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Particulate Matter Exposures and Adult-onset Asthma and COPD in the Nurses' Health Study

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Exposure to ambient air pollution has been associated with acute respiratory effects, including acute exacerbations of asthma and chronic obstructive pulmonary disease (COPD) [1, 2]. However, evidence on the association of long-term exposure to air pollution and incidence of asthma or COPD is limited, with most studies focused on asthma in children [3]. Among adults, recent reviews for both asthma [3] and COPD [4] discuss several studies that demonstrate either no increased risk or a suggestion of risk associated with traffic-related pollutants. With few exceptions [5, 6, 7], most have not used robust exposure assessments, large cohorts, or fine particulate exposures. Using previously validated spatiotemporal exposure models [8], we examined the association between long-term exposure to particulate matter (PM) air pollution and incident cases of adult-onset asthma and COPD from 1992-2000 in the U.S. Nurses' Health Study (NHS).

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The NHS is a prospective cohort of 121,701 female nurses who were between 30 and 55 years of age at the start of follow-up in 1976. Participants complete mailed questionnaires every two years on a multitude of risk factors and health outcomes, including asthma, emphysema, and chronic bronchitis. Response rates are over 90% for each follow-up cycle. We defined cases as those reporting a physician diagnosis of asthma or COPD on biennial questionnaires and who subsequently reported use of an asthma medication within the past 12 months or reported a diagnostic test at the time of COPD diagnosis on supplemental questionnaires (1998 and 2000). These case definitions have been previously validated for both asthma [9] and COPD [10]. Time-varying ambient exposure estimates at each participant's residence to PM ≤ 2.5 μm ($PM_{2.5}$), ≤ 10 μm (PM_{10}), and between 2.5 and 10 μm in aerodynamic diameter ($PM_{10-2.5}$) were assessed using nationwide spatiotemporal models that incorporated data from multiple pollution monitor networks and various geospatial predictors [8]. Model predictions of exposure were available monthly from January 1988. We also examined the effect of residential distance to primary or secondary roads, as a proxy for traffic-related exposures, in separate regression models. Participants were divided into three categories (0–50, 50–200, and ≥ 200 m) corresponding to the closest distance of their residence to an A1, A2, or an A3 road [11].

Follow-up began in 1992 to allow for calculation of four-year moving average PM exposures and continued through 2000, the date of the last supplemental questionnaire. Cox proportional hazards models were used to examine whether asthma or COPD was associated with four-year average exposure to $PM_{2.5}$, PM_{10}, or $PM_{10-2.5}$. Basic models were adjusted for region and stratified by age and calendar year. Fully-adjusted models included potential confounders selected *a priori* based on previous literature and included: age, time period, geographic region, BMI, alcohol consumption, physical activity, census-tract median household income, Western dietary pattern [12], second hand smoke exposure at home and work, smoking status and pack-years smoked. Stratified models were used to examine effect modification by smoking status. Sensitivity analyses restricted to non-movers or to participants residing within metropolitan statistical areas (MSAs) were conducted. To examine the effect of varying exposure averaging times, separate models were run with two-year, three-year, or total cumulative (since 1988) moving average PM exposures. We excluded prevalent cases of asthma or COPD at baseline, as well as participants missing exposure or year of diagnosis.

There were 934 incident cases of asthma among 104,254 participants during 796,208 person-years of follow-up, and 372 incident cases of COPD among 103,838 participants during 795,964 person-years of follow-up. Incident asthma cases were primarily among never smokers (43%; n=400) and former smokers (45%; n=417), while the majority of COPD cases were among current smokers (58%; n=214) and former smokers (30%; n=111). Mean PM exposures over the follow-up period were 24.0 $\mu g/m^3$ (SD: 6.3), 14.2 (SD: 3.2), and 9.8 (SD: 4.4) for PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$, respectively. The average age during follow-up was 61.5 years (SD: 7.4).

