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Associations of Mortality with Long-Term Exposures to Fine and Ultrafine Particles, Species and Sources: Results from the California Teachers Study Cohort

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Running title: Long-term exposures to fine and ultrafine particles

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Abstract

Background: While several cohort studies report associations between chronic exposure to fine particles ($PM_{2.5}$) and mortality, few have studied the effects of chronic exposure to ultrafine (UF) particles. In addition, few studies have estimated the effects of the constituents of either $PM_{2.5}$ or UF particles.

Methods: We used a statewide cohort of over 100,000 women from the California Teachers Study who were followed from 2001 through 2007. Exposure data at the residential level were provided by a chemical transport model that computed pollutant concentrations from over 900 sources in California. Besides particle mass, monthly concentrations of 11 species and 8 sources or primary particles were generated at 4 km grids. We used a Cox proportional hazards model to estimate the association between the pollutants and all-cause, cardiovascular, ischemic heart disease (IHD) and respiratory mortality.

Results: We observed statistically significant ($p < 0.05$) associations of IHD with $PM_{2.5}$ mass, nitrate elemental carbon (EC), copper (Cu), and secondary organics and the sources gas- and diesel-fueled vehicles, meat cooking, and high sulfur fuel combustion. The hazard ratio estimate of 1.19 (95% CI: 1.08, 1.31) for IHD in association with a 10-$\mu g/m^3$ increase in $PM_{2.5}$ is consistent with findings from the American Cancer Society cohort. We also observed significant positive associations between IHD and several UF components including EC, Cu, metals, and mobile sources.

Conclusions: Using an emissions-based model with a 4 km spatial scale, we observed significant positive associations between IHD mortality and both fine and ultrafine particle species and sources. Our results suggest that the exposure model effectively measured local exposures and facilitated the examination of the relative toxicity of particle species.

Introduction

Several cohort studies have reported associations of long-term exposure to fine particles ($PM_{2.5}$ or particulate matter less than 2.5 microns in diameter) with cardiovascular mortality (Hoek et al. 2013; Laden et al. 2006; Lipsett et al. 2011; Pope et al. 2002). Since $PM_{2.5}$ is a heterogeneous mix of particle sizes and chemistry and is generated from multiple sources, the specific constituents and sources of concern have not been fully elucidated. Until recently, among the constituents of $PM_{2.5}$, long-term exposures (i.e., one year or more) for cohort studies have only been generated for sulfates and black carbon (Dockery et al. 1993; Pope et al. 1995; Smith et al. 2009). In addition, because of the difficulty in measuring exposure, there has been little focus to date on the health effects of long-term exposure to ultrafine (UF) particles (particles < 0.1 micron in diameter).

Epidemiologic analysis of the effects of particulate matter constituents is hindered by their spatial heterogeneity and the reliance on a few fixed site monitors to represent exposures in large metropolitan areas. For example, for PM_{10} (particles less than 10 microns in diameter), many metropolitan areas have only a small proportion of their total population within 15 km of a monitor such as New York (3.5%) Detroit (23%), Boston (39%), Seattle (31%), and Philadelphia (35%) (US EPA 2009). The proportion for those above age 65 years, a well-documented susceptible subgroup, who are within 15 km are only slightly higher: New York (4%), Detroit (27%), Boston (41%), Seattle (32%), and Philadelphia (38%). While coverage for $PM_{2.5}$ is much higher given its spatial homogeneity, its constituents are known to be spatially variable and often very localized (Kim et al. 2005). The exposure misclassification will be even greater for measurement of mass and constituents of UF particles given their spatial heterogeneity (Sakurai

et al. 2003; Sioutas et al. 2005). Some cohort studies have made use of Land Use Regression (LUR) models to estimate $PM_{2.5}$ or nitrogen dioxide (Beelen et al. 2014) at finer spatial scales but LUR models for particle sources or species are not widely available.

In a previous study, the relation between mortality and long-term exposure to constituents of $PM_{2.5}$ was examined using data from the California Teachers Study (CTS) cohort (Ostro et al. 2011). Started in 1995, the CTS is a prospective study of over 130,000 current and former female teachers and administrators identified through the State Teachers Retirement System. Due to limited data on particle species, this earlier report relied on $PM_{2.5}$ data collected and further analyzed by the U.S. Environmental Protection Agency at eight fixed site monitors as part of the Speciation Trends Network (US EPA 2008). The 24-hr averaged measurements were usually obtained on an every third- or sixth-day basis. To minimize exposure misclassification, catchment buffer areas of 8 and 30 km were drawn around each monitor. The 30 km buffer is likely too large to capture exposure contrasts of many of the species while the 8 km buffer significantly reduced the sample size resulting in more unstable estimates and reduced statistical power. Although these buffers were an improvement over studies using a single or multiple monitors to represent exposure over large metropolitan areas, they may not sufficiently measure concentrations of many of the PM constituents, such as elemental carbon (EC) and transition metals that are known to exhibit high spatial variance. Specifically, Hu et al. (2014a; 2014b) reported significant bias for several species of fine and UF particles when comparing the central-site monitor readings applied to the entire metropolitan area population versus our estimated population-weighted concentrations. The latter are derived as the product (both at the 4 km grid scale) of the population and our model-based estimates of the pollutants. Model estimates are highly correlated ($r > 0.8$) with observations at the monitoring locations. For example, for the

seven major California Metropolitan Statistical Areas that had available data, the estimated population-weighted concentrations for EC were generally lower than central monitor predictions, with a maximum bias of -50% in Los Angeles and an average bias of -33%. While measurement and model predictions were in good agreement at the monitor locations, the bias was introduced by spatial variability around the monitor.

For the current study, we combined data from the CTS with newly developed exposure data generated from the UCD/CIT (University of California Davis/California Institute of Technology) model (J. Hu et al., unpublished data). The UCD/CIT chemical transport model uses calculated meteorological fields and emissions estimates for different sources to predict airborne particulate matter concentrations. Particulate matter emissions are assigned a size and composition distribution based on measurements in source-testing experiments. The source-identity of all particulate matter emissions is retained through the simulated atmosphere. In the present study, ground-level mass concentrations for 50 PM constituents were estimated over the major population regions in California at a 4 km resolution for the period of 2000-2007. For many species of fine and UF particles, model predictions are highly correlated with measured values, particularly for longer averaging times (>2 weeks). For example, correlations were greater than 0.8 for comparisons between annual modeled and measured concentrations of 10 different $PM_{2.5}$ components for 5 of the 7 metropolitan regions with available monitoring data (Hu et al. 2014b).

