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ORIGINAL ARTICLE

Traffic-related Air Pollution and Lung Cancer Incidence
The California Multiethnic Cohort Study

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Abstract

Rationale: Although the contribution of air pollution to lung cancer risk is well characterized, few studies have been conducted in racially, ethnically, and socioeconomically diverse populations.

Objectives: To examine the association between traffic-related air pollution and risk of lung cancer in a racially, ethnically, and socioeconomically diverse cohort.

Methods: Among 97,288 California participants of the Multiethnic Cohort Study, we used Cox proportional hazards regression to examine associations between time-varying traffic-related air pollutants (gaseous and particulate matter pollutants and regional benzene) and lung cancer risk ($n = 2{,}796$ cases; average follow-up = 17 yr), adjusting for demographics, lifetime smoking, occupation, neighborhood socioeconomic status (nSES), and lifestyle factors. Subgroup analyses were conducted for race, ethnicity, nSES, and other factors.

Measurements and Main Results: Among all participants, lung cancer risk was positively associated with nitrogen oxide (hazard ratio [HR], 1.15 per 50 ppb; 95% confidence interval [CI], 0.99–1.33), nitrogen dioxide (HR, 1.12 per 20 ppb; 95% CI, 0.95–1.32), fine particulate matter with aerodynamic diameter <2.5 μm (HR, 1.20 per 10 μg/m^3; 95% CI, 1.01–1.43), carbon monoxide (HR, 1.29 per 1,000 ppb; 95% CI, 0.99–1.67), and regional benzene (HR, 1.17 per 1 ppb; 95% CI, 1.02–1.34) exposures. These patterns of associations were driven by associations among African American and Latino American groups. There was no formal evidence for heterogeneity of effects by nSES (P heterogeneity > 0.21), although participants residing in low-SES neighborhoods had increased lung cancer risk associated with nitrogen oxides, and no association was observed among those in high-SES neighborhoods.

Conclusions: These findings in a large multiethnic population reflect an association between lung cancer and the mixture of traffic-related air pollution and not a particular individual pollutant. They are consistent with the adverse effects of air pollution that have been described in less racially, ethnically, and socioeconomically diverse populations. Our results also suggest an increased risk of lung cancer among those residing in low-SES neighborhoods.

Keywords: air pollution; lung cancer; racial and ethnic disparities; socioeconomic disparities

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Data availability: The Multiethnic Cohort investigators and institutions affirm their intention to share the research data consistent with all relevant NIH resource/data-sharing policies. Data requests should be submitted through Multiethnic Cohort online data request system at https://www.uhcancercenter.org/for-researchers/mec-data-sharing.

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At a Glance Commentary

Scientific Knowledge on the Subject: Although the contribution of air pollution to lung cancer risk is well characterized, few studies have been conducted in racially, ethnically, and socioeconomically diverse populations.

What This Study Adds to the Field: The findings in this large multiethnic study are consistent with the adverse effects of air pollution that have been described in less racially, ethnically, and socioeconomically diverse populations and suggest an increased risk of lung cancer among those residing in neighborhoods of low socioeconomic status.

It is well established that exposure to outdoor air pollution, and airborne particulate matter (PM) specifically, contributes to the development of lung cancer. In 2013, the International Agency for Research on Cancer classified outdoor air pollution and PM as carcinogenic to humans based on evidence from experimental and epidemiological studies (1). A meta-analysis of 15 observational studies of lung cancer risk and exposure to fine PM with aerodynamic diameter <2.5 μm ($PM_{2.5}$), accounting for smoking and socioeconomic status, reported that a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 16% increase in lung cancer risk (2). In a large U.S. study based on data from the Surveillance, Epidemiology, and End Results program, a 10 $\mu g/m^3$ increase in county-level $PM_{2.5}$ estimates was associated with a 19% increased risk of lung cancer (3). Other components of the air pollution mixture have also been investigated. For example, a meta-analysis of 20 observational studies estimated the associations of exposures to nitrogen oxides (NO_X) and nitrogen dioxide (NO_2) with lung cancer incidence and mortality in North America, Europe, and Asia, finding that a 10 $\mu g/m^3$ increase was associated with a 4% and 3% increase in risk of lung cancer incidence and mortality, respectively (4). Other gaseous pollutants, such as carbon monoxide (CO) resulting from the combustion of fossil and biomass fuels as well as ozone (O_3) formed in the atmosphere when NO_X reacts with hydrocarbons in the presence of sunlight, have also been associated with lung cancer risk (5–7).

Patterns of exposure to air pollution and potential confounding and modifying factors vary across populations. Several studies have documented a higher burden of air pollution exposure in low neighborhood socioeconomic status (nSES) areas, which typically have more residents from minoritized racial and ethnic populations than higher SES areas (8). Yet, few studies have investigated whether the associations between air pollutants and lung cancer risk differ by nSES and across racial and ethnic groups (9, 10). Such investigations of SES- and racial and ethnic-specific associations can inform the origins of inequities in lung cancer risk.

We conducted a prospective cohort study of long-term air pollution exposures and lung cancer incidence from 1993–2013 among 97,288 African American, European American, Japanese American, and Latino American participants from the California component of the MEC (Multiethnic Cohort Study) (11). Approximately 95% of the study participants resided in Los Angeles County, a region in the United States with the highest levels of outdoor air pollution despite recent declines (12) and documented inequities in air pollution levels across neighborhoods defined by minoritized racial and ethnic groups and low SES (13, 14). The study was further motivated by prior findings from the MEC of strong differences in risk for smoking-caused lung cancer across the racial and ethnic groups in the study (15, 16). The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Boards at the University of California, San Francisco; University of Hawaii; and University of Southern California.

