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The Association Between Ambient Air Pollutants and Pancreatic Cancer in the Multiethnic Cohort Study

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Abstract

Background: Prior studies examining the association between ambient air pollutants and pancreatic cancer have been conducted in racially/ethnically homogeneous samples and have produced mixed results, with some studies supporting evidence of an association with fine particulate matter.

Methods: To further investigate these findings, we estimated exposure levels of particulate matter ($PM_{2.5}$, PM_{10},) and oxides of nitrogen (NO_X, and NO_2) using kriging interpolation for 100,527 men and women from the Multiethnic Cohort Study, residing largely in Los Angeles County from 1993 through 2013. We measured the association between these air pollutants and incident pancreatic cancer using Cox proportional hazards models with time-varying pollutant measures, with adjustment for confounding factors.

Results: A total of 821 incident pancreatic cancer and 1,660,488 person-years accumulated over the study period, with an average follow-up time of over 16 years. $PM_{2.5}$ (per 10 μg/m^3)

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

was associated with incident pancreatic cancer (hazard ratio [HR] = 1.61; 95% CI, 1.09, 2.37). This $PM_{2.5}$ -association was strongest among Latinos (HR = 3.59; 95% CI, 1.60, 8.06) and ever smokers (HR = 1.76; 95% CI, 1.05, 2.94). There was no association for PM_{10} (HR = 1.12; 95% CI, 0.94, 1.32, per 10 μg/m^3), NO_X (HR = 1.14; 95% CI, 0.88, 1.48, per 50 ppb), or NO_2 (HR = 1.14; 95% CI, 0.85, 1.54, per 20 ppb).

Conclusions: Our findings support prior research identifying an association between fine particulate matter, $PM_{2.5}$, and pancreatic cancer. Although not statistically heterogeneous, this association was most notable among Latinos and smokers. Future studies are needed to replicate these results in an urban setting and in a racially/ethnically diverse population.

Keywords

Pancreatic Cancer; PDAC; Air Pollution; $PM_{2.5}$; Multiethnic

Introduction:

Pancreatic cancer is now the fourth leading cause of cancer-related death in the United States (Siegel et al. 2019), accounting for over 56,000 new cases and 45,000 pancreatic cancer deaths in 2019 (Siegel et al. 2019). Pancreatic cancer is projected to be the second leading cause of cancer death by 2040 (Rahib et al. 2021). A dismal five year survival of nine percent stems from the lack of effective screening for this disease (Kardosh et al. 2018; Siegel et al. 2019) and the high proportion (~80%) of pancreatic cancer diagnosed at a late stage. These characteristics highlight the importance of identifying modifiable personal and environmental risk factors that can be used in primary prevention strategies.

The burden of pancreatic cancer varies across racial/ethnic groups; the incidence is highest in African Americans and lowest in whites and Latinos (Liu et al. 2019), but incidence rates are elevated among Native Hawaiians and Japanese Americans in the Multiethnic Cohort (MEC) (Huang et al. 2019). Numerous factors, most notably, smoking (Huang et al. 2019; Lynch et al. 2009), type 2 diabetes (Batabyal et al. 2014; Huang et al. 2019), diet quality (Arem et al. 2013), body mass index (BMI) (Arslan et al. 2010; Aune et al. 2012; Huang et al. 2019), and common genetic variants (Bogumil et al. 2020) have been associated with pancreatic cancer risk.

In 2013, the International Agency for Research on Cancer classified outdoor air pollution, which includes $PM_{2.5}$, as a carcinogen for humans based largely on evidence for lung cancer (*International Agency for Research on Cancer (IARC) monographs on the evaluation of carcinogenic risks to humans: outdoor air pollution* 2016). However, the evidence for pancreatic cancer is still sparse with inconsistent results (Ancona et al. 2015; Coleman et al. 2020; Turner et al. 2017; Wang et al. 2018) from four mortality cohort studies, conducted in the United States (Coleman et al. 2020; Turner et al. 2017), Italy (Ancona et al. 2015), and China (Wang et al. 2018). Three studies, including one prospective cohort (Turner et al. 2017) and two retrospective cohorts (Coleman et al. 2020; Wang et al. 2018) investigated the role of particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$) as the exposure, and one study (Ancona et al. 2015) examined the role of particulate matter less than 10 μm (PM_{10}). Exposure to $PM_{2.5}$ was not associated with risk of pancreatic cancer in

both US studies (Coleman et al. 2020; Turner et al. 2017) but was positively associated with risk in a Chinese study (hazard ratio = 1.16, 95% CI: 1.13, 1.20, per 10 μg/m^3) (Wang et al. 2018); PM_{10} was also associated with risk of pancreatic cancer in an Italian study (Ancona et al. 2015). These mixed results may be related, in part, to study population differences (including number of pancreatic cancer cases), differences in air pollutants investigated, not using time-varying exposure measures (Coleman et al. 2020), and limited confounder control (Ancona et al. 2015; Wang et al. 2018).