Below, we report our findings of an analysis of the associations of long-term exposure to 19 constituents and sources of both $PM_{2.5}$ and UF particles on mortality from all natural causes, cardiovascular disease, ischemic heart disease (IHD), and pulmonary disease.

Methods

Data

The CTS is a prospective study of 133,479 current and former female teachers and administrators who completed baseline questionnaires mailed to them in 1995 to investigate the incidence of breast cancer in public school teachers and administrators, as described in detail in Bernstein et al. (2002). Subsequent questionnaires were mailed to CTS participants in 1997 and 2000. The design and on-going follow-up of the CTS cohort is a multi-institutional collaboration involving researchers with diverse and complementary areas of expertise. Record linkage is conducted annually to mortality files administered by the California Department of Public Health. In addition, residential addresses of each CTS participant were updated annually for the mailing of newsletters. The mean age of CTS participants at enrollment was 54, with 90% between ages 30 and 80. The cohort is multi-ethnic but primarily non-Hispanic white (86.7%) and born in the United States (93.6%). For this study, we used cohort follow-up data from January 2001 through July 2007. Women under age 30 at the start of the study were excluded in order to focus on mid-life and older women. Use of data on human subjects in the main CTS cohort study was reviewed and initially approved by the California Committee for the Protection of Human Subjects, Health and Human Services Agency, and by the institutional review boards (IRB) for each participating institution in June 1995 and annually thereafter. Informed consent was obtained upon entry into the cohort. Analysis for this manuscript was approved in August 2013 by the IRB of the Cancer Prevention Institute of California, the center of one of the Principal Investigators (PR).

Health outcomes

In this analysis, we focused on associations between long-term exposures and mortality. Deaths were assigned codes based on the International Classification of Diseases, volume 10 (ICD-10) for the following outcomes: all-cause deaths excluding those with an external cause (A00-R99), cardiovascular deaths (I00-I99), IHD deaths (I20-I25), and pulmonary deaths (C34, J00-J98). Person-days at risk were calculated as the number of days starting from January 1, 2001 until the earliest of three dates: (i) the date of death; (ii) a move out of California for at least four months; or (iii) July 31, 2007, the end of follow-up for this analysis. If a woman moved out of state for less than four months exposures during that time were not included in the calculations of the long-term average. Women who died from a cause other than the outcome of interest during the follow-up period were censored at the time of their deaths.

Air pollution exposure estimates

The UCD/CIT chemical transport model was used to estimate ground-level concentrations of 50 PM constituents over the major population regions in California using a 4-km grid resolution for the period from 2000 through 2007 (Hu et al. 2014a; Hu et al. 2014b). A sensitivity analysis conducted at 250 m resolution over Oakland CA (Joe et al. 2014) indicated that 4 km resolution captures 55-70% of concentration variability within the urban area.

Using the extensive emissions inventory in California, the model calculations track the mass and number concentrations of the PM constituents in particle diameters ranging from 0.01 to 10 μm through calculations that describe emissions, transport, diffusion, deposition, coagulation, gas- and particle-phase chemistry, and gas-to-particle conversion (Hu et al. 2014d). The model solves the coupled set of differential equations that describe how atmospheric

processes change pollutant concentrations in regularly spaced atmospheric grid cells. Thus, the predicted exposure concentrations primarily reflect the balance between emissions inventories of fresh particles and meteorological fields that drive dispersion and chemical reaction.

Model predictions were saved at hourly time resolution and averaged to longer times as needed. Predicted concentrations were evaluated against ambient measurements at all available locations and times. $PM_{2.5}$ mass predictions had a mean fractional bias within ±0.3 (meeting accepted performance criteria) at 52 sites out of the total 66 sites across California after correcting for bias in the dust emissions as many studies have shown that dust emissions in the current emission inventory are overestimated (J. Hu et al., unpublished data). Good correlations between predictions and measurements ($r > 0.8$) were demonstrated for many of the $PM_{2.5}$ and UF species at most of the monitoring stations, particularly for the monthly, seasonal and annual averages. For example, monthly $PM_{2.5}$ nitrates were correlated with measurements with $r = 0.76$ (15 sites), monthly $PM_{2.5}$ EC were correlated with measurements with $r = 0.94$ (8 sites), and monthly $PM_{2.5}$ concentrations of potassium, chromium, zinc, iron, titanium, arsenic, calcium, manganese, and strontium were correlated with measurements with $r \geq 0.8$ (5 sites out of a total of 8). For EC in the UF range, the correlation was above r=0.9 for 117 available measurements made at 13 locations during 9 intensive field campaigns that each lasted several weeks (Hu et al. 2014b). The quality of the model predictions summarized above reflects the accuracy of the emissions inventories that have been refined over three decades in California, the development of reactive chemical transport models that include important aerosol transformation mechanisms, and the development of prognostic meteorological models that allow for long simulations of historical meteorology.

Coarse particle predictions (2.5 μm < Dp < 10 μm) have only undergone preliminary comparisons to measurements and were not used for exposure estimates in the current study. Likewise, UF number concentrations were not used because our modeling did not include nucleation, the process by which particles are formed directly from gas molecules, which would greatly impact this parameter. UF mass concentrations are highly correlated with particle surface area (Kuwayama et al. 2013) and serve as a good metric for the potential exposure to UF particles. The measured correlation between UF mass and particle surface was 0.97 in Fresno, a typical city in central California. For many of the fine and UF species, Hu et al. (2014a) observed strong spatial variability within metropolitan areas (Figure 1).