Methods

Study Subjects

The MEC is a large population-based prospective cohort study of older U.S. adults, full details of which are available elsewhere (11). Briefly, from 1993 through 1996, 96,810 males and 118,441 females 45–75 years of age largely from five self-reported racial and ethnic groups (African American, European American, Japanese American, Latino American, and Native Hawaiian), residing in Hawaii or California (primarily Los Angeles County), were enrolled. Participants completed a baseline questionnaire that surveyed demographic characteristics, anthropometrics, reproductive history, and other lifestyle factors. Participants were followed prospectively for diagnosis of incident invasive lung cancer through routine linkages with the California Cancer Registry and Hawaii Tumor Registry, and for vital status through linkages to the National Death Index and state death certificate files. Lung cancer histologic types (adenocarcinoma, squamous cell carcinoma, small cell, and large cell) were obtained from the cancer registries and classified according to Lewis and colleagues (17). For this study, 105,359 eligible MEC participants had lived in California at baseline and had no lung cancer diagnosis before cohort entry (i.e., reported on baseline questionnaire or through linkage with the tumor registry). We also excluded participants with missing smoking information ($n = 7{,}974$) and invalid addresses ($n = 97$), resulting in 97,288 participants for analysis. Participants were followed from the date of cohort entry (1993–1996) to the earliest date of diagnosis of invasive lung cancer, death, or December 31, 2013 (end of follow-up), whichever came earlier (mean $\pm$ SD follow-up time, 16.53 ± 5.38 yr). Over this period 2,796 incident lung cancer cases were identified.

Study Participant Characteristics

Participant characteristics considered were those associated with lung cancer risk. These included age at cohort entry; race and ethnicity; sex; and baseline variables including family history of lung cancer in first-degree relatives (no, yes); education

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(high school graduate or less, some college, college graduate, graduate school); marital status (married, separated, divorced, or widowed, single); work history (with six categories that combine industries, occupations employed for 10 years or more [yes: manufacturing enterprises (i.e., government regulation of manufacturing), or no: none of those enterprises] and longest worked occupation classifications [office work only, labor/craft only, or both]); nonsteroidal antiinflammatory drug use (no, yes); body mass index (BMI) (underweight [$<$18.5 kg/m^2] or normal weight [18.5–24.9 kg/m^2], overweight [25–29.9 kg/m^2], and obese [$\geqslant$30 kg/m^2]); smoking status (never, current, former); alcohol intake per day (nondrinker, one drink, two or more drinks); moderate or vigorous physical activity (none, quartiles); energy intake (quintiles); red meat intake (quintiles); and processed red meat intake (quintiles). In addition, our model accounted for smoking by calculating the duration of smoking (pack-years of smoking), taking into account quitting probabilities that were allowed to depend on average number of cigarettes per day, race, ethnicity, interaction of race and ethnicity with cigarettes per day, and participant time on study (16).

Address History, Geocoding, and nSES

The MEC actively maintains accurate and up-to-date addresses on all participants via periodic mailings of newsletters, follow-up questionnaires, and linkages to administrative databases and registries. For the 97,288 California MEC participants included in this study, 167,859 residential addresses were recorded across the study period. Residential addresses were geocoded to latitude and longitude coordinates using point or street locators. Geocoded addresses were linked to 1990 (1993–1996 baseline addresses), 2000 (1997–2005 addresses), and 2010 (2006–2013 addresses) U.S. Census block groups. A composite measure of nSES was based on principal component analysis of seven census-based indicators of SES from census data: education, median household income, percentage living 200% below poverty level, percentage blue-collar workers, percentage older than 16 years in workforce without job, median rent, and median house value; nSES was the first principal component extracted from the correlation matrix of these variables (18, 19). The nSES index was assigned to participants' census block group at baseline (diagnosis), death, or censoring time and categorized into quintiles based on the nSES distribution of all Los Angeles County block groups. Low and high nSES were defined as quintiles 1–3 and 4–5, respectively (20–22).

Air Pollution Exposure Assessment

We used established approaches to estimate air pollutant concentrations at residential locations across the study period (1993–2013) as previously described (23, 24). For gaseous traffic-related pollutants, based on empirical Bayesian kriging interpolation, largely exposures from regional emission sources (25) were estimated using air monitoring data routinely collected by the U.S. Environmental Protection Agency for NO_x, NO_2, PM_{10}, CO, and ozone (O_3) (1993–2013) and $PM_{2.5}$ (2000–2013). $PM_{2.5}$ concentrations for 1993–1999 were estimated from a published spatiotemporal model based on PM_{10}, meteorology, and land use data at the monitoring sites with PM_{10} measurements (26) that were further interpolated using empirical Bayesian kriging. We herein refer to the above $PM_{2.5}$ concentrations derived from PM_{10} and land use data in the 1990s and monitored $PM_{2.5}$ measurements since 2000 as krigged $PM_{2.5}$. In addition, concentrations of $PM_{2.5}$ were obtained from the fine-resolution geoscience-derived model outputs (27). This model provides validated and publicly available $PM_{2.5}$ outputs at a 1-km resolution over North America by statistically fusing chemical transport modeling (GEOS-Chem) outputs and satellite observations of aerosol optical depth with ground-based observations using a geographically weighted regression. We herein refer to this as satellite-based $PM_{2.5}$. The satellite-based $PM_{2.5}$ concentrations were generally consistent with ground $PM_{2.5}$ measurements (R^2 of 0.6–0.85 since 1999 when $PM_{2.5}$ measurements are available; R^2 of 0.45–0.6 in 1993–1998 when comparing to $PM_{2.5}$ derived from PM_{10} measurements in the absence of $PM_{2.5}$ measurements) (27). For NO_x and NO_2 based on a land-use regression (LUR) model, regional and local source emissions were estimated using air monitoring data from spatially dense air monitoring campaigns (2006–2007) as well as spatial data on land use and traffic characteristics. For temporal adjustment of LUR-based NO_x and NO_2 concentrations, monthly scaling factors were applied based on long-term data from monitors nearest to the participants' residences (28, 29). For benzene, the U.S. Environmental Protection Agency–measured monthly data (1993–2016) were used from air monitors located within a 20 km radius buffer from residential addresses with $<$50% missing air monitoring data (24). Individual exposures were calculated by combining the estimated concentrations over time (monthly) and space at residential locations (latitude and longitude as the geographic unit) with time lived at these locations. Correlation matrices of the air pollutants is presented in the online supplement in Tables E1 (overall and by race and ethnicity) and E2 (by baseline nSES).