In this cohort, there was no consistent evidence of an association between exposure to PM and incident asthma or COPD (Table 1). In fully adjusted models, the hazard ratios (HRs) for a 10-ug/m^3 increase in four-year average PM_{10}, $PM_{2.5}$, or $PM_{10-2.5}$ were 0.94 (95%CI:

0.84-1.06), 0.90 (95%CI: 0.73-1.12), and 0.93 (95%CI: 0.77-1.13) for asthma, and 0.91 (95%CI: 0.76-1.10), 0.93 (95%CI: 0.66-1.31), and 0.83 (95%CI: 0.60-1.14) for COPD, respectively. There was a suggestion of higher risk for COPD across all size fractions of PM among never smokers, though no statistically significant associations were observed among this subpopulation. In addition, no statistically significant associations were observed for residential proximity to roads with incident asthma or COPD. In sensitivity analyses, we found comparable results after limiting to non-movers or MSA residents (Supplementary Table 1), and results were consistent in separate models using different exposure averaging times (Supplementary Table 2).

There are few previous studies examining the association between exposure to PM and adult-onset asthma to which we can compare our results. In their analysis of the Sister Study, a U.S. cohort of predominantly non-Hispanic white women, Young et al (2014) found a suggestion of increased risk of adult-onset asthma with $PM_{2.5}$ (HR 1.20; 95% CI 0.99-1.46 per 3.6 μg/m^3). Additionally, a recent meta-analysis of six cohorts participating in the European Studies on Chronic Air Pollution Effects (ESCAPE) project found non-significant positive associations with PM_{10} (OR 1.04; 95% CI: 0.88, 1.23 per 10 μg/m^3) and $PM_{2.5}$ (OR 1.04; 95% CI: 0.88, 1.23 per 5 μg/m^3) and a non-significant negative association with $PM_{10-2.5}$ (OR 0.98; 95% CI: 0.87, 1.14 per 5μg/m^3) [7]. No evidence of modification by smoking status was found in stratified analysis [7].

Our results are similar to those from other studies of long-term exposure to PM and incidence of COPD. A study of four cohorts participating in the ESCAPE project found no association with PM and incident COPD, however traffic intensity on the nearest major road was positively associated with incident COPD in females and never smokers [6].

Many of the current hypotheses on the pathophysiologic mechanisms linking ambient air pollution to incident asthma or COPD focus on the role of pollution-induced oxidative stress and free radical reactions that may lead to airway damage and inflammation [13, 14]. These concepts could help explain our findings of lower risk of asthma and COPD among current smokers, as cigarette smoke may saturate the same pathways [15] and minimize any additional adverse effect from ambient particles. However, it should be noted that the relatively few incident cases of asthma among current smokers, and COPD among never smokers, limited our assessment of risk in these subgroups.

Though this study used advanced and validated spatiotemporal models to estimate PM exposure, some exposure misclassification was unavoidable due to date of diagnosis being limited to self-reported year of first physician diagnosis on the supplemental questionnaires. Thus, our exposure estimates for cases may have been separated from the month of self-reported diagnosis by up to six months. In response, we chose a longer (four year) exposure averaging metric and considered other averaging times in sensitivity analyses. The spatiotemporal models also did not account for differences in time–activity patterns, time spent outdoors, or time spent at the residence. Though mechanisms of action may take decades of exposure, we were limited to a shorter follow-up period due to the availability of pollution data and the date of the last supplemental asthma/COPD questionnaire. Though we used validated case definitions of a self-reported physician diagnosis, we could not exclude

the possibility of undiagnosed or unreported disease. Additionally, some incident cases of asthma may represent forgotten or undiagnosed reactivations from earlier in life, a limitation shared by most studies of adult-onset asthma. Generalizability of these findings outside of this cohort of predominantly white nurses may be limited. In conclusion, we found no evidence that long-term exposure to particulate matter increased the risk of incident asthma or COPD in this cohort.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Hazard Ratios and 95% Confidence Intervals of the Association of Incident Asthma and COPD with Four-year Cumulative Average Particulate Matter Exposures[a] or Residential Proximity to Road Categories[b] in the Nurses' Health Study