Based on previous studies (Ostro et al. 2007; Ostro et al. 2011; Peng et al. 2009; Zanobetti et al. 2009) we chose to examine a subset of the available constituents. Additionally, some constituents were eliminated given their high inter-correlation or low concentrations. Thus, for each particle size, we analyzed the following constituents: copper (Cu), iron (Fe), manganese (Mn), Nitrate, EC, organic carbon (OC), "other" species (i.e., mineral dusts and constituents not measured), "other" metals (those besides Cu, Fe, and Mn that were explicitly resolved), and secondary organic aerosol (SOA). SOA formation was simulated with the mechanism in EPA's Community Multi-scale Air Quality (CMAQ) model version 4.7 (Carlton et al. 2010). SOAs were divided into anthropogenic (SOA_ant: derived from long-chain alkanes, xylenes, toluenes and benzene and their oligomers) and biogenic (SOA_bio: derived from isoprenes, monoterpenes, sesiquiterpenes and their oligomers). Nitrate was not estimated for the UF size fraction. Additional estimates were provided for sources of primary aerosols including on-road gasoline, off-road gasoline, on-road diesel, off-road diesel, wood smoke, meat cooking,

high sulfur fuel combustion (including distillate oil, marine vessel fuel, aircraft jet fuel, liquid and solid waste fuel), and "other anthropogenic".

Ultimately, the exposure metrics were combined with the updated addresses Monthly individual exposure estimates were developed through spatial linkage of the geocoded residential addresses. All residences within a given grid in a given month were assigned the modeled pollutant value for that grid for that period. The average long-term pollution exposure for a participant was obtained by calculating the mean of her monthly averages. At the time of each death, the long-term average for each individual remaining in the cohort was recalculated, allowing comparison between the decedent's long-term average exposure and those of the members remaining in the risk set.

Covariates

The individual-level covariates included as explanatory variables in the regression models were based on previous results from air pollution studies for this cohort (Lipsett et al. 2011). Specifically, the covariates included twenty individual-level covariates (a total of 58 terms): age (divided into two-year categories between ages 30 and 79, three-year categories between ages 80 and 88, and one category for women aged 89 and older); race (non-Hispanic White, other (African-American, Hispanic, Asian, Pacific Islander, and Native American) or unknown); marital status (married/living with partner, not married, and unknown); smoking status (never, former, and current smokers) and pack-years of smoking (continuous variable for former and current smokers); second-hand smoke exposure (none, household exposure, unknown); body mass index (BMI) (16-19 kg/m^2, 20-24, 25-29, 30-39, 40-55); lifetime physical activity (tertiles, unknown); alcohol consumption (beer (no/yes/unknown), wine

(no/yes/unknown), liquor (no/yes/unknown)); average daily dietary intake of fat (tertiles, unknown), fiber (tertiles, unknown), and calories (tertiles, unknown); menopausal status and hormone replacement therapy use combined (pre-menopausal, peri/post-menopausal and no HT use, peri/post menopausal and past HT use, peri/post-menopausal and current use of estrogen, peri/post-menopausal and current use of estrogen plus progestin, and unknown menopausal status or HT use; family history of myocardial infarction (yes/no) or stroke (yes/no); and use of blood pressure medication (low, medium, high, unknown) or aspirin (low, medium, high, unknown). Data on all individual-level variables except marital status (which was assessed in the 2000 questionnaire) were obtained from the baseline questionnaire.

Statistical methods

We fitted Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between each pollutant and the outcomes of interest. We examined each pollutant with a separate regression model adjusted for the covariates described above. The Cox model was stratified by age and race/ethnicity. To ensure that we would be examining associations with chronic rather than acute exposures, study exposures began in January 2000, the cohort follow-up began in January 2001 and both continued until July 2007. Two additional sensitivity analyses were conducted. First, we reran the models after including six Census-derived contextual (neighborhood) variables including income (median household income), income inequality (percent below poverty level), education (percent with college degree), population size, racial composition (percent white, percent black, percent Hispanic) and unemployment (percent unemployed). These variables were derived from the 2000 census at the block group level based on the subject's residence at the time of the baseline

questionnaire. These variables represent social, economic, and environmental settings at a group level that may be associated with disease outcomes at the individual level. As such, they may provide additional control for residual confounding. The second sensitivity analysis involved two-pollutant models for a selected set of constituents for the outcome IHD mortality. Specifically, we took the constituent of $PM_{2.5}$ and UF particles with the highest HR and ran additional regressions that included each of the other constituents in the same particle size. The HR and CIs are presented for a change in their respective interquartile ranges (IQRs) unless otherwise noted. Statistical significance was based on a p-value < 0.05 and model goodness-of-fit was based on the Akaike information criterion (AIC). The analysis was conducted using PHREG in SAS software.

Results

Of the 133,479 women who completed a baseline questionnaire we excluded 21,302 with no pollution data (of which 14,670 had a lack of information on residential addresses and 6,632 lived in areas for which exposure estimates were not available), 1,363 women who had died or moved before the start of follow-up, 406 who were less than age 30 in January 2001, 4,684 who had unknown or outlier body mass index (BMI), 3,609 who were missing smoking data, 14 who were excluded because they consented to be included only in breast cancer studies and 217 who had less than 6 months of pollution values during January 2000 through December 2000, leaving a total of 101,884 women eligible for the study. The average length of follow-up was 6.3 years with total person-years of 642,269. A total of 6,285 deaths occurred during the follow-up from January 2001 through July 2007; of these, 2,400 were due to cardiovascular diseases, 1,085 were due to IHD and 929 were due to pulmonary diseases. As indicated in Table 1, the average age of

eligible cohort members at the start of follow-up was 57 years, 86% of these women were non-Hispanic white and 5% were current smokers. Table 2 summarizes the mean and distributions of the concentrations of $PM_{2.5}$ and UF constituents used in the analysis. For example, the mean of $PM_{2.5}$ was 17.9 $\mu g/m^3$ with OC (3.9 $\mu g/m^3$) and nitrate (3.7 $\mu g/m^3$) as the largest constituents. For UFs, the mean was 1.3 $\mu g/m^3$ with OC the largest contributor at 0.9 $\mu g/m^3$.

A majority of the species were moderately to highly correlated (r = 0.5 to 0.8) (see supplemental tables S1 and S2). $PM_{2.5}$ nitrates had correlations of 0.55, 0.43, 0.65 and 0.84 with EC, OC, Cu and SOA_ant, respectively. For UFs, EC had correlations of 0.67, 0.19 and 0.40 with OC, Cu, and SO_ant, respectively. The average inter-constituent correlation for $PM_{2.5}$ was 0.59 and for UFs was 0.64. The implications of these correlations are described in the discussion section below.