Statistical Analysis

We estimated the risk of lung cancer incidence in relation to air pollution exposure using Cox proportional hazards regression with monthly time-varying exposure variables. The Cox regression model used calendar month and year as the time variable and defined a series of risk sets based on month and year at diagnosis of each lung cancer event (index case) using age at cohort entry (1-year age groups) as a stratum variable. Each risk set consisted of all MEC participants who remained alive and uncensored at the time of lung cancer diagnosis. For each member of each risk set (including the index case) based on his or her residential history, we computed an average air pollutant exposure for the period starting from the time of cohort entry (month and year) up to the time of lung cancer diagnosis of the index case in each risk set. This average exposure was used as the independent variable. Models were adjusted for demographics and lung cancer risk factors, including race and ethnicity; sex; education; marital status; smoking intensity, duration, and cessation (16); family history of lung cancer; occupation; nSES at baseline and time of event; nonsteroidal antiinflammatory drug use; BMI; alcohol drinking; physical activity; intake of energy; and red meat and processed meat. Table E3 presents the mean concentrations of krigged vs. kriging NO_X for these covariates. Minimally adjusted models that included only race, ethnicity, sex, and smoking intensity, duration, and smoking cessation (16) were also examined and showed similar associations to the full model (Table E4).

Hazard ratios (HRs) and 95% confidence intervals (CIs) for common fixed size increases in air pollutants were calculated to allow for comparing effect

estimates with previous reports. For NO_x, we chose 50 ppb, which was close to the interquartile range (IQR) of the krigged (51.6 ppb) and the LUR (41.7 ppb) estimates. For NO_2, we used 20 ppb consistent with the IQRs of krigged (16.4 ppb) and LUR (18.2 ppb) estimates. For PM_{10} and $PM_{2.5}$, we used 10 $\mu g/m^3$; this value was close to the IQR of krigged PM_{10} (9.0 $\mu g/m^3$) and higher than satellite-based $PM_{2.5}$ (3.3 $\mu g/m^3$) and krigged $PM_{2.5}$ (3.8 $\mu g/m^3$). For CO and O_3, we used 1,000 ppb and 10 ppb, respectively, close to the IQRs of krigged CO (743.6 ppb) and krigged O_3 (9.2 ppb). For regional benzene, we used 1 ppb, and the IQR was 1.2 ppb. We checked the proportional hazards assumption for each pollutant in a model with all covariates by graphing Schoenfeld residuals against time and found no violations.

As we observed racial, ethnic, and nSES differences in average air pollutant exposures (Tables E5 and E6), subgroup analyses were conducted to assess differences in effect estimates by race, ethnicity, and baseline nSES. In addition, we examined differences in effect estimates by sex, smoking status, and lung cancer histology at diagnosis. We assessed heterogeneity of effects for each pollutant and subgroup using a global simultaneous test of interaction based on the Wald test. To test for differences in associations by histology, we conducted a competing risk analysis using a Lunn-McNeil augmentation approach (30, 31), where each histology was fit by a cause-specific model in a separate stratum. We used the Wald test to compare the parameter estimates across histological cell types.

We applied the Lin and Wei (32) covariance sandwich estimator to our overall lung cancer model to account for correlation structure among covariates, including clustering by geographic area. As similar results were observed, we present the lung cancer model without this estimator.

All *P* values are two-sided with a significance level of 0.05. Analyses were performed using SAS 9.2 statistical software (SAS Institute).

Results

The study population consisted of 41,248 males and 56,040 females (32% African American, 14% European American, 12% Japanese American, 41% Latino American participants) with racial and ethnic differences in the distribution of education, marital status, occupation, BMI, smoking, alcohol intake, and other lung cancer risk factors (Table 1). African American (36%) and Latino American (26%) participants were more likely to live in the lowest nSES (quintile 1) at baseline in comparison with Japanese American (5%) and European American (8%) participants. Higher average NO_X exposures were observed for African American and Latino American in comparison to Japanese American and European American participants (Table E5). Across almost all pollutants, higher average exposures were seen among participants residing in low- versus high-SES neighborhoods at baseline (Table E6).

Table 2 presents associations of air pollutant exposures assessed by kriging interpolation, satellite-based $PM_{2.5}$ (27), and regional benzene with lung cancer incidence among California MEC participants overall and by race and ethnicity. Exposures to NO_X (per 50 ppb), NO_2 (per 20 ppb), $PM_{2.5}$ (per 10 $\mu g/m^3$), CO (per 1,000 ppb), and also regional benzene (per 1 ppb) were positively associated with lung cancer risk in all participants combined. For satellite-based $PM_{2.5}$ and regional benzene exposures, increased risks of lung cancer were observed (HR, 1.20; 95% CI, 1.01–1.43 and HR, 1.17; 95% CI, 1.02–1.34, respectively). NO_X exposure was borderline statistically significant (HR, 1.15; 95% CI, 0.99–1.33). For O_3 (per 10 ppb), which was inversely correlated with NO_X (correlation coefficient, −0.74) and NO_2 (−0.56; Table E1), an inverse association with lung cancer risk was observed (HR, 0.85; 95% CI, 0.74–0.97). We conducted 2-, 5-, and 7-year lagged analyses for NO_X and O_3 and observed similar results (data not shown).