In this study, we examined the association between ambient air pollutants ($PM_{2.5}$, PM_{10}, nitrogen dioxide (NO_2), and nitrogen oxides (NO_X)) and pancreatic cancer risk in a racially/ethnically diverse population, while accounting for the limitations seen in prior studies.

Materials and Methods

Study Participants

The MEC is a population-based, prospective cohort of over 215,000 men and women in California and Hawaii. Details of the cohort and enrollment have previously been described (Kolonel et al. 2000). Study participants were identified using the Department of Motor Vehicles, voter registration lists, and Health Care Financing Administration files. Enrollment occurred between 1993 and 1996. Participants were between 45 and 75 years old at the time of enrollment and were from one of five major racial/ethnic groups (African American, Japanese American, Latino, Native Hawaiian and white). Covariate information was obtained via a mailed baseline questionnaire to collect data on demographics, diet, smoking and other lifestyle factors, anthropometric measures, and reproductive history (among women). This analysis was restricted to MEC participants who resided in Southern California, largely Los Angeles County, at study enrollment through follow-up.

Incident pancreatic cancers were identified through annual linkage to the California Cancer Registry, part of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. Pancreatic cancer was identified using ICD-O-3 site codes C25.0–C25.9. Vital status and cause of death were obtained through linkage to the National Death Index and state death certificate files. A total of 100,527 Southern California MEC participants were our population at risk as they completed the baseline questionnaire, reported a valid address that could be geocoded at the parcel or street segment level across the study period, had valid estimates of air pollutant levels (Cheng et al. 2019), and did not have pancreatic cancer prior to cohort entry (Supplementary Figure 1). There were 821 incident pancreatic cancer cases over the study period.

Address history

The details of address history, geocoding, and neighborhood SES (nSES) data for MEC participants have been described in a previous publication (Cheng et al. 2019). In brief, current and past address information is recorded for MEC participants based on periodic mailings of newsletters, follow-up questionnaires, administrative data linkages, and registry linkages. Using this information, participant addresses were geocoded to land parcels or street segments over the study period (1993–2013). Invalid address records were excluded if

the end time of a residence was prior to study start date or the start time of a residence was after the study end date. Geocoded addresses were then linked to U.S. Census block groups based on the year. Based on the block group and residential address history at baseline and time of censorship, each participant was assigned a composite measure of nSES which was then categorized into quintiles based on the nSES distribution of Los Angeles County.

Exposure Assessment

Kriging interpolation was used to estimate each participant's exposure levels for $PM_{2.5}$, PM_{10}, NO_2, and NO_X (Wu et al. 2020; Cheng et al. 2019). Kriging uses spatial interpolation to estimate exposure levels given spatiotemporally measured air pollutant levels from monitoring stations and location of residence. Measured concentrations were obtained from the U.S. Environmental Protection Agency routine air monitoring data. NO_2, NO_X, and PM_{10} were available for the years 1993–2013, and $PM_{2.5}$ from 2000 to 2013. $PM_{2.5}$ concentrations for the years prior to 2000 were estimated using a spatiotemporal model that uses PM_{10} measurements, meteorological factors, and spatiotemporal characteristics to extrapolate $PM_{2.5}$ values in California (L. Li et al. 2017). In the cases of incomplete address records or incomplete air pollution data, exposure levels were imputed using last known estimates (Cheng et al. 2019). Participants with more than 50% imputed data were removed from analysis.

Statistical Analysis

We used Cox regression to examine the association between each air pollutant and incident pancreatic cancer. Due to variation in air pollutant levels over time, time-varying exposure variables were used to estimate time-weighted monthly average pollutant levels for each participant-month. We used participants' age in months as the timescale for this analysis and defined a series of risk sets based on month at diagnosis of each pancreatic cancer event (index case). Using age as a timescale for analysis of cohort study designs has been shown to produce least biased measures of association (Cologne et al. 2012; Korn et al. 1997) and adjusts for the effects of age in model fitting. Each risk set consisted of all MEC participants who remained alive and uncensored at the age of the pancreatic cancer diagnosis. For each member of the risk set (including the index case), we computed the average exposure from the time of cohort entry (month/year) up to the time that the risk set member reached the age of the index case based on each participant's residential history. Participants were censored at time of pancreatic cancer diagnosis, death, or end of follow-up (Dec 31, 2013). In the case of tied event times, the Efron approximation was used.