In the Cox proportional hazards regression analysis for $PM_{2.5}$, the only statistically significant association ($p < 0.05$) observed between constituents and all-cause mortality was for the source of high sulfur fuel combustion (HR = 1.03; 95% CI: 1.01, 1.05 for a change in its IQR) , and there were no statistically significant associations with pulmonary disease mortality (see Supplemental Table S3). For cardiovascular disease mortality, statistically significant associations were demonstrated only for nitrate (HR = 1.10; 95% CI: 1.02, 1.18) and high sulfur fuel combustion (HR = 1.05, 95% CI: 1.02, 1.09). Associations with p-values < 0.10 were observed for $PM_{2.5}$ mass (HR = 1.05, 95% CI: 0.99, 1.12) and SOA_ant (HR = 1.06, 95% CI: 0.99, 1.13) (Table S3). As summarized in Table 3 and Figure 2, however, there were many statistically significant associations with IHD mortality. Among the constituents, the highest statistically significance were with nitrate (HR = 1.28; 95% CI: 1.16, 1.42) and SOA_ant (HR =

1.23, 95% CI: 1.11, 1.36), both of which had higher HRs and fit the data slightly better, based on the (lower) AIC, than that of $PM_{2.5}$ mass (HR = 1.18; 95% CI: 1.08, 1.30). Among the emission sources, we found statistically significant associations between IHD and all four of the vehicle sources, meat cooking, and high sulfur content fuel combustion.

For UFs, no statistically significant associations were observed for either all-cause or pulmonary mortality (Supplemental Material Table S4). For cardiovascular mortality, significant associations were noted for Cu (HR = 1.03; 95% CI: 1.00, 1.05), and the sources of high sulfur fuel combustion (HR = 1.04; 95% CI: 1.01, 1.07). However, many statistically significant associations were again demonstrated for IHD mortality (Table 3). Among the species, this includes Cu, Fe, EC, OC, other compounds and metals, SOA_ant and SOA_bio. The largest estimated associations were for SOA_ant (HR = 1.25, 95% CI: 1.13, 1.39), EC (HR = 1.15, 95% CI: 1.06, 1.26) and other metals (HR = 1.13, 95% CI: 1.05, 1.21), each of which had lower p-values and slightly better fitting models based on AIC than did UF mass (HR =1.10, 95% CI: 1.02, 1.18). Many of the other constituents also had better model fits than $PM_{2.5}$. Among the sources, associations were seen for both on and off-road diesel and gasoline, meat cooking, high sulfur fuel combustion and other anthropogenic sources.

The analysis of IHD mortality showed that while $PM_{2.5}$ mass had a lower p-value than UF mass, UF mass and each of the UF constituents provided a better fit and had a lower p-value than their corresponding $PM_{2.5}$ constituent (except for Mn for which there was no statistical significance for either particle size).

In our sensitivity analysis, we found that adding the six contextual variables to the model did not quantitatively alter any of the results (HR or p-value) except in one case where $PM_{2.5}$

SOA_bio became non-significant (data not shown). We also examined two-pollutant models with the $PM_{2.5}$ constituent with the largest effect estimate for IHD ($PM_{2.5}$ nitrate) in a regression with each of the other $PM_{2.5}$ constituents. Likewise, we examined two-pollutant models for UF (SOA_ant) with each of the other UF constituents (Tables 4 and 5). For the two-pollutant models with $PM_{2.5}$ nitrate, the HRs for nitrate were basically unchanged and none of the other $PM_{2.5}$ constituents, including mass, were statistically significant. For UFs SOA_ant, the HR was again basically unchanged and only one other constituent, Cu, was also statistically significantly related to IHD mortality.

Discussion

Our analysis of long-term exposure to the mass and constituents of $PM_{2.5}$ and UF particles revealed several statistically significant associations with all-cause, cardiovascular, and IHD mortality. For $PM_{2.5}$, high sulfur content fuel combustion was associated with all three endpoints, and nitrates were associated with cardiovascular and IHD mortality. Several other constituents reached statistical significance with IHD mortality including $PM_{2.5}$ mass, Cu, EC, and the SOAs, as well as the sources including gas- and diesel-fueled vehicles, meat cooking, and high sulfur fuel combustion. Among the $PM_{2.5}$ constituents, based on their associated IQRs, nitrate had the highest HR and provided the best fit of the data. For UFs, constituents such as SOA_ant, EC and "other" metals exhibited statistically significant associations with IHD mortality, as did all of the mobile sources and high sulfur fuel combustion. For both $PM_{2.5}$ and UF particles, several constituents generated higher HRs based on their relevant IQRs than their associated mass measurements and in some cases (e.g, UF mass versus SOA_ant) the differences were statistically significant based on methodology suggested by Schenker and Gentleman

(2001). In addition, for all of the constituents, there were better model fits, based on AIC, for UFs than for $PM_{2.5}$.

In a previous analysis of the CTS (based on 73,489 women), exposures to $PM_{2.5}$ were estimated utilizing data from 77 existing monitors located throughout the state. (Lipsett et al. 2011). Smoothed surfaces were produced through inverse distance weighting and grids of 250 meters were created. Monthly concentrations were assigned to residents within each grid with the added constraint that participants were required to be within 30 km of a monitor. That study produced an HR for the association of $PM_{2.5}$ and IHD mortality of 1.20 (95% CI: 1.02, 1.41) for a 10-$\mu g/m^3$ increase in $PM_{2.5}$. This result comports with the HR estimate (converted to 10 $\mu g/m^3$ change) in the current study of 1.19 (95% CI: 1.08, 1.31). Our estimate is also similar to those for IHD mortality based on analyses of the American Cancer Society (ACS) cohort in which the HRs for a 10-$\mu g/m^3$ increase in $PM_{2.5}$ were 1.18 (95% CI: 1.14, 1.23) for the U.S. and 1.11 (95% CI: 1.05, 1.18) for California (Jerrett et al. 2013; Pope et al. 2002). They were also comparable to those of the Harvard Six-City Study of 1.26 (95% CI: 1.08, 1.47) (Laden et al. 2006) for a 10-$\mu g/m^3$ increase in $PM_{2.5}$.