There were no statistically significant differences in associations across the four racial and ethnic groups (Table 2). However, African American and Latino American participants with the larger sample sizes displayed patterns of associations consistent with those for all racial and ethnic groups combined. In multipollutant models including all kriging pollutants, satellite-based $PM_{2.5}$ (27), and benzene, benzene had the strongest association with lung cancer risk (data not shown).

Findings of separate analyses for participants residing in low (Q1–Q3) and high (Q4–Q5) nSES at baseline are presented in Table 3. Among participants living in low SES neighborhoods, an increased risk of lung cancer was associated with NO_X (HR, 1.20; 95% CI, 1.01–1.43) and a decreased risk with O_3 (HR, 0.80; 95% CI, 0.68–0.95) was seen. In contrast, these pollutants were not associated with lung cancer among participants living in high-SES neighborhoods. There were no statistically significant differences in associations by nSES (*P* values > 0.21).

For NO_X and NO_2, the HRs were relatively larger among those who had never smoked in comparison to former and current smokers, although there was no formal evidence in heterogeneity of effects by smoking status (Table 4). Among current smokers, O_3 was negatively associated with lung cancer risk (HR, 0.81; 95% CI, 0.66–0.99), whereas regional benzene was positively associated with risk (HR, 1.25; 95% CI, 1.01–1.54).

Relatively similar patterns of associations were observed among men and women (Table E7) and across histological cell types (Table E8).

LUR NO_X was inversely associated with lung cancer risk (HR, 0.83; 95% CI, 0.73–0.94), with a consistent pattern of association across racial and ethnic groups (Table E9).

No statistically significant associations were observed between krigged $PM_{2.5}$ and lung cancer risk overall and across racial and ethnic groups (Table E10).

Discussion

In this prospective study of 97,288 California MEC participants, we found positive associations for traffic-related air pollutant exposures (NO_X, NO_2, CO, satellite-based $PM_{2.5}$, and benzene) with risk of lung cancer in a large multiethnic population. Similar patterns of associations were observed among African American and Latino American participants, the two largest racial and ethnic groups in the California MEC, representing 73% of the study population. Although no formal evidence of heterogeneity in effects by nSES was observed, suggestive associations for NO_x and NO_2, indicators of traffic-related air pollution, were observed among participants residing in low-SES neighborhoods, and no associations were seen for those in high-SES neighborhoods.

Many low-SES communities in the United States experience high levels of air pollution that may contribute to inequities in air pollution–related health outcomes (8).

Table 1. Distributions of Lung Cancer Risk Factors and Neighborhood Factors by Race/Ethnicity among California Multiethnic Cohort Study Participants at Baseline, 1993–1996

	All		African American		European American		Japanese American		Latino American		Native Hawaiian	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
All	97,288	100	31,103	100	13,756	100	12,028	100	40,239	100	162	100
Race/Ethnicity												
African American	31,103	32	31,103	100	—	—	—	—	—	—	—	—
European American	13,756	14	—	—	13,756	100	—	—	—	—	—	—
Japanese American	12,028	12	—	—	—	—	12,028	100	—	—	—	—
Latino American	40,239	41	—	—	—	—	—	—	40,239	100	—	—
Native Hawaiian	162	0	—	—	—	—	—	—	—	—	162	100
Sex												
Male	41,248	42	11,003	35	4,881	35	5,844	49	19,432	48	88	54
Female	56,040	58	20,100	65	8,875	65	6,184	51	20,807	52	74	46
Family history of lung cancer in first degree relative												
No	92,111	95	29,217	94	12,702	92	11,272	94	38,768	96	152	94
Yes	5,177	5	1,886	6	1,054	8	756	6	1,471	4	10	6
Education*												
⩽High school graduate	49,286	51	12,958	42	5,043	37	3,666	30	27,557	68	62	38
Some college	28,292	29	11,259	36	4,331	31	4,301	36	8,333	21	68	42
College graduate	10,060	10	3,528	11	2,049	15	2,521	21	1,943	5	19	12
Graduate school	8,976	9	3,191	10	2,285	17	1,506	13	1,983	5	11	7
Marital status*												
Married	58,911	61	14,032	45	8,787	64	8,955	74	27,020	67	117	72
Separated/divorced/widowed	30,730	32	14,509	47	3,871	28	1,979	16	10,339	26	32	20
Single	6,619	7	2,097	7	998	7	1,037	9	2,475	6	12	7
Employment in a manufacturing enterprise and occupational category												
No and office	42,759	44	14,757	47	11,659	29	78	48	7,803	65	8,462	62
No and labor/craft	12,471	13	3,678	12	7,075	18	22	14	797	7	899	7
No and office/labor/craft	24,910	26	8,355	27	11,885	30	34	21	1,839	15	2,797	20
Yes and office	4,201	4	1,060	3	1,683	4	15	9	726	6	717	5
Yes and labor/craft	10,176	10	2,513	8	6,339	16	11	7	648	5	665	5
Yes and office/labor/craft	2,771	3	740	2	1,598	4	2	1	215	2	216	2
NSAID use*												
No	36,217	37	9,628	31	5,009	36	6,638	55	14,873	37	69	43
Yes	55,893	57	19,433	62	8,322	61	5,022	42	23,023	57	93	57
BMI, kg/m^2 *												
Underweight/normal	33,015	34	8,119	26	5,844	42	7,771	65	11,224	28	57	35
Overweight	39,713	41	12,286	40	5,096	37	3,632	30	18,635	46	64	40
Obese	23,311	24	9,797	32	2,782	20	613	5	10,078	25	41	25
Smoking status												
Never	44,551	46	12,265	39	5,807	42	5,868	49	20,539	51	72	44
Current smoker	16,635	17	7,156	23	2,354	17	1,389	12	5,702	14	34	21
Former smoker	36,102	37	11,682	38	5,595	41	4,771	40	13,998	35	56	35
Cigarettes per day among ever-smokers												
⩽10	27,683	52	9,925	53	2,643	33	2,182	35	12,898	65	35	39
11–20	16,504	31	6,515	35	2,723	34	2,494	40	4,734	24	38	42
21–30	5,581	11	1,646	9	1,578	20	1,012	16	1,329	7	16	18
⩾31	2,969	6	752	4	1,005	13	472	8	739	4	1	1