Variables considered for inclusion in analysis were age at cohort entry (<50, 50–54, 55–59, 60–64, 65–69, >70), sex (male, female), diabetes status at baseline (yes, no), body mass index (BMI) at baseline (<25, 25–29, >30 kg/m^2, missing), smoking status at baseline (never, former smokers ≥ 20 pack-years, former smokers < 20 pack-years, current smokers <20 pack-years, current smokers ≥ 20 pack-years, missing, current smokers- unknown pack-year, former smokers -unknown pack-year), birth year (1918–1922, 1923–1927, 1928–1932, 1933–1937, 1938–1942, 1943–1948), nSES at baseline and at censorship (quintiles: Q1 (lowest), Q2, Q3, Q4, Q5(highest), missing).

The proportional hazards assumption for all covariates was assessed using a test of correlation between Schoenfeld residuals and time. All models were adjusted for race/ethnicity, BMI, nSES at enrollment, nSES at censorship, and age at cohort entry. We stratified models by smoking and diabetes status due to the violation of the proportional hazards assumption for these variables (Supplementary Table 1). In addition to the primary analyses we conducted a series of sensitivity analyses to assess the robustness of the results. First, we tested models that included the Alternative Healthy Eating Index (AHEI) 2010 diet score, alcohol consumption, and occupational history. We then considered stratification on age at cohort entry to allow for differing baseline hazards across entry age to assess for possible cohort effects by birth year (Korn et al. 1997). Next, we tested models that did not include the first five years of follow-up to account for higher levels of measurement error of time-weighted average measures at the beginning of the study. We then examined the alternative relationships between air pollutants and pancreatic cancer, such as quartile categories and the inclusion of quadratic terms of the air pollutant measures as a test for non-(log) linearity. Finally, we tested NO_2-adjusted models for PM_{10}, and $PM_{2.5}$. We found little difference in associations of our main effect in these sensitivity analyses, so we only present our initial model results.

A unit change was selected for each pollutant based on what is most commonly reported in epidemiologic studies, which for most pollutants are similar to the interquartile range of each pollutant measure ($PM_{2.5}$: 10 μg/m^3, PM_{10}: 10 μg/m^3, NO_X: 50 ppb, NO_2: 20 ppb) (Cheng et al. 2019). Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were reported for each pollutant for all subjects combined. Additionally, we present stratified results and tests of heterogeneity by sex, race/ethnicity, smoking status, moving status (whether participants changed address over the study period), BMI, and nSES at baseline. Heterogeneity p-values were generated using product terms between pollutant levels and each stratification variable, while allowing for separate baseline hazards for each strata level.

Results

This analysis was based on 100,527 CA MEC participants totaling 1,660,488 person-years, and an average follow-up time of over 16 years. The largest portion of participants were Latinos (42.4%), followed by African Americans (31.9%), whites (13.6%), and Japanese Americans (12.1%) (Table 1). African-American and Japanese American participants tended to be older. Latino and African-American participants had the highest prevalence of diabetes and obesity. Across groups, Latinos had the highest time-weighted average exposure levels for $PM_{2.5}$, PM_{10}, and NO_2 over the study period. Inspection of the air pollutant concentration distributions showed no abnormal patterns.

$PM_{2.5}$ exposure was associated with risk of pancreatic cancer (HR = 1.61; 95% CI, 1.09, 2.37, per 10 μg/m^3; Figure 1). We observed some differences in effect sizes across stratification variables but none were significantly heterogeneous. For example, in analyses by race/ethnicity, the association was strongest among Latinos (HR = 3.59; 95% CI, 1.60, 8.06). Risk estimates were similar in men and women although the association was statistically significant in women only (HR = 1.67; 95% CI, 1.01, 2.74). The association

with $PM_{2.5}$ was somewhat stronger in ever smokers (HR = 1.76; 95% CI, 1.05, 2.94), participants who moved during the study period (HR = 1.80; 95% CI, 1.12, 2.89), and in the middle BMI category (BMI 24–29 HR = 2.15, 95% CI, 1.15, 4.04).

The results were similar in a fully adjusted model which also considered work history, AHEI 2010, alcohol consumption, in the models with the first 5 years of follow-up time removed from analysis, and in the NO_2-adjusted model. The quartile-based categorical models also showed the continuous measure of $PM_{2.5}$ to properly capture the association between the air pollutant and pancreatic cancer risk (results not shown). There was a slight attenuation of the association with $PM_{2.5}$ when treating age at cohort entry as a strata variable rather than as a covariate (HR = 1.44; 95% CI, 0.95, 2.17).

