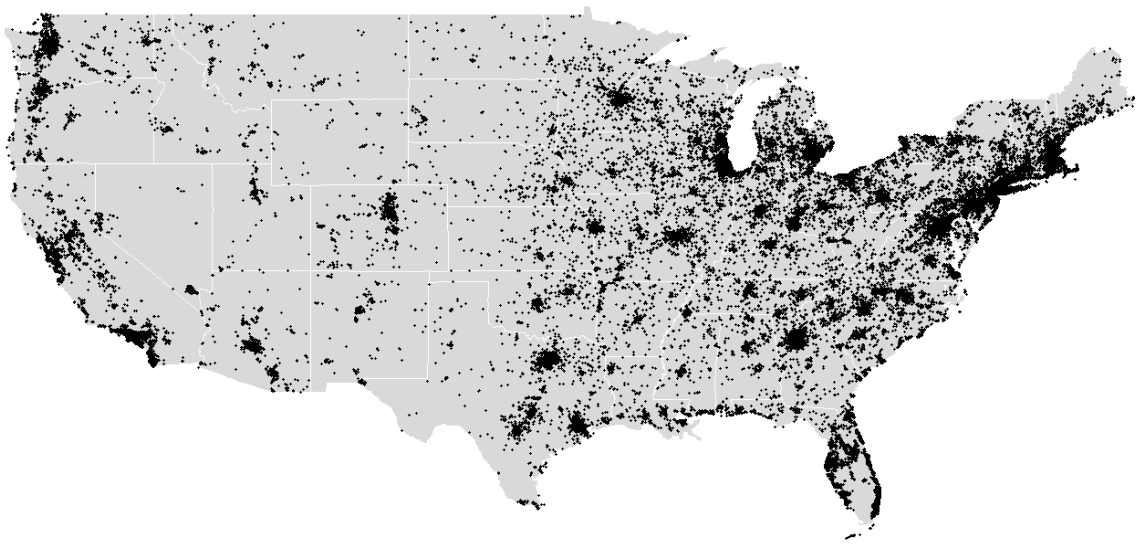


Figure 1: Sister Study baseline home address locations (AK, HI, and Puerto Rico not shown)