(*Continued*)

Table 1. (*Continued*)

	All		African American		European American		Japanese American		Latino American		Native Hawaiian	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Time since quit among former smokers, yr												
⩽5	7,797	22	2,986	26	1,085	19	734	15	2,981	21	11	20
6–15	16,244	45	4,507	39	2,799	50	2,603	55	6,312	45	23	41
>15	12,061	33	4,189	36	1,711	31	1,434	30	4,705	34	22	39
Duration of smoking among ever-smokers, yr												
<20	24,329	46	7,795	41	3,245	41	2,842	46	10,407	53	40	44
20–40	20,946	40	8,157	43	3,355	42	2,578	42	6,817	35	39	43
>40	7,462	14	2,886	15	1,349	17	740	12	2,476	13	11	12
Alcohol intake*												
Nondrinker	49,002	50	16,797	54	5,431	39	7,029	58	19,668	49	77	48
1 drink	29,739	31	8,696	28	4,827	35	3,100	26	13,064	32	52	32
2 or more drinks	14,436	15	4,244	14	2,781	20	1,434	12	5,949	15	28	17
Physical activity, hours in moderate or vigorous activity/d*												
No: 0	7,480	8	2,130	7	653	5	317	3	4,370	11	10	6
Quartile 1: 0.11–0.32 (M); 0.11–0.32 (F)	16,820	17	5,750	18	1,715	12	1,786	15	7,545	19	24	15
Quartile 2: 0.36–0.71 (M); 0.36–0.57 (F)	25,672	26	9,136	29	3,467	25	3,307	27	9,731	24	31	19
Quartile 3: 0.82–1.43 (M); 0.713–1.18 (F)	21,632	22	6,756	22	3,332	24	3,082	26	8,418	21	44	27
Quartile 4: 1.54–13.29 (M); 1.21–13.29 (F)	22,984	24	6,243	20	4,403	32	3,400	28	8,885	22	53	33
Energy intake, kcal/d*												
Quintile 1: 488.85–1,439.49 (M); 425.20–1,175.43 (F)	18,634	19	7,569	24	2,503	18	2,127	18	6,415	16	20	12
Quintile 2: 1,439.66–1,909.07 (M); 1,175.44–1,559.77 (F)	18,630	19	6,003	19	3,171	23	2,905	24	6,514	16	37	23
Quintile 3: 1,909.09–2,432.75 (M); 1,559.81–1,981.89 (F)	18,639	19	5,593	18	2,982	22	2,900	24	7,137	18	27	17
Quintile 4: 2,432.78–3,259.80 (M); 1,981.93–2,658.18 (F)	18,636	19	5,321	17	2,701	20	2,388	20	8,195	20	31	19
Quintile 5: 3,259.86–8,670.39 (M); 2,658.19–7,401.34 (F)	18,638	19	5,251	17	1,682	12	1,243	10	10,420	26	42	26
Red meat intake, g/d*												
Quintile 1: 0–10.02 (M); 0–7.21 (F)	18,636	19	6,661	21	3,367	24	2,284	19	6,308	16	16	10
Quintile 2: 10.02–16.40 (M); 7.21–12.82 (F)	18,635	19	6,168	20	2,921	21	2,546	21	6,963	17	37	23
Quintile 3: 16.40–22.77 (M); 12.82–18.64 (F)	18,632	19	5,920	19	2,618	19	2,612	22	7,451	19	31	19
Quintile 4: 22.77–31.26 (M); 18.64–26.63 (F)	18,643	19	5,878	19	2,242	16	2,436	20	8,047	20	40	25
Quintile 5: 31.26–215.89 (M); 26.64–184.98 (F)	18,631	19	5,110	16	1,891	14	1,685	14	9,912	25	33	20
Processed meat intake, g/d*												
Quintile 1: 0–3.05 (M); 0–1.95 (F)	18,641	19	4,918	16	3,262	24	2,522	21	7,918	20	21	13
Quintile 2: 3.05–5.63 (M); 1.95–3.94 (F)	18,631	19	4,728	15	2,822	21	2,441	20	8,616	21	24	15
Quintile 3: 5.63–8.50 (M); 3.94–6.39 (F)	18,646	19	5,168	17	2,575	19	2,574	21	8,290	21	39	24
Quintile 4: 8.50–13.00 (M); 6.39–10.15 (F)	18,632	19	6,209	20	2,336	17	2,341	19	7,710	19	36	22
Quintile 5: 13.00–172.79 (M); 10.15–122.10 (F)	18,627	19	8,714	28	2,044	15	1,685	14	6,147	15	37	23
Baseline nSES*												
Quintile 1: low	23,346	24	11,167	36	1,085	8	585	5	10,491	26	18	11
Quintile 2	25,021	26	9,077	29	2,159	16	1,479	12	12,284	31	22	14
Quintile 3	19,544	20	4,985	16	2,963	22	2,931	24	8,620	21	45	28
Quintile 4	17,417	18	4,428	14	3,690	27	3,663	30	5,592	14	44	27
Quintile 5: high	11,914	12	1,437	5	3,846	28	3,359	28	3,239	8	33	20

Definition of abbreviations: BMI = body mass index; NSAID = nonsteroidal antiinflammatory drug; nSES = neighborhood socioeconomic status.
*Does not add to 100% because of missing data.