We did not find an association between PM_{10} and pancreatic cancer risk (HR = 1.12; 95% CI, 0.94, 1.32, per 10 $\mu g/m^3$; Figure 1) in men and women combined. However, there was an elevated risk among Latinos (HR = 1.45; 95% CI, 1.00, 2.09, race/ethnicity p-heterogeneity = 0.48). Risk of pancreatic cancer was not significantly associated with exposure to NO_X and NO_2 (NO_X HR = 1.14; 95% CI, 0.88, 1.48, per 50 ppb; NO_2 HR = 1.14; 95% CI, 0.85, 1.54, per 20 ppb; Figure 2), but there was a suggested association between risk and NO_X exposure among Latinos (HR = 1.72; 95% CI, 1.00, 2.94).

Discussion

This is the first prospective study to examine the association between ambient air pollutants and pancreatic cancer risk in a multiethnic population using time varying exposures. Our most notable finding was the significant association between $PM_{2.5}$ and pancreatic cancer risk. There was no significant association between pancreatic cancer and PM_{10} or gaseous pollutants. Although there was no significant heterogeneity in subgroup analyses, a suggestion of stronger risk associations among Latinos, the largest ethnic subgroup in this study, was evident.

Our finding for $PM_{2.5}$ adds to the accumulating body of evidence supporting PM as a risk factor for pancreatic cancer. The association between $PM_{2.5}$ and pancreatic cancer mortality was investigated in three prior studies, with effect estimates ranging from 0.95, per 10 $\mu g/m^3$, in the Cancer Prevention Study II (Turner et al. 2017), to 1.16 using national mortality data from China (Wang et al. 2018), and 1.09 in the US using National Health Interview Survey data (Coleman et al. 2020). “Near-source” associations from the CPSII, where pollutant levels were estimated using land-use regression, were slightly more similar to what is seen in our current, and in prior, studies (HR = 1.44, 95% CI: 1.00, 2.15, per 10 $\mu g/m^3$) (Turner et al. 2017).

Although kriging is a commonly used method to estimate air pollution exposure levels, prior studies have used different methods of pollutant estimation making it more difficult to compare results. Turner et al., used a modified land use regression (LUR) model that incorporates roadways and greenspace surrounding air monitoring stations as well as Bayesian interpolation of spatiotemporal residuals to estimate national $PM_{2.5}$ measures (Turner et al. 2017). The Bayesian interpolation component of the model adds a level of

robustness to $PM_{2.5}$ estimation; however, a high density of monitoring stations is needed to produce the best measures. Wang et al, estimated district-level pollutant concentrations using satellite-based estimates, ground measurements, and chemical transport simulations (Wang et al. 2018). This is a more recently developed method of air pollutant estimation and is limited in distinguishing between pollutant types (Jerrett et al. 2005). Satellite-based estimates are more commonly used for large or remote regions, likely used in this study due to the large-scale and remote regions of China. In contrast to both LUR and satellite-based estimates, kriging relies only on measured values to estimate concentrations at participant's addresses and does not incorporate factors such as land use or geography. The exclusion of these factors may harm pollutant concentration estimation in cases where data monitoring stations are sparse. However, in our study, the U.S. EPA Air Quality System has a high density of monitoring stations in Southern California, where most MEC participants resided in this study.

Differences in air pollutant levels across these studies in addition to air pollutant estimation methods may explain some variation in results. The highest $PM_{2.5}$ levels reported in some regions in China by Wang et al., were over 10 times the average concentrations we observed (Wang et al. 2018). Similarly, in both the Cancer Prevention Study II and in the National Health Interview Study (Turner et al. 2017; Wang et al. 2018), estimated $PM_{2.5}$ concentrations were, on average, slightly lower than what we observed in the MEC, largely in the Los Angeles area. Less variation or lower concentrations of $PM_{2.5}$ may prevent some studies from identifying an association. In addition to variation in pollutant levels, the chemical composition of $PM_{2.5}$ is known to vary globally, and within the United States (Harrison et al. 2000). Since both prior US-based studies had similar follow-up dates to ours the differing associations may be due to regional $PM_{2.5}$ composition.

In this study, we observed variation in pollutant associations by race/ethnicity. Notably, the associations for PM_{10} and $PM_{2.5}$ were strongest among Latinos, however a test of heterogeneity showed no statistically significant difference between ethnic groups. It is possible the increased concentrations of these exposures among Latinos may result from a greater portion of Latinos living proximate to major roads (Wu et al. 2020). Although additional adjustment for occupation did not attenuate results, residual confounding by occupation may positively bias the association within this racial/ethnic group.