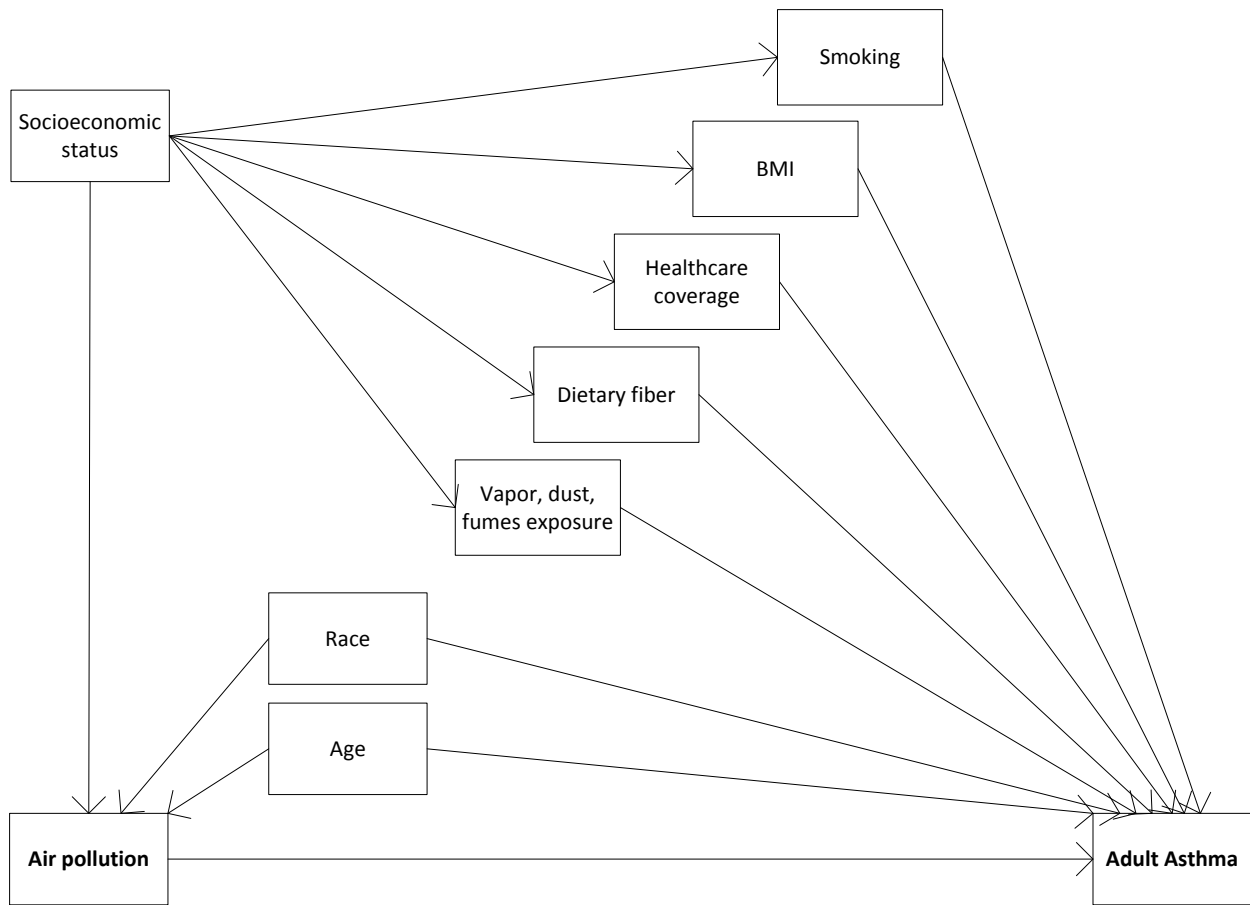


Figure 2: Causal model of air pollution, asthma, and potential confounders

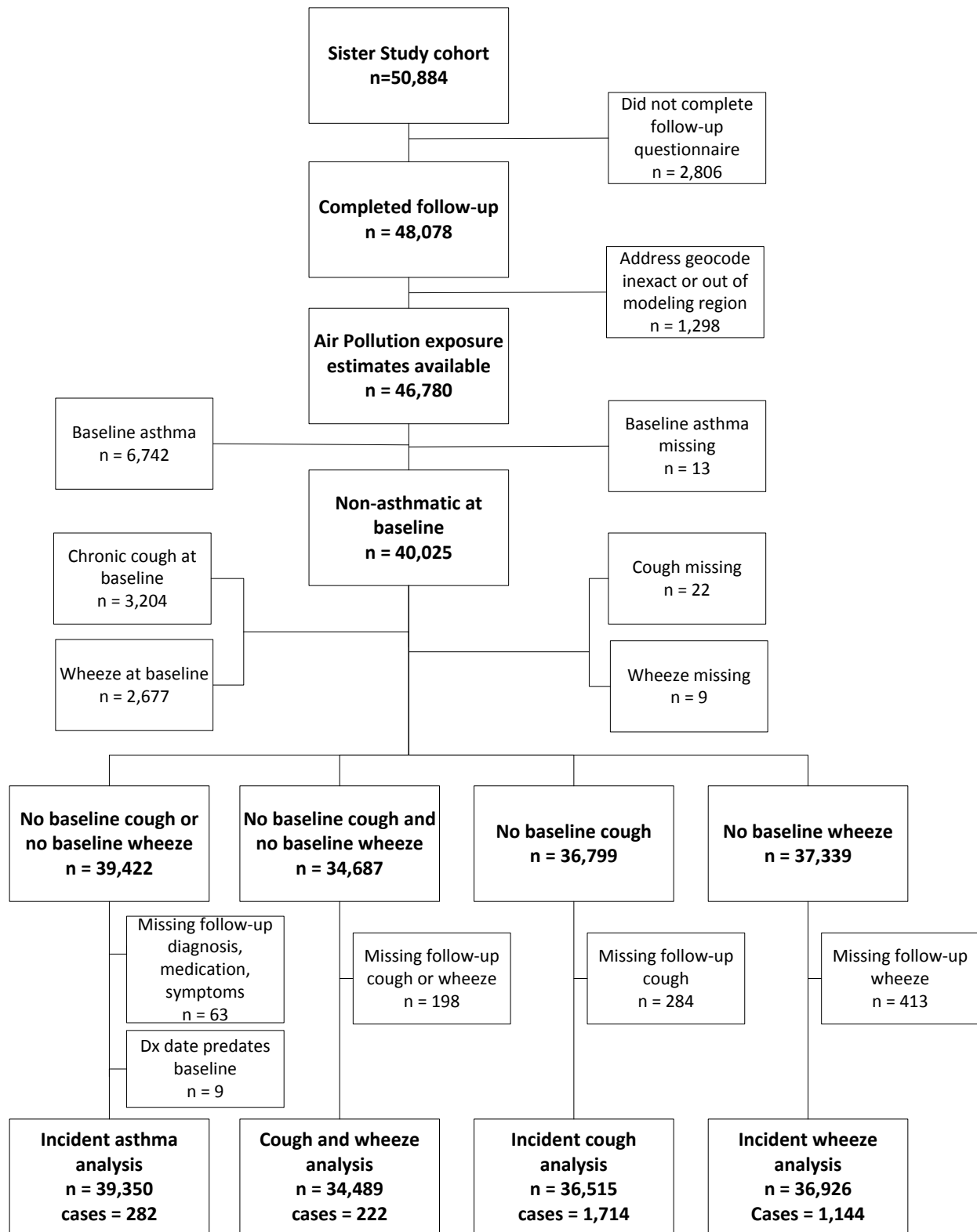


Figure 3: Study populations and exclusions

Table 1a: Population Characteristics by Quartiles of PM_{2.5} exposure (µg/m³)

	[1.89,8.77]	(8.77,10.8]	(10.8,12.4]	(12.4,18]	Missing
n	12367	12367	12367	12367	1416
Age (years)	55.7 ± 8.9	55.3 ± 9.1	54.9 ± 8.9	54.6 ± 9.0	55.0 ± 8.7
<i>Percent missing</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>
BMI	27.0 ± 5.7	27.5 ± 6.1	27.5 ± 6.0	28.1 ± 6.5	28.0 ± 5.7
<i>Percent missing</i>	<i>0.4</i>	<i>0.3</i>	<i>0.3</i>	<i>0.4</i>	<i>0.4</i>
Daily fiber consumption (g)	17.4 ± 8.5	17.0 ± 8.3	17.0 ± 8.6	16.8 ± 8.6	13.8 ± 8.7
<i>Percent missing</i>	<i>1.8</i>	<i>1.9</i>	<i>2.2</i>	<i>2.8</i>	<i>4.5</i>
Baseline Smoking status					
Current smoker	7.3	8.4	8	9.2	7.8
Never smoked	52.8	53.1	53.6	54.6	66.5
Past smoker	37.8	36.3	36	33.8	24
Social smoker	2.2	2.2	2.4	2.4	1.8
<i>Percent missing</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0.7</i>
Education					
Less than high school	0.8	1.1	1	1.2	8.8
High school or GED	13.7	14.8	14.9	13.1	14