Table 2. Associations of Gaseous and Particulate Matter Air Pollutants and Benzene with Risk of Lung Cancer Overall and by Race/Ethnicity among California Multiethnic Cohort Study Participants, 1993–2013

Air Pollutant	All				African American				European American				Japanese American				Latino American				*P* het by Race/ Ethnicity
	Cases (*n*)	HR	95% CI	*P* Value	Cases (*n*)	HR	95% CI	*P* Value	Cases (*n*)	HR	95% CI	*P* Value	Cases (*n*)	HR	95% CI	*P* Value	Cases (*n*)	HR	95% CI	*P* Value	
NO_X*	2,712	1.15	(0.99–1.33)	0.06	1,210	1.12	(0.92–1.37)	0.25	501	0.87	(0.60–1.27)	0.46	319	0.83	(0.45–1.52)	0.54	678	1.30	(0.89–1.89)	0.17	0.70
NO_2*	2,775	1.12	(0.95–1.32)	0.19	1,272	1.12	(0.89–1.42)	0.33	501	0.82	(0.55–1.23)	0.33	319	1.18	(0.62–2.24)	0.61	679	1.31	(0.84–2.04)	0.24	0.14
PM_{10}*	2,775	0.99	(0.91–1.08)	0.84	1,272	0.95	(0.84–1.06)	0.34	501	0.92	(0.71–1.19)	0.53	319	1.27	(0.83–1.93)	0.27	679	1.11	(0.86–1.44)	0.43	0.71
$PM_{2.5}$†	2,769	**1.20**	**(1.01–1.43)**	**0.04**	1,266	1.12	(0.89–1.41)	0.32	501	1.12	(0.74–1.69)	0.60	318	0.81	(0.39–1.68)	0.57	680	1.15	(0.71–1.86)	0.57	0.82
CO*	2,775	1.29	(0.99–1.67)	0.06	1,272	1.18	(0.84–1.66)	0.35	501	0.71	(0.34–1.51)	0.38	319	0.96	(0.25–3.69)	0.95	679	1.52	(0.68–3.42)	0.31	0.23
O_3*	2,775	**0.85**	**(0.74–0.97)**	**0.02**	1,272	**0.78**	**(0.64–0.95)**	**0.01**	501	1.13	(0.83–1.54)	0.43	319	0.96	(0.49–1.85)	0.89	679	0.89	(0.63–1.26)	0.51	0.11
Benzene	2,678	**1.17**	**(1.02–1.34)**	**0.03**	1,239	1.13	(0.91–1.41)	0.26	468	0.94	(0.69–1.28)	0.68	307	**1.62**	**(1.04–2.52)**	**0.03**	660	1.12	(0.82–1.54)	0.46	0.90

Definition of abbreviations: CI = confidence intervals; HR = hazard ratio; NO_X = nitrogen oxides; *P* het = *P* for heterogeneity; $PM_{2.5}$ = fine particulate matter with aerodynamic diameter <2.5 μm; PM_{10} = fine particulate matter with aerodynamic diameter <10 μm.
HR represent the increase in lung cancer per 50 ppb NO_X, 20 ppb NO_2, 10 mg/m^3 PM_{10}, 10 mg/m^3 $PM_{2.5}$, 1,000 ppb CO, 10 ppb O_3, 1 ppb benzene. Models were adjusted for race/ethnicity (among all), sex, education, marital status, smoking intensity and duration, family history of lung cancer, occupation, neighborhood socioeconomic status, nonsteroidal antiinflammatory drug use, body mass index, drinking, physical activity, energy intake, red meat intake, and processed meat intake with age at cohort entry as the stratum variable. Because of small counts, racial/ethnic-specific associations for Native Hawaiians are not presented. Values in bold represent $P < 0.05$.
*Assessed by kriging interpolation.
†Satellite based.

In this study, we observed higher average concentrations of NO_x, NO_2, PM_{10}, satellite-based $PM_{2.5}$, CO, and benzene among participants residing in low- versus high-SES neighborhoods at baseline, and for an identical unit of NO_x and NO_2 exposure an increased risk of lung cancer was seen in low-SES neighborhoods, whereas no association was seen in high-SES neighborhoods. Neighborhood factors such as the social and community context (e.g., racial and ethnic segregation) may be embodied in psychosocial stress that could influence adverse health outcomes related to air pollution (33). Among neighborhoods with higher proportions of minoritized racial and ethnic groups, built environment factors (e.g., proximity to truck routes, ports, storage, warehouses, poor housing quality) may increase coexposure of other environmental factors (e.g., unmeasured air toxics) that may have synergistic adverse air pollution–related health effects.

Air pollution is a heterogeneous mixture that includes gaseous pollutants, PM, and air toxics from a variety of sources. From this complex mixture, it is a challenge to dissect any effects of individual pollutants, given their high degree of correlation and the commonality of sources. Consequently, we interpret the observed associations with the various air pollutants as reflecting a general association between lung cancer and traffic-related air pollution, not any particular pollutant. Our hazard ratio estimate for satellite-based $PM_{2.5}$ per 10 μg/m^3 (HR, 1.20; 95% CI, 1.01–1.43) was generally similar to the meta-analysis estimate (HR, 1.16; 95% CI, 1.09–1.23) for $PM_{2.5}$ and lung cancer risk that was obtained from 15 cohort studies published since 2004 that accounted for smoking and socioeconomic status (2). The positive association with nitric oxide assessed by kriging interpolation supports the influence of traffic-related air pollutants, as it represents a key ambient marker of urban air pollution produced predominantly and directly by fuel combustion (34). Our HR estimates, scaled to per 10 μg/m^3 NO_X (HR, 1.02; 95% CI, 1.00–1.04) and NO_2 (HR, 1.03; 95% CI, 0.99–1.08), were similar to the 3% and 4% increased risks of lung cancer, respectively, reported by a large meta-analysis (4). Similar increased risk associations with CO were reported in prior studies of lung cancer mortality (5). In conjunction with the increased risk associations we observed for regional benzene, the associations with various