It is unclear how $PM_{2.5}$ affects risk of pancreatic cancer, as most cancer research of air pollutants has focused on lung cancer. Particle size likely plays a role in the mechanism. The larger particle sizes, PM_{10}, were not associated with pancreatic cancer risk in this study. Since $PM_{2.5}$ is a characteristic of the particle size, the composition can vary. The major components of $PM_{2.5}$ that are likely most relevant to cancer etiology are organic compounds, metals, and polycyclic aromatic hydrocarbons (PAH) (Harrison et al. 2000; Philip et al. 2014). These compounds may affect cancer risk through increasing oxidative stress and inflammation, as observed in the airways (Zhang et al. 2016), and formation of DNA adducts (Demetriou et al. 2015). In addition to these commonly discussed hypotheses, there are two mechanisms more specific to the pancreas. Firstly, air pollution may increase risk of pancreatic cancer through heavy metal accumulation in the pancreas. Metals from tobacco smoke are known to accumulate in the body through inhalation and absorption through the

lungs or from swallowing during mucociliary clearance. Smokers and non-smokers with pancreatitis and pancreatic cancer are shown to have elevated concentrations of heavy metals in the pancreas (Carrigan et al. 2007; Amaral et al. 2012), likely due to smoking and other environmental or occupational exposures. These findings support the stronger association we observe among smokers in the $PM_{2.5}$ analysis which may be due to the synergistic effect of smoking on metal accumulation and exposure to $PM_{2.5}$-bound PAHs. Although the bioaccumulation of metals from air pollutants may increase the risk of pancreatic cancer, this has only been studied in the context of smoking, occupational exposures, and animal studies (Barone et al. 2016; Amaral et al. 2012).

Second, air pollution may increase the risk of diabetes mellitus which may, in turn increase risk of pancreatic cancer, however it is still unclear to what degree air pollutants affect diabetes (Y. Li et al. 2019). One meta-analysis estimates a 10% increase in risk (HR = 1.10, 95% CI: 1.02, 1.18) of incident type 2 diabetes per 10 $\mu g/m^3$ increase in concentration of $PM_{2.5}$ (Eze et al. 2015).

There are several strengths to this study. First, since the MEC is composed of a racially/ethnically diverse population, we were able to measure the association between air pollution and pancreatic cancer in the multiethnic population and stratified by ethnic/racial group. Second, multiple prior studies did not have participant address information for estimation of air pollutants and, as the result, used region-level pollutants for each participant (Coleman et al. 2020; Wang et al. 2018). In this study we used participants' geocoded addresses across their residential histories to better capture exposure variation and allow for a more precise estimate of each participant's exposure levels. No prior study included updated residential addresses (Ancona et al. 2015; Coleman et al. 2020; Turner et al. 2017). Finally, we were able to include a comprehensive list of potential confounders in our analyses.

There are also some limitations to this study. First, we lacked exposure information for participants prior to enrollment, and at each participant's workplace. In a large National Human Activity Pattern Survey study, it was estimated that Californians spent less than 70% of their time at home (Klepeis et al. 2001) and that around 6% of their day was spent in an enclosed vehicle (Klepeis et al. 2001), which may confer pollutant exposure levels that vary by vehicle type (Cepeda et al. 2017). Measurement error from these sources may result in non-differential information bias, as method of commute may be associated with air pollution levels at residence and pancreatic cancer, through unmeasured confounders; however, it is not possible to identify the degree to which differential bias (non-random error) is affecting results without information on commuting and work-related pollution exposures (Jurek et al. 2008). Second, although pollutant estimates were updated monthly, covariate information used baseline measures and changes in covariate levels over time were not accounted for in analysis.

In conclusion, using kriging estimates of time-varying air pollutants exposure, we identified an association between pancreatic cancer and $PM_{2.5}$ levels in a multiethnic cohort of Southern California residents. This association was strongest among Latinos, which may likely be due to increased exposure levels. Compared to previous studies showing a significant association with $PM_{2.5}$, we observed a larger risk estimate. Due to the variation in