Some college	20.4	20.3	18.5	19.7	13.8
Bachelors	27.7	25.8	27	27.1	29.3
Associate, tech, or nursing	14.8	15.1	13.7	12.9	17.2
Masters/Doctoral	22.6	22.9	25	26.1	16.9
<i>Percent missing</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0.3</i>
Race					
Black	2.1	5.1	9.4	19.9	6.7
Hispanic	3.5	3.4	2.5	3.3	57.2
Non-Hispanic White	91.8	88.6	85.7	74.4	31.9
Other	2.6	2.9	2.4	2.4	4.2
<i>Percent missing</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0.4</i>
Childhood SHS exposure	46.8	48.1	47.1	47.9	37
<i>Percent missing</i>	<i>0.2</i>	<i>0.2</i>	<i>0.2</i>	<i>0.2</i>	<i>0.8</i>
Healthcare coverage	96.3	96.1	96.4	95.8	94.8
<i>Percent missing</i>	<i>7.3</i>	<i>7.8</i>	<i>7.5</i>	<i>9</i>	<i>10.4</i>
Occupational dust exposure	20.9	21.8	22.6	23.6	37.8
<i>Percent missing</i>	<i>1.7</i>	<i>1.8</i>	<i>1.9</i>	<i>2</i>	<i>1.8</i>
Occupational fumes exposure	23.9	23.4	23.4	23.9	27.1
<i>Percent missing</i>	<i>1.9</i>	<i>1.9</i>	<i>2.1</i>	<i>2.3</i>	<i>1.8</i>

Continuous variables are expressed as mean ± standard deviation. Percents are calculated as percent of non-missing except italicized in rows which are total percents.