	Full Cohort		Never Smoker		Former Smoker		Current Smoker	
	Basic[c]	Adjusted[d]	Basic[c]	Adjusted[d]	Basic[c]	Adjusted[d]	Basic[c]	Adjusted[d]
Asthma								
Modeled PM Fraction								
PM_{10}	0.92(0.82,1.03)	0.94(0.84,1.06)	0.97(0.82,1.15)	0.98(0.83,1.17)	0.95(0.80,1.13)	0.96(0.80,1.14)	0.64(0.46,0.91)	0.66(0.47,0.94)
$PM_{2.5}$	0.87(0.70,1.08)	0.90(0.73,1.12)	0.88(0.64,1.21)	0.90(0.65,1.23)	0.97(0.70,1.34)	0.98(0.71,1.36)	0.55(0.29,1.02)	0.57(0.30,1.07)
$PM_{10-2.5}$	0.89(0.73,1.08)	0.93(0.77,1.13)	1.02(0.77,1.35)	1.04(0.79,1.38)	0.89(0.66,1.20)	0.90(0.67,1.21)	0.48(0.26,0.88)	0.50(0.27,0.92)
Distance to Road (m)								
50-199	0.91(0.77,1.07)	0.90(0.77,1.07)	0.96(0.74,1.25)	0.96(0.74,1.25)	0.85(0.66,1.09)	0.84(0.66,1.08)	0.98(0.61,1.56)	0.93(0.58,1.51)
0-49	1.15(0.94,1.40)	1.13(0.93,1.38)	1.21(0.89,1.65)	1.20(0.88,1.64)	1.18(0.89,1.57)	1.14(0.85,1.51)	1.02(0.55,1.89)	1.04(0.56,1.94)
COPD								
Modeled PM Fraction								
PM_{10}	0.92(0.76,1.11)	0.91(0.76,1.10)	1.12(0.69,1.81)	1.14(0.70,1.87)	0.91(0.64,1.28)	0.90(0.64,1.27)	0.83(0.63,1.08)	0.87(0.67,1.13)
$PM_{2.5}$	0.87(0.61,1.23)	0.93(0.66,1.31)	1.17(0.47,2.90)	1.23(0.50,3.06)	0.94(0.50,1.78)	1.00(0.53,1.88)	0.72(0.45,1.15)	0.82(0.51,1.31)
$PM_{10-2.5}$	0.88(0.64,1.21)	0.83(0.60,1.14)	1.19(0.54,2.65)	1.22(0.54,2.76)	0.80(0.44,1.44)	0.74(0.41,1.34)	0.78(0.50,1.22)	0.80(0.51,1.25)
Distance to Road (m)								
50-199	1.07(0.83,1.38)	0.98(0.76,1.27)	1.22(0.60,2.45)	1.28(0.63,2.59)	1.05(0.66,1.68)	0.93(0.57,1.49)	0.96(0.68,1.35)	0.91(0.64,1.29)
0-49	1.05(0.76,1.45)	0.96(0.69,1.32)	0.65(0.22,1.92)	0.67(0.23,1.98)	1.07(0.60,1.93)	1.04(0.58,1.90)	1.04(0.68,1.57)	1.01(0.66,1.55)

[a] Models are for 1992-2000 and for 10 μg/m^3 increase in Four-year Cumulative Average Particulate Matter Exposures. There were 104,254 participants (796,208PY, 934 cases) included in the asthma analysis and 103,838 participants (795.964PY, 372 cases) included in the COPD analysis.

[b] Models are for 1992-2000 and use distance of ≥200m as the reference group. There were 81,231 participants (620,818PY, 767 cases) in the asthma analysis and 82,616 participants (633,138PY, 306 cases) in the COPD analysis.

Included A1-A3 *Categories as defined by U.S. Census Bureau, 2014*

A1 (primary roads, typically interstate highways, with limited access, division between the opposing directions of traffic, and defined exits)

A2 (primary major, non-interstate highways and major roads without access restrictions)

A3 (smaller, secondary roads, usually with more than two lanes)

[c] Models adjusted for age, time period, and geographic region

[d] Additionally adjusted for BMI, alcohol consumption, physical activity, census-tract median household income, Western dietary pattern (Varraso, 2007), second hand smoke exposure at home and work, smoking status (when not stratified by status) and pack years