published results, additional studies using prospective cohorts with time-varying measures of pollutant levels and comprehensive confounder control are needed to confirm the association of particulate matter with pancreatic cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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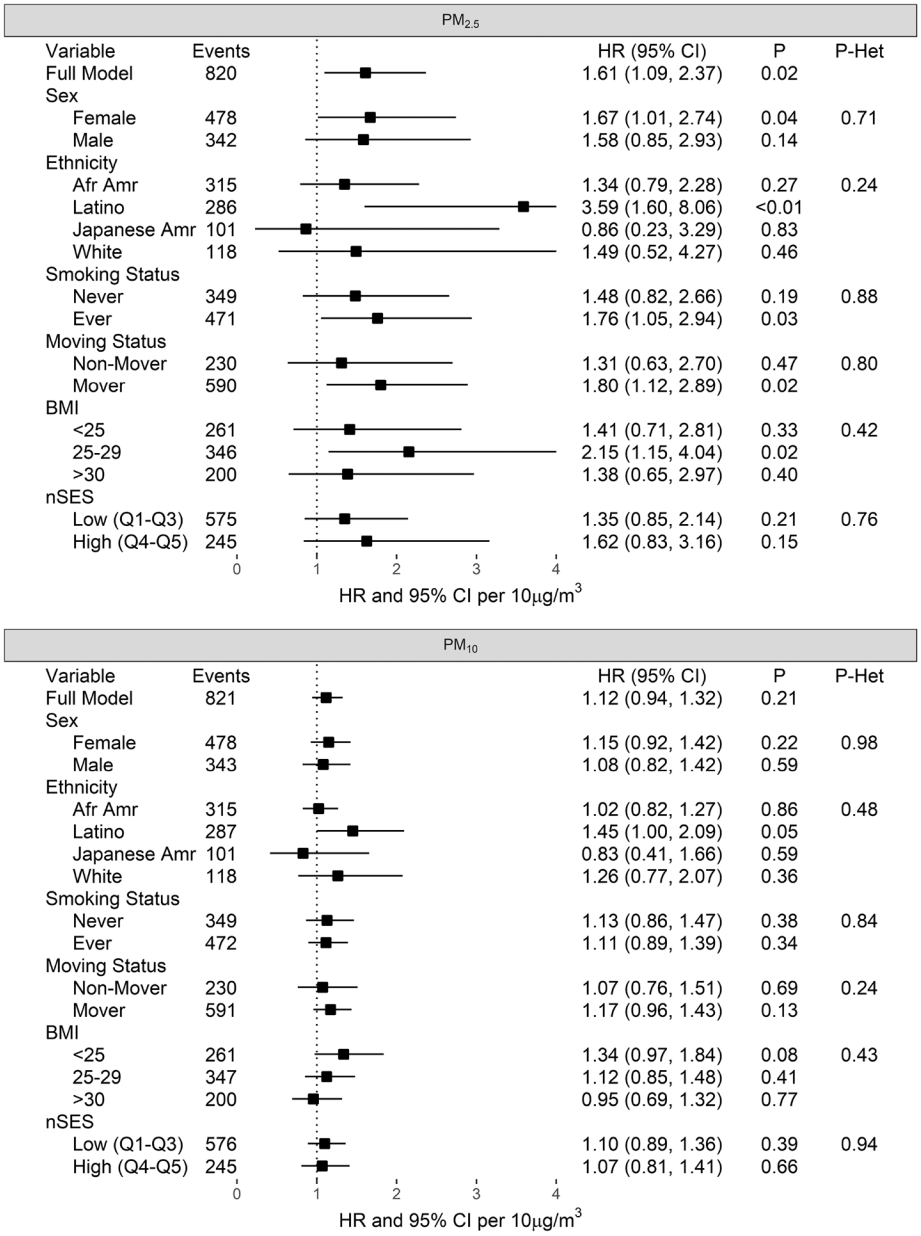

Figure 1: Association between Particulate Matter and Pancreatic Cancer

Abbreviations: Afr Amr: African American; BMI: Body mass index (kg/m^2); Japanese Amr: Japanese American; HR: Hazard ratio and corresponding 95% confidence interval; nSES: Neighborhood socioeconomic status; p: p-value for test for hazard ratio=1; p-het: p-value for test of heterogeneity of stratification variables.