We can also compare the estimates of a few constituents of $PM_{2.5}$ with those obtained in a prior analysis of a smaller subset (n = 43,220) of the CTS (Ostro et al. 2011). In this prior analysis, we used a 30 km buffer catchment area around each of eight USEPA Speciation Trends Network monitors. The HR for cardiovascular mortality associated with a 1-$\mu g/m^3$ increase in nitrate in the previous study was 1.03 (95% CI: 1.01, 1.06) versus the current study estimate of 1.02 (95% CI: 1.01, 1.04). For EC, the previous study generated an HR of 1.11 (95% CI: 0.91, 1.36) for a 1-$\mu g/m^3$ change compared with 1.05 (95% CI: 0.98, 1.11) in the current study.

Several cohort studies have estimated the effects of EC or its correlates on cardiovascular mortality. For example, Smith et al. (2009) estimated its effects among 352,000 participants in the ACS cohort and reported a relative risk (RR) of 11% (95% CI: 3, 19) per $\mu g/m^3$. The estimated RR of coronary heart disease mortality associated with EC was 1.08 (95% CI: 1.04, 1.12) per $\mu g/m^3$ in a cohort study in Vancouver, Canada (Gan et al. 2011). In addition, the RR of cardiovascular mortality from long-term exposure to black smoke, another EC correlate which measures the light reflectance of particles was reported in cohort studies in the Netherlands and Scotland (Beelen et al. 2008; Beverland et al. 2012). Based on a conversion factor calculated by Janssen et al. (2011), the HRs were 1.04 (95% CI: 0.95, 1.12) and 1.06 (95% CI: 1.0, 1.11) per $\mu g/m^3$ of EC, respectively. Finally, a recent study examined the effect of $PM_{2.5}$ components and sources using a subset of the national ACS cohort. The results of the Cox regression model for IHD were generally supportive of our findings. Among the components measured, they observed statistically significant associations with IHD for EC and several of the metals (e.g., iron, lead, nickel and zinc). Nitrates were not included in the ACS study but statistical associations were observed for sulfur, likely from the combustion or coal and residual oil, which was not included in our study. In addition, among the sources, traffic was dominant in both studies.

We did not estimate any positive associations with long-term exposure to wood smoke although associations of short-term exposure with respiratory outcomes have been reported (Naeher et al. 2007). This may be a due to the episodic nature of the wood smoke or to possible confounding by SES. In California, most of the population-weighted exposure occurred in relatively high income counties, such as San Francisco, San Mateo and Santa Clara, where greater longevity prevails.

Given its large spatial variability, assessing exposure to UF particles among participants in cohort studies has been challenging. As such, very few studies have measured or estimated long-term exposures to UFs at a fine enough spatial gradient to examine its impact on health. As an alternative, several studies have attempted to estimate the effects of exposure to traffic, often a major source of UFs, using metrics such as nitrogen dioxide, distance to major roadways, and/or local traffic density (Health Effects Institute 2010). In general, within the first 250 meters or so of a major roadway, UFs may be highly correlated with other pollutants such as black carbon, nitrogen dioxide, and carbon monoxide. However, the relation between UFs and these other pollutants, especially away from major roadways, is not precise and the correlations may be fairly low (Sioutas et al. 2005; Zhu et al. 2008).In contrast, several studies have estimated the effects of daily changes in UFs where only the time-varying component is needed (Forastiere et al., 2005; Peters et al., 2009; Atkinson et al., 2010). The previous studies were based on counts of UFs rather than mass, so their estimates are not directly comparable to ours. In support of these and our findings on UFs, Delfino et al. (2009) followed a panel of 60 elderly subjects with coronary artery disease and reported associations between biomarkers of inflammation and several components of UF particles, including EC and primary OC. Other animal and human studies have implicated transition metals in generating inflammation and oxidative stress (Chen and Lippmann 2009; Costa and Dreher 1997; Gurgueira et al. 2002).

Our study has both strengths and limitations. Among the strengths are the relatively large size of the cohort, the low prevalence of active smoking, and the relative similarity of occupational status and activity patterns. These factors all help to reduce residual confounding in our estimates. Second, the study population included a large number of women at risk of developing cardiovascular disease by virtue of their age and post-menopausal status. Third,

because of the level of spatial detail in the pollution estimates and the information on residential history, the temporal and spatial resolution of the pollution exposure is enhanced relative to many previous cohort studies. One limitation is that the study was restricted to women, and these women were not necessarily representative of all women. Second, only about 1,000 women were diagnosed with IHD or pulmonary mortality, which may introduce some instability in the risk estimates. Third, our estimates could be impacted by possibly correlated and unmeasured co-pollutants. Fourth, there was high inter-correlation (most between 0.5 and 0.8) among the particle constituents, different levels of uncertainty and bias in their modeled estimates, and potentially different exposure patterns. These factors could impact the estimates of their relative toxicity. The high correlations reflect: (1) a consistent chemical signature of multiple pollutants associated with PM emitted from major sources; (2) that some elements are dominated by a small number of sources and/or (3) the similarity of certain pollutants from different sources such as gasoline and diesel vehicles. A similar range of inter-correlation among the constituents was reported by Ostro et al. (2011), which used monitored values for the same cohort as the current study, but only included eight metropolitan areas. Thus the high correlations are not simply a result of the modeling methodology. However, this feature does make it difficult to identify unique components and sources that are associated with adverse health effects. Fifth, stationary sources contribute less than 15% of the $PM_{2.5}$ in California (ARB 2013) so sources such as coal burning and industrial processes and their specific constituents are not included in this study. Finally, while our exposure method had some significant enhancements over previous assessments, some misclassification will continue to exist.

Nevertheless, this study represents an innovative effort to estimate the effects of long-term exposure to the constituents of two pollutants, fine and ultrafine particles, which are

ubiquitous in our environment. As such, it provides evidence of the public health impact of a subset of these constituents and helps contribute to our understanding of air pollution-related cardiovascular disease.

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Table 1. Descriptive statistics for health and covariate variables for women in the analysis.