Table 3. Associations of Gaseous and Particulate Matter Air Pollutants and Benzene with Risk of Lung Cancer by Neighborhood Socioeconomic Status among California Multiethnic Cohort Study Participants, 1993–2013

Air Pollutant	Low nSES (Quintiles 1–3)				High nSES (Quintiles 4–5)				*P* het by nSES
	Cases (*n*)	HR	95% CI	*P* Value	Cases (*n*)	HR	95% CI	*P* Value	
NO_X*	1,953	**1.20**	**(1.01–1.43)**	**0.03**	757	1.01	(0.76–1.34)	0.94	0.31
NO_2*	2,003	1.20	(0.97–1.47)	0.09	770	1.00	(0.75–1.35)	0.98	0.39
PM_{10}*	2,003	0.99	(0.88–1.10)	0.80	770	1.01	(0.86–1.19)	0.88	0.76
$PM_{2.5}$†	2,000	1.23	(0.99–1.53)	0.06	767	1.14	(0.86–1.52)	0.36	0.71
CO*	2,003	1.31	(0.97–1.78)	0.08	770	1.20	(0.72–2.00)	0.50	0.80
O_3*	2,003	**0.80**	**(0.68–0.95)**	**0.01**	770	0.99	(0.75–1.29)	0.91	0.21
Benzene	1,959	1.20	(1.00–1.43)	0.05	717	1.14	(0.91–1.43)	0.26	0.77

Definition of abbreviations: CI = confidence intervals; HR = hazard ratio; NO_X = nitrogen oxides; nSES = neighborhood socioeconomic status; *P* het = *P* for heterogeneity; $PM_{2.5}$ = fine particulate matter with aerodynamic <2.5 μm; PM_{10} = fine particulate matter with aerodynamic diameter <10 μm. HR represent the increase in lung cancer per 50 ppb NO_X, 20 ppb NO_2, 10 mg/m^3 PM_{10}, 10 mg/m^3 $PM_{2.5}$, 1,000 ppb CO, 10 ppb O_3, 1 ppb benzene. Models were adjusted for race/ethnicity (among all), sex, education, marital status, smoking intensity and duration, family history of lung cancer, occupation, neighborhood socioeconomic status, nonsteroidal antiinflammatory drug use, body mass index, drinking, physical activity, energy intake, red meat intake, and processed meat intake with age at cohort entry as the stratum variable. Because of small counts, racial/ethnic-specific associations for Native Hawaiians are not presented. Values in bold represent $P < 0.05$.
*Assessed by kriging interpolation.
†Satellite based.

combustion-related pollutants jointly underscore the importance of traffic, as CO and benzene are largely emitted by gasoline-powered vehicles and show large concentration declines with distance from roadways (35). On a mechanistic basis, CO itself would not contribute to carcinogenicity, but it is a specific indicator of traffic-related air pollution (36, 37). We recognize the temporal decline in CO and benzene concentrations during the study period in Los Angeles (38, 39), which has been captured by using time-varying exposure estimates. In a subgroup analysis with available $PM_{2.5}$ species (black carbon, sulfate, and nitrate) information for the period 2000–2013, we observed a suggestive positive association with black carbon only (HR, 1.09; 95% CI, 0.99–1.21; $P = 0.09$). This supports our positive associations with CO and benzene and the role traffic-related air pollution plays in lung cancer risk.

Prior investigations of benzene and lung cancer have largely focused on occupational exposures to benzene (40). In a Canadian case–control study of lung cancer, outdoor ambient benzene was based on a land use regression model, and the estimated odds ratio was 1.84 (95% CI, 1.26–2.68) per 0.15 μg/m^3 (0.05 ppb) increase in benzene after adjusting for demographics, secondhand smoke, BMI, and family history of cancer (41). Our findings add further support for an increased risk of lung cancer associated with outdoor ambient benzene exposure. Although benzene is a well-known leukemogen found in cigarette smoke and gasoline, the finding of an association with regional benzene exposure (per 1 ppb) was seen both in current smokers (HR, 1.25) and never-smokers (HR, 1.28), supporting the importance of benzene as one of the most common traffic-related air pollutants in the environment.

The inverse association we observed with O_3 is likely attributable to the negative correlation between O_3 and NO_X concentrations due to the photochemical reaction between O_3 and nitric oxide (42), thus also reflecting the NO_X association and marking traffic as a source of inhaled carcinogens. The lack of an association with LUR NO_X may reflect the use of a model developed in 2006–2007 with temporal adjustment that may not capture sufficiently local traffic pollutants during the 1990s, an exposure period likely relevant for our study population given the long latency period of lung cancer.

Although we observed the adverse impacts of traffic-related air pollution on the risk of lung cancer mainly in the metropolitan Los Angeles area, we should not ignore the impact of other fossil-fuel sources, such as the burning of coal in other parts of the world. Coal is more widely used in generating energy in developing countries (43, 44). Coal smoke has been consistently associated with lung cancer risk (45), and the reliance on coal as an energy source has been linked to lung cancer risk in an analysis based on data from 83 countries (46).

The absence of an association with krigged $PM_{2.5}$ may be explained by misclassification in exposure assessment for historical $PM_{2.5}$ concentrations (1993–1999), for which $PM_{2.5}$ concentrations were modeled based on measured PM_{10} together with meteorological and spatial data in the absence of measured $PM_{2.5}$ data (26) and further spatially interpolated by krigging. This is particularly relevant given the long latency period of lung cancer of 10–30 years (47), for which accurate historical concentrations of $PM_{2.5}$ are important. The associations we identified between satellite-based $PM_{2.5}$ and lung cancer risk speak to the more refined exposure assessment across the entire study period from 1993–2013 with the use of chemical transport modeling coupled with satellite- and ground-based data (27).