Table 1b: Population Characteristics by Quartiles of NO₂ exposure (ppb)

	[0.729,6.77]	(6.77,9.31]	(9.31,12.6]	(12.6,31.5]	Missing
n	12367	12367	12367	12367	1416
Age (years)	55.7 ± 8.8	54.9 ± 9.0	54.9 ± 9.0	55.1 ± 9.1	55.0 ± 8.7
<i>Percent missing</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>
BMI	27.5 ± 5.8	27.5 ± 5.9	27.6 ± 6.2	27.6 ± 6.3	28.0 ± 5.7
<i>Percent missing</i>	<i>0.3</i>	<i>0.4</i>	<i>0.4</i>	<i>0.4</i>	<i>0.4</i>
Daily fiber consumption (g)	16.9 ± 8.3	16.8 ± 8.3	17.1 ± 8.6	17.3 ± 8.7	13.8 ± 8.7
<i>Percent missing</i>	<i>1.5</i>	<i>2.1</i>	<i>2.3</i>	<i>2.9</i>	<i>4.5</i>
Baseline Smoking status					
Current smoker	8.6	7.7	7.9	8.7	7.8
Never smoked	53.6	54.8	53.9	51.7	66.5
Past smoker	35.7	35.2	35.8	37.3	24
Social smoker	2.1	2.3	2.3	2.4	1.8
<i>Percent missing</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0.7</i>
Education					
Less than high school	1.1	0.9	0.9	1.2	8.8
High school or GED	16.8	15.2	13.1	11.4	14
Some college	21.2	19.7	19.1	19	13.8
Bachelors	24.9	26.8	27.7	28.1	29.3
Associate, tech, or nursing	16.6	14.6	13.6	11.7	17.2
Masters/Doctoral	19.3	22.9	25.6	28.7	16.9
<i>Percent missing</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0.3</i>
Race					
Black	4.6	7.8	10.6	13.4	6.7
Hispanic	2.1	2.6	2.8	5.2	57.2
Non-Hispanic White	90.3	87.3	84.2	78.7	31.9
Other	3	2.3	2.3	2.7	4.2
<i>Percent missing</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0.4</i>
Childhood SHS exposure	46.5	47.2	47.1	49	37
<i>Percent missing</i>	<i>0.2</i>	<i>0.3</i>	<i>0.2</i>	<i>0.2</i>	<i>0.8</i>
Healthcare coverage	96.2	96.2	96	96.1	94.8
<i>Percent missing</i>	<i>7.3</i>	<i>7.7</i>	<i>7.7</i>	<i>8.8</i>	<i>10.4</i>
Occupational dust exposure	23	21.6	21.6	22.7	37.8
<i>Percent missing</i>	<i>1.7</i>	<i>1.9</i>	<i>1.9</i>	<i>1.9</i>	<i>1.8</i>
Occupational fumes exposure	25	23.4	23	23.3	27.1
<i>Percent missing</i>	<i>1.8</i>	<i>2</i>	<i>2.1</i>	<i>2.1</i>	<i>1.8</i>

Continuous variables are expressed as mean ± standard deviation. Percents are calculated as percent of non-missing except italicized in rows which are total percents.

Table 2: Effect Estimates for Primary and Secondary Analyses

Exposure (IQR)	Outcome	Minimally Adjusted		Fully Adjusted	
		OR (95% CI)	P Value	OR (95% CI)	P Value
PM _{2.5} (3.53 µg/m ³)	Incident Asthma	1.19 (0.99, 1.42)	0.059	1.20 (0.99, 1.45)	0.069
	Cough and Wheeze	0.98 (0.81, 1.19)	0.855	0.93 (0.74, 1.15)	0.491
	Cough	0.98 (0.91, 1.06)	0.621	0.95 (0.88, 1.02)	0.175
	Wheeze	1.17 (1.07, 1.28)	0.001	1.13 (1.02, 1.25)	0.015
	Asthma Recurrence	1.24 (0.87, 1.76)	0.236	1.20 (0.79, 1.82)	0.388
NO ₂ (5.84 ppb)	Incident Asthma	1.12 (0.97, 1.28)	0.123	1.12 (0.96, 1.30)	0.150
	Cough and Wheeze	1.00 (0.85, 1.18)	0.977	1.01 (0.84, 1.22)	0.907
	Cough	0.99 (0.93, 1.05)	0.680	1.00 (0.93, 1.07)	0.930
	Wheeze	1.05 (0.98, 1.13)	0.151	1.08 (1.00, 1.17)	0.053
	Asthma Recurrence	1.00 (0.75, 1.32)	0.989	1.00 (0.71, 1.40)	0.989

*Adjusted for Age

†Adjusted for age, BMI, Race, education, occupational exposure to vapor or fumes, occupational exposure to dust, baseline smoking status, age started smoking, packs per day per day at baseline, smoked since baseline, childhood second-hand smoke exposure, any healthcare coverage, dietary fiber consumption per day.

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