Covariate	Percentage or mean ± SD
Age at January 2001 (yr)	57.3 ± 13.8
Race (% non-Hispanic white)	86.4
Smoking status:	
Never smoker	68.4
Former smoker	26.9
Current smoker	4.7
Total pack-years	14.7 ± 17.1
Adult second-hand smoke exposure	48
BMI (kg/m^2)	24.9 ± 5.1
Married/living with partner	46.6
Non-drinker	32.2
Menopausal status and HT use:	
Premenopausal	41.0
Peri/postmenopausal and no hormone therapy use	11.9
Peri/postmenopausal and current/past hormone therapy use	33.9
Unknown menopausal status/hormone therapy use	13.2
Dietary fat (g/d)	56.3 ± 26.8
Dietary fiber (g/d)	15.2 ± 6.4
Dietary calories (kcal/d)	1,595.4 ± 556.4
Physical activity (h/wk)	4.41 ± 4.0
Family history of heart disease	54.4
Taking hypertension medication/aspirin	34.3

All characteristics were reported on baseline questionnaire, except marital status which was reported on the 2000 questionnaire.

Table 2. Distribution of fine and UF particles species and sources.

	$PM_{2.5}$ Mean (μg/m^3)	25th %ile	Median	75th %ile	UF Mean (ng/m^3)	25th %ile	Median	75th %ile
Pollutant								
Mass	17.9	13.1	18.2	22.8	1293	778	1214	1747
Cu	0.5[a]	0.2[a]	0.4[a]	0.6[a]	0.03	0.01	0.01	0.03
Fe	0.4	0.3	0.4	0.5	1.3	0.9	1.3	1.6
Mn	7.7[a]	5.7[a]	7.9[a]	9.8[a]	0.05	0.02	0.03	0.05
Nitrate	3.7	1.5	3.5	5.4	-	-	-	-
EC	1.1	0.6	1.0	1.5	113	63	103	156
OC	3.9	2.4	3.7	5.2	908	507	845	1238
Other Compounds	2.9	2.1	2.9	3.6	36	18	29	47
Other Metals[b]	1.0	0.7	1.0	1.2	21	12	19	28
SOA_biogenic	0.1	0.1	0.1	0.1	17	9	16	24
SOA_anthropogenic	0.1	0.05	0.1	0.1	23	11	23	34
Sources of primary particles								
On-road gasoline	0.3	0.2	0.3	0.5	109	49	90	157
Off-road gasoline	0.2	0.1	0.1	0.2	34	16	29	49
On-road diesel	0.4	0.2	0.4	0.6	62	33	58	88
Off-road diesel	1.0	1.0	1.0	1.4	93	53	83	126
Wood smoke	1.4	0.5	0.9	1.8	310	105	205	437
Meat cooking	1.1	0.4	0.8	1.6	115	46	86	174
High sulfur fuel combustion	0.4	0.1	0.3	0.5	49	10	21	64
Other anthropogenic	7.0	5.2	7.2	9.0	502	253	403	653

[a]Concentrations x1000; [b]Metals besides Cu, Fe, and Mn.

Table 3. Hazard ratios (HR) and 95% confidence interval (CI) for associations of $PM_{2.5}$ and UF particles with Ischemic Heart Disease Mortality.

	$PM_{2.5}$				UF			
	IQR ($\mu g/m^3$)	**HR[a] (95% CI)**	**p-value**	**AIC**	**IQR (ng/m^3)**	**HR[a] (95% CI)**	**p-value**	**AIC**
Pollutant								
Mass	9.6	1.18 (1.08, 1.30)	<0.001	14011	969	1.10 (1.02, 1.18)	0.01	13896
Cu	0.4[b]	1.09 (1.04, 1.15)	<0.001	14015	0.02	1.06 (1.03, 1.09)	<0.0001	13890
Fe	0.2	1.06 (0.97, 1.16)	0.17	14023	0.8	1.03 (1.00, 1.06)	<0.05	13899
Mn	4.0[b]	1.06 (0.99, 1.13)	0.12	14023	0.03	1.00 (0.99, 1.01)	0.62	13902
Nitrate	3.9	1.28 (1.16, 1.42)	<0.0001	14003	-	-		-
EC	0.8	1.14 (1.05, 1.24)	<0.01	14015	93	1.15 (1.06, 1.26)	<0.001	13891
OC	2.8	1.08 (0.99, 1.17)	0.07	14022	731	1.08 (1.01, 1.15)	<0.05	13898
Other Compounds	1.4	1.07 (0.99, 1.15)	0.08	14022	29	1.10 (1.04, 1.16)	<0.001	13892
Other Metals[c]	0.5	1.08 (0.99, 1.18)	0.09	14022	17	1.13 (1.05, 1.21)	<0.01	13892
SOA biogenic	0.1	1.08 (1.00, 1.17)	<0.05	14021	14	1.10 (1.02, 1.19)	<0.01	13896
SOA anthropogenic	0.1	1.23 (1.11, 1.36)	<0.0001	14009	24	1.25 (1.13, 1.39)	<0.001	13884
Sources of primary particles								
On-road gasoline	0.3	1.12 (1.04, 1.22)	<0.01	14017	108	1.12 (1.04, 1.22)	<0.01	13894
Off-road gasoline	0.2	1.14 (1.04, 1.24)	<0.01	14016	33	1.14 (1.04, 1.24)	<0.01	13894
On-road diesel	0.4	1.13 (1.03, 1.23)	<0.01	14018	56	1.13 (1.03, 1.24)	<0.01	13895
Off-road diesel	0.8	1.13 (1.05, 1.23)	<0.05	14015	73	1.14 (1.05, 1.23)	<0.01	13892
Wood smoke	1.3	0.97 (0.90, 1.04)	0.38	14024	332	0.95 (0.89, 1.02)	0.20	13900
Meat cooking	1.2	1.08 (1.00, 1.17)	<0.05	14021	128	1.11 (1.03, 1.20)	<0.01	13895
High sulfur fuel combustion	0.4	1.08 (1.02, 1.13)	<0.05	14017	54	1.08 (1.04, 1.12)	<0.0001	13888
Other anthropogenic	3.8	1.09 (1.00, 1.19)	0.05	14021	400	1.06 (1.01, 1.10)	0.01	13896

[a]HRs stratified for age and race and adjusted for smoking status, smoking pack-years, adult second-hand smoke exposure, BMI, marital status, alcohol consumption, physical activity, menopausal status and HT use combined, family history of heart disease, hypertension medication/aspirin use, dietary fat, fiber and caloric intake. [b]Concentrations x1000. [c]Metals other than Cu, Fe, and Mn.