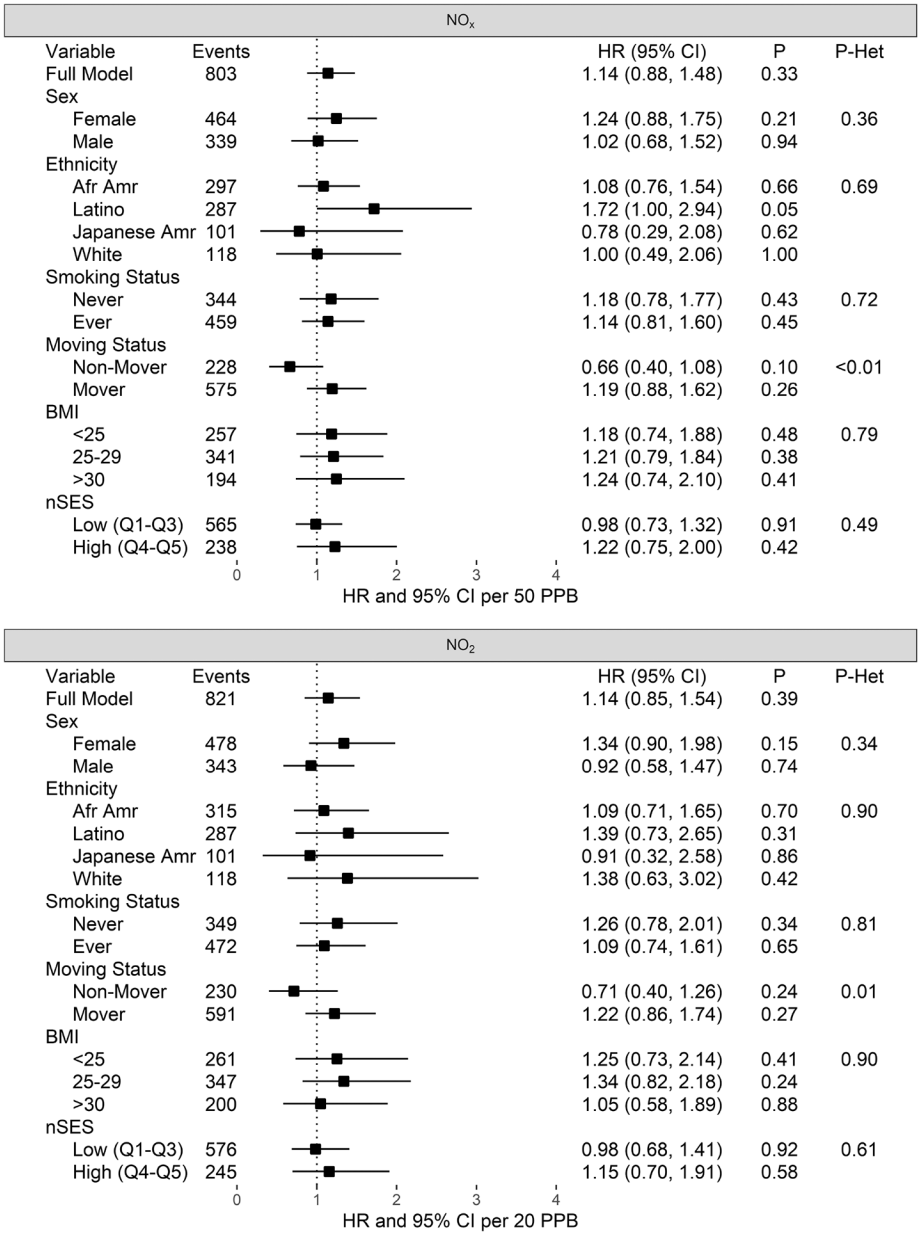

Figure 2: Association between Nitrogen Dioxide, Nitrogen Oxides, and Pancreatic Cancer

Abbreviations: Afr Amr: African American; BMI: Body mass index (kg/m^2); Japanese Amr: Japanese American; HR: Hazard ratio and corresponding 95% confidence interval; nSES: Neighborhood socioeconomic status; p: p-value for test for hazard ratio=1; p-het: p-value for test of heterogeneity of stratification variables.

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Table 1:

Cohort Baseline Characteristics

	Combined (n = 100,527)		Latino (n = 42,647)		African American (n = 32,038)		White (n = 13,663)		Japanese American (n = 12,179)	
	n	%	n	%	n	%	n	%	n	%
Cases										
Case	821	0.8	287	0.7	315	1	118	0.9	101	0.8
Age at Entry										
<50	12,058	12.0	4,861	11.4	4,329	13.5	1,407	10.3	1,461	12.0
50–54	13,042	13.0	5,851	13.7	4,232	13.2	1,467	10.7	1,492	12.2
55–59	18,158	18.1	9,478	22.2	4,581	14.3	2,424	17.8	1,675	13.8
60–64	19,277	19.2	9,981	23.4	4,430	13.8	2,757	20.2	2,109	17.3
65–69	19,044	18.9	7,076	16.6	6,852	21.4	2,763	20.2	2,353	19.3
>70	18,948	18.8	5,400	12.7	7,614	23.8	2,845	20.8	3,089	25.4
Sex										
Male	42,828	42.6	20,495	48.1	11,519	36.0	4,872	35.7	5,942	48.8
Female	57,699	57.4	22,152	51.9	20,519	64.0	8,791	64.3	6,237	51.2
Diabetes										
No	86,223	85.8	35,830	84.0	26,892	83.9	12,530	91.7	10,971	90.1
Yes	14,304	14.2	6,817	16.0	5,146	16.1	1,133	8.3	1,208	9.9
BMI (kg/m^2)										
<25	33,849	33.7	11,836	27.8	8,337	26.0	5,793	42.4	7,883	64.7
25–29	41,113	40.9	19,765	46.3	12,599	39.3	5,079	37.2	3,670	30.1
>30	24,068	23.9	10,672	25.0	10,031	31.3	2,751	20.1	614	5.1
Missing	1,497	1.5	374	0.9	1,071	3.4	40	0.3	12	0.1
Smoking Status										
Never	43,443	43.2	20,195	47.4	11,878	37.1	5,570	40.8	5,800	47.6
Quit ≥ 20 pack-years	7,439	7.4	1,958	4.6	2,353	7.3	1,825	13.4	1,303	10.7
Quit < 20 pack-years	28,075	27.9	11,913	27.9	9,151	28.6	3,581	26.2	3,430	28.2
Current <20 pack-years	10,208	10.1	4,041	9.5	4,570	14.3	887	6.5	710	5.8
Current ≥ 20 pack-years	5,987	6.0	1,556	3.6	2,388	7.5	1,383	10.1	660	5.4
Missing	2,276	2.3	1,493	3.5	497	1.5	174	1.3	112	0.9