Several biological mechanisms by which air pollutants influence carcinogenesis have been proposed. Combustion-related air pollution includes mutagens such as polycyclic aromatic hydrocarbons that have been linked to DNA damage in the formation of polycyclic aromatic hydrocarbon–DNA adducts (48). Higher concentrations of DNA adducts in white blood cells have been observed among subjects who were more heavily exposed to air pollution (49). In addition, DNA adduct concentrations in lung tissues have correlated well with concentrations in white blood cells among patients with lung cancer (48, 50–52). Air pollutants have also been

Table 4. Associations of Gaseous and Particulate Matter Air Pollutants and Benzene with Risk of Lung Cancer by Smoking Status among California Multiethnic Cohort Study Participants, 1993–2013

Air Pollutant	Never-Smokers				Former Smokers				Current Smokers				*P* het by Smoking Status
	Cases (*n*)	HR	95% CI	*P* Value	Cases (*n*)	HR	95% CI	*P* Value	Cases (*n*)	HR	95% CI	*P* Value	
NO_X*	337	1.40	(0.88–2.22)	0.15	1,056	1.14	(0.91–1.42)	0.26	1,319	1.14	(0.92–1.41)	0.24	0.43
NO_2*	346	1.33	(0.80–2.22)	0.28	1,078	1.14	(0.88–1.48)	0.32	1,351	1.12	(0.88–1.44)	0.36	0.17
PM_{10}*	346	1.01	(0.77–1.33)	0.96	1,078	1.02	(0.89–1.17)	0.77	1,351	1.00	(0.88–1.14)	0.98	0.31
$PM_{2.5}$†	345	0.86	(0.54–1.38)	0.53	1,076	1.10	(0.84–1.43)	0.48	1,348	1.21	(0.94–1.56)	0.14	0.97
CO*	346	1.17	(0.51–2.68)	0.72	1,078	1.38	(0.93–2.07)	0.11	1,351	1.36	(0.92–1.99)	0.12	0.97
O_3*	346	0.77	(0.49–1.21)	0.26	1,078	0.92	(0.75–1.14)	0.45	1,351	**0.81**	**(0.66–0.99)**	**0.04**	0.78
Benzene	337	1.28	(0.86–1.91)	0.22	1,035	1.07	(0.87–1.32)	0.52	1,306	**1.25**	**(1.01–1.54)**	**0.04**	0.99

For definitions of abbreviations, *see* Table 2.

HR represent the increase in lung cancer per 50 ppb NO_X, 20 ppb NO_2, 10 mg/m^3 PM_{10}, 10 mg/m^3 $PM_{2.5}$, 1,000 ppb CO, 10 ppb O_3; 1 ppb benzene. Models were adjusted for race/ethnicity, sex, education, marital status, family history of lung cancer, occupation, neighborhood socioeconomic status, nonsteroidal antiinflammatory drug use, body mass index, drinking, physical activity, energy intake, red meat intake, and processed meat intake with age at cohort entry as the stratum variable. For former and current smokers, smoking intensity and duration were also included for adjustment. Smoking status assessed at baseline. Values in bold represent $P < 0.05$.

*Assessed by kriging interpolation.

†Satellite based.

linked to increased inflammation (53) and oxidative stress (54) that involves the release of reactive oxygen species and proinflammatory cytokines, leading to tissue and organ damage (55, 56). In addition, epigenetic changes in DNA methylation and accelerated epigenetic aging may be a possible mechanism (57) by which air pollution influences lung cancer development.

The strengths of this study include its racially, ethnically, and socioeconomically diverse study population. In addition, we assessed long-term air pollutant exposures, covering a study period of up to 21 years with detailed residential histories that allowed us to capture time-varying exposures. With the extensive questionnaire data, we were able to account for detailed repeated smoking behaviors relevant for lung cancer incidence.

There are limitations to our study that warrant consideration. We did not have information on ambient air pollutant exposures aside from residential locations (e.g., no information about work, transportation, or outdoor exposures other than at residences) or indoor exposures. Although we were able to account for neighborhood- and individual-level (i.e., education) SES, we did not have information on other individual-level measures of SES (e.g., income) and did not evaluate other measures of structural and social determinants of health. In addition, we did not have detailed occupational information that could result in some residual confounding in our results. We had limited sample size for some subgroup analyses that may have reduced the power to detect heterogeneity in effects. We recognize the possibility of chance findings given the number of comparisons made, and the multiple comparison framework of Goldberg and Silbergerld (58) can be applied to evaluate our findings. Given the multiplicity of carcinogens in PM in outdoor air, a specific PM component is unlikely to be responsible for the carcinogenicity of PM (59). Nevertheless, further studies to evaluate additional $PM_{2.5}$ species may be informative and refine our understanding of the pathogenesis related to air pollution.

We recognize the importance of measurement error in our exposure assessment of air pollutants, a well-recognized issue with model-based exposure estimates (60, 61). In a sensitivity analysis,

we inversely weighted average exposures by the average standard error and found slightly larger effect sizes and narrower confidence intervals, indicating stronger associations after we took into consideration exposure measurement error (data not shown). In addition, we expect that measurement error would not be differential by case status. Stram and colleagues (62) showed that score tests for nonzero effects were not altered when corrected for nondifferential measurement error. Therefore, estimates significant before error correction will not be declared nonsignificant after error correction.

In conclusion, this study provides further evidence of the adverse effects of traffic-related air pollutants on lung cancer incidence in a large multiethnic population, with suggestive findings of greater harms in low-SES neighborhoods. This work calls for strengthening environmental regulations and focused studies of the underlying structural and social determinants of health contributing to environmental health inequities. ■

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