Table 4. Hazard ratios (HR) and 95% confidence interval (CI) for ischemic heart disease mortality for two-pollutant models of $PM_{2.5}$ nitrate with each of the other constituents.

	$PM_{2.5}$ constituent			$PM_{2.5}$ nitrate		
Pollutant	**IQR ($\mu g/m^3$)**	**HR[a] (95% CI)**	**p-value**	**IQR ($\mu g/m^3$)**	**HR[a] (95% CI)**	**p-value**
Mass	9.6	1.03 (0.91, 1.18)	0.61	3.9	1.25 (1.07, 1.45)	<0.05
Cu	0.4[b]	1.02 (0.94, 1.10)	0.67	3.9	1.26 (1.11, 1.44)	<0.001
Fe	0.2	0.92 (0.82, 1.03)	0.14	3.9	1.35 (1.19, 1.54)	<0.0001
Mn	4.0[b]	0.94 (0.85, 1.04)	0.23	3.9	1.34 (1.18, 1.53)	<0.0001
Nitrate	-	-	-	3.9	1.28 (1.16, 1.42)	<0.0001
EC	0.8	1.04 (0.94, 1.14)	0.49	3.9	1.25 (1.11, 1.42)	<0.001
OC	2.8	1.00 (0.91, 1.09)	0.94	3.9	1.29 (1.15, 1.44)	<0.0001
Other compounds	1.4	0.96 (0.87, 1.05)	0.34	3.9	1.33 (1.17, 1.51)	<0.0001
Other metals[c]	0.5	0.93 (0.83, 1.04)	0.21	3.9	1.35 (1.18, 1.53)	<0.0001
SOA biogenic	0.1	0.95 (0.86, 1.05)	0.31	3.9	1.34 (1.17, 1.53)	<0.0001
SOA anthropogenic	0.1	0.97 (0.78, 1.21)	0.78	3.9	1.32 (1.05, 1.66)	0.02

[a]HRs stratified for age and race and adjusted for smoking status, smoking pack-years, adult second-hand smoke exposure, BMI, marital status, alcohol consumption, physical activity, menopausal status and HT use combined, family history of heart disease, hypertension medication/aspirin use, dietary fat, fiber and caloric intake. [b]Concentrations x1000. [c]Metals other than Cu, Fe, and Mn.

Table 5. Hazard ratios (HR) and 95% confidence interval (CI) for ischemic heart disease mortality for two-pollutant models of anthropogenic UF secondary organic aerosols with each of the other constituents.

	UF constituent			UF SOA anthropogenic		
Pollutant	**IQR (ng/m^3)**	**HR[a] (95% CI)**	**p-value**	**IQR (ng/m^3)**	**HR[a] (95% CI)**	**p-value**
Mass	969	1.03 (0.94, 1.12)	0.56	24	1.19 (1.08, 1.31)	<0.001
Cu	0.02	1.39 (1.05, 1.83)	0.02	24	1.16 (1.06, 1.28)	0.001
Fe	0.8	1.01 (0.97, 1.06)	0.63	24	1.20 (1.09, 1.31)	<0. 001
Mn	0.03	1.00 (0.99, 1.01)	0.95	24	1.21 (1.11, 1.32)	<0.0001
EC	93	1.04 (0.93, 1.16)	0.52	24	1.18 (1.05, 1.32)	0.006
OC	731	1.02 (0.95, 1.10)	0.61	24	1.20 (1.09, 1.31)	<0.001
Other compounds	29	1.06 (1.00, 1.13)	0.06	24	1.17 (1.07, 1.29)	<0.001
Other metals[b]	17	1.07 (0.96, 1.18)	0.22	24	1.17 (1.06, 1.29)	0.002
SOA biogenic	14	0.99 (0.92, 1.07)	0.82	24	1.22 (1.09, 1.36)	<0.001
SOA anthropogenic	-	-	-	24	1.25 (1.13, 1.39)	< 0.001

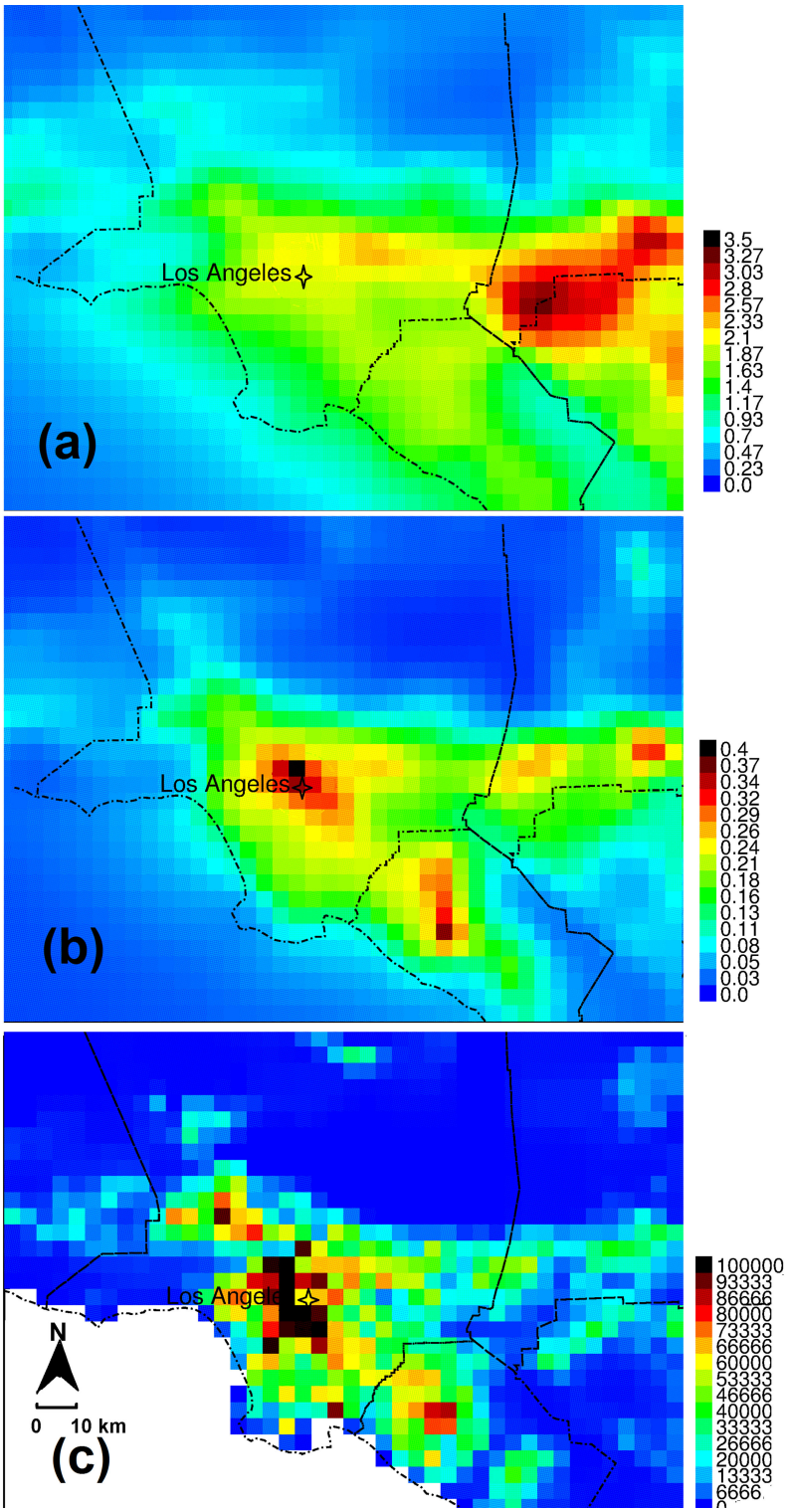
[a]HRs stratified for age and race and adjusted for smoking status, smoking pack-years, adult second-hand smoke exposure, BMI, marital status, alcohol consumption, physical activity, menopausal status and HT use combined, family history of heart disease, hypertension medication/aspirin use, dietary fat, fiber and caloric intake. [b]Metals other than Cu, Fe, and Mn.