Current Unknown Pack-year	419	0.4	152	0.4	223	0.7	32	0.2	12	0.1
Quit Unknown Pack-year	2,680	2.7	1,339	3.1	978	3.0	211	1.5	152	1.3
Birth Year										
1918–1922	14,232	14.2	4,035	9.5	5,775	18.0	2,306	16.9	2,116	17.4
1923–1927	19,500	19.4	6,619	15.5	7,570	23.6	2,774	20.3	2,537	20.8
1928–1932	19,105	19.0	9,160	21.5	5,122	16.0	2,605	19.1	2,218	18.2
1933–1937	17,214	17.1	8,562	20.1	4,605	14.4	2,258	16.5	1,789	14.7
1938–1942	16,599	16.5	8,679	20.3	4,320	13.5	2,113	15.5	1,487	12.2
1943–1948	13,877	13.8	5,592	13.1	4,646	14.5	1,607	11.7	2,032	16.7
Number of Moves During Follow-up										
1	59,636	59.3	23,475	55.0	19,567	61.1	8,056	59.0	8,538	70.1
2	20,706	20.6	9,181	21.5	6,106	19.0	3,078	22.5	2,341	19.2
3	10,985	10.9	5,235	12.3	3,388	10.6	1,503	11.0	859	7.1
4	5,193	5.2	2,640	6.2	1,656	5.2	607	4.4	290	2.4
5 or more	4,007	4.0	2,116	5.0	1,321	4.1	419	3.1	151	1.2
Baseline Pollutant Concentration[1,2]	**Mean (SD)**	**Median**	**Mean (SD)**	**Median**	**Mean (SD)**	**Median**	**Mean (SD)**	**Median**	**Mean (SD)**	**Median**
$PM_{2.5}$ μg/m^3	15.4 (1.7)	15.7	15.4 (1.4)	15.2	15.7 (1.8)	16.2	15.3 (1.6)	15.5	15.3 (1.9)	15.0
PM_{10} μg/m^3	39.4 (5.4)	40.4	39.9 (4.9)	38.7	39.5 (6)	41.1	39.4 (5.4)	39.7	37.7 (5.1)	37.4
NO_2 PPB	38.1 (5.8)	38.9	40.3 (5)	41.7	35.8 (6.1)	37.4	37.7 (5.7)	38.3	36.9 (4.7)	36.7
NO_X PPB	85.2 (15.9)	89.4	85.5 (13.3)	87.5	88.4 (20.1)	95.1	81.4 (14.7)	83.6	80 (10.9)	80.3
Pollutant Concentration Over Study Period [2,3]										
$PM_{2.5}$ μg/m^3	16.4 (1.7)	16.6	16.7 (1.4)	16.8	16.1 (2.1)	16.4	16.1 (1.8)	16.4	16.3 (1.4)	16.3
PM_{10} μg/m3	35.4 (4)	35.5	36.4 (3.3)	36.1	34.3 (4.9)	34.0	35.5 (3.8)	35.6	34.6 (3)	34.4
NO_2 PPB	28.8 (5.1)	29.0	29.7 (4.5)	29.7	28.3 (5.6)	28.0	28.5 (5.5)	28.9	27.6 (4.5)	27.3
NO_X PPB	62.4 (14)	61.8	62.4 (12.4)	61.8	64.8 (16.4)	63.7	59.8 (14.2)	58.8	59.5 (11.5)	58.1

1. Average measure over first year of follow-up.

2. Participant number in calculation differs based on pollutant, see supplement.

3. Average measure over the whole study period.