Figure Legends

Figure 1. Modeled concentrations of $PM_{2.5}$ nitrate (a), ultrafine anthropogenic secondary organic aerosols (b) and population in the Los Angeles Basin (c) using 4 k grids (the star in the figures indicates the site of the US EPA monitor).

Figure 2. Association of $PM_{2.5}$ Constituents and Sources with Ischemic Heart Disease Mortality (Hazard Ratios and 95% Confidence Intervals Using Interquartile Range).

Figure 1.


Los Angeles
(a)
3.5
3.27
3.03
2.8
2.57
2.33
2.1
1.87
1.63
1.4
1.17
0.93
0.7
0.47
0.23
0.0
Los Angeles
(b)
0.4
0.37
0.34
0.32
0.29
0.26
0.24
0.21
0.18
0.16
0.13
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Los Angeles
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(c)
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33333
26666
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13333
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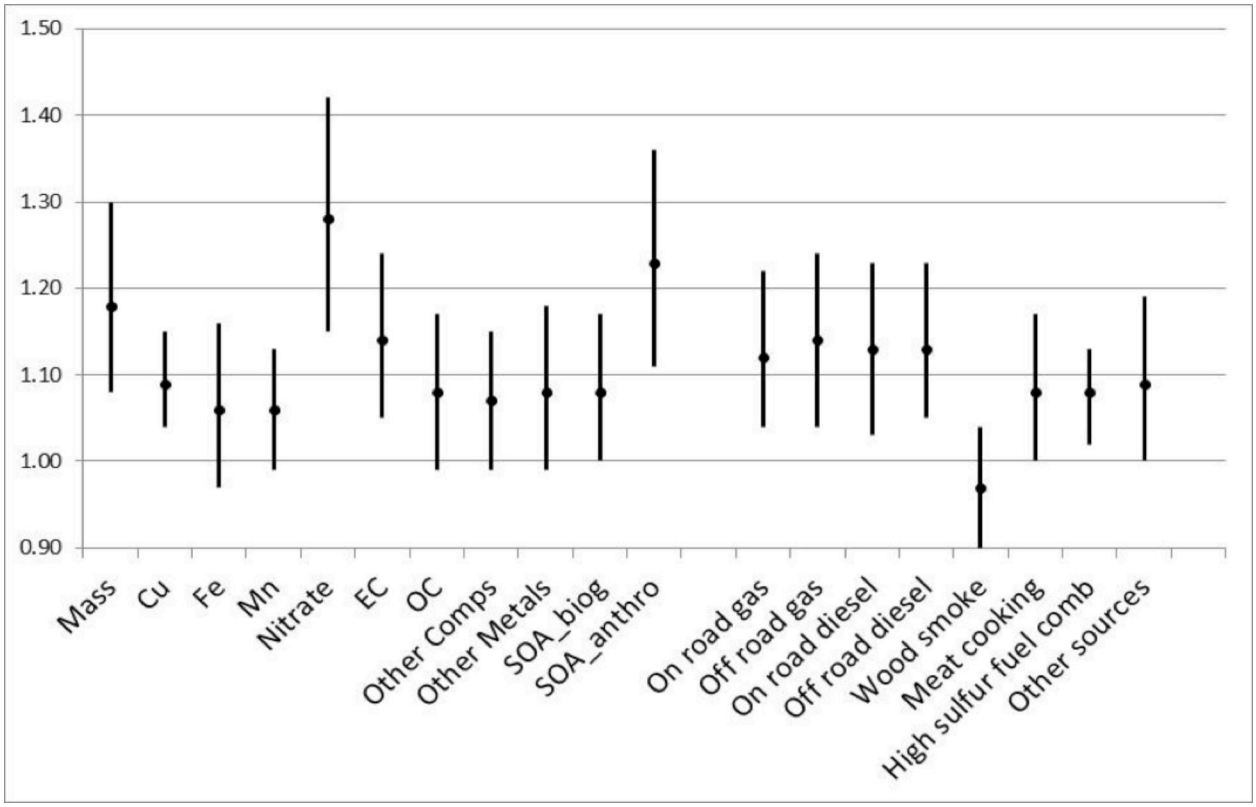
Figure 2.


1.50
1.40
1.30
1.20
1.10
1.00
0.90
Mass
Cu
Fe
Mn
Nitrate
EC
OC
Other Comps
Other Metals
SOA_biog
SOA_anthro
On road gas
Off road gas
On road diesel
Off road diesel
Wood smoke
Meat cooking
High sulfur fuel comb
Other sources