# A Closer Look at Air Pollution-Mortality Relationships for California Members of the American Cancer Society Cohort

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**Abstract.** Estimates of public health benefits attributed to cleaner air are largely based on studies of spatial differences in long-term mortality rates. However, such studies tend to suffer from lack of specificity, such as uncertain exposures and neglected confounders and co-pollutants. Here we use meta-analyses to re-examine the results of Jerrett et al. (2011), comprising 992 estimates of long-term mortality-air pollution relationships among California members of a national cohort, with follow-up from 1982 to 2000. These risk estimates include strong and significant *positive* (harmful) spatial relationships for heart disease and strong and significant *negative* (beneficial) relationships for other causes including cancer, thus raising questions of causality and credibility. Excess risk estimates for all-cause deaths were essentially randomly distributed around zero. Relative model fits were not compared by Jerrett et al., thus precluding identification of the "best" models on this basis. However, only a selected few of these 992 estimates are emphasized in the Jerrett report. By considering the results as a whole, we find major differences among these relationships according to the regression model selected and methods of estimating exposures, none of which specifically considered latency periods. Strong correlations among the various pollutants considered make it difficult to define any "true" relationships; we found no significant differences among their risk estimates. Relationships with deaths from all causes should be the basis for air pollution control policies and, in a study of this regulatory importance, it is important to discuss both positive and negative findings and to consider the entire suite of results rather than a few that happen to conform to *a priori* regulatory objectives and were apparently selected for that reason

## Introduction

Michael Jerrett and a group of co-investigators (2011) studied long-term relationships between ambient air quality and survival among California members of the American Cancer Society's Second Cancer Prevention Study (ACS CPS II), under contract to the California Air Resources Board (CARB). Their 148-page report was subject to extensive peer review by a panel of invited experts, most of whose comments were not incorporated in the final published version of the report. Since the original survey data were not available to outside investigators, this paper uses detailed meta-analyses of the published results to reexamine the Jerrett report in the light of the critical review comments.

The Jerrett report provides results from 992 Cox proportional hazard regressions:

- 8 causes of deaths, including "all causes" and several overlapping categories
- 2 types of Cox models (standard Cox [SC] and random effects [RE])
- 5 different regression models, accounting for different levels of confounding (only 4 models were used in most cases)
- 36 up to 6 different methods of estimating current exposures for up to 6 different air pollutants, involving both individual and zip-code average estimates:

6 methods for $PM_{25}$
2 methods for ozone
3 methods for $NO_2$
1 method for $PM_{10}$
1 method for $SO_4^{2-}$
3 methods for road proximity.

Jerrett et al. presented each of these 16 sets of regression results in separate tables of either 64 or 80 model results (depending on whether 4 or 5 models were used), comprising relative risks and 95% confidence limits for the pollutants and selected interaction variables, based on interquartile ranges (IQRs). Note that $SO_4^{2-}$ is a constituent of $PM_{2.5}$ (the only one considered), which in turn is a constituent of $PM_{10}$. Jerret et al. did not evaluate associations with $SO_2$ nor CO, which represent typical indicators for large stationary and vehicular traffic pollution sources, respectively.

Further, there are no indications that underestimation of confidence intervals resulting from multiple testing was considered, of which the search for the "best" exposure model may be a prime example (Westfall and Young,1993). In this regard, the entire analysis of Jerrett et al. could be considered "data dredging", as discussed by Rothman and Greenland (1998).

As may seen by the emphasis on $PM_{2.5}$ (which is described as the "primary motivation" for the project) shown above, the Jerrett project was ostensibly intended to support CARB regulations for this pollutant, including those proposed for diesel-powered vehicles (Diesel engines emit small particles that comprise another constituent of $PM_{2.5}$ that was not specifically included in the Jerrett report). However, the report's overarching conclusion is quite broad and could apply to a number of previous studies:

> *We conclude that combustion-source air pollution is significantly associated with premature death in this large cohort of Californians.*

However, there are some major omissions: The conclusions did *not* say that these significant positive findings are limited to deaths from cardiovascular causes, that significant negative (beneficial) relationships were found for cancer, and that no evidence for longitudinal (time-dependent) effects of $NO_2$ or ozone were found for cardiovascular mortality, in spite of historically high ozone levels in Southern California. The analysis also failed to consider latency periods required for the development of new cases of the chronic diseases considered.

## Reanalysis Methods

### Regression Models Used by Jerrett et al.

Table 1 lists the independent variables used in the Jerrett models, which are listed in order of successive inclusion. Models 1-4 were carried through all variations in exposure estimates; Model 5 was limited to "individual land-use regression" (LUR) exposure estimates. Regressions were not stratified by age at death.

Model 1 includes a selected set of individual characteristics similar to those used by Pope et al. (1995, 2002). Model 2 adds selected "ecological" variables that are only available as averages over counties or zip codes. Lipfert et al. (2000) found that such ecological variables can have important effects on mortality risk estimates. Potentially important factors not considered by Jerrett include climate, existing medical conditions, personal income, and access to medical care, each of which has been shown to be an

important predictor of mortality, even at the county level. Models 3-5 add dummy variables in an attempt to account for urban-rural gradients favoring urbanized areas where the ACS cohort members seem to have lower mortality rates, especially in Los Angeles. Such reversals of the expected urban-rural survival rates have been noted by others, who propose explanations in terms of rural pollution sources (Hendryx et al., 2010 ) and/or reduced access to medical care (Ezzati et al., 2008). However, the approach of Jerrett et al. is to simply offset these mortality differences with dummy variables and to assume that the derived pollution dose-response factors still apply, with no explanations of the offsets. Despite these reservations, we used results for all 5 models in the meta-analysis to examine the effects of model complexity.

**Table 1 Independent Variables Included in the Jerrett Regression Models**

| Model # | Variables |
|---|---|
| 1 | Individual characteristics only |
| | (similar to the original national-level ACS studies) |
| | smoking habits |
| | educational level |
| | body-mass index (BMI) and $BMI^2$ |
| | alcohol consumption |
| | occupational exposure |
| | dietary indices |
| 2 | Individual + ecological variables |
| | median household income |
| | % below 125% of poverty level |
| | % unemployed |
| | % with less than high school education |
| | Gini income inequality coefficient |
| | % Caucasian residents |
| 3 | + indicator variable for Los Angeles (LAI) |
| 4 | LAI + separate $PM_{2.5}$ effect for Los Angeles (LAI*$PM_{2.5}$) |
| 5 | + indicator variables for Fresno, Los Angeles, San Diego, Sacramento, San Francisco |

Note: the Jerrett report does not specify whether Models 3-5 also included the 6 ecological variables; we assumed they did.

**Inter-Relationships among Cause-of-Death Categories**

Standard vital statistics reports tend to show positive spatial relationships between age-adjusted mortality rates for cancer and heart disease, presumably because of common socio-economic factors. Table 2 shows the cause of death categories considered, of which only all causes, CHD, respiratory, and "other" may be considered non-overlapping. Since the sums of CHD, respiratory, and "other" deaths are about 2% less than all causes, it appears that traumatic deaths (external causes) may have also been excluded from "other" causes. However, this relatively minor discrepancy is unlikely to influence the overall conclusions of this meta-analysis.

**Table 2 Causes and Numbers of Death Considered**

| | | |
|---|---|---|
| 1. | "all causes" (n=18744) | all ICD9 codes |
| 2. | cardiovascular (CVD) (7649) | ICD9 390-459 |
| 3. | ischemic heart disease (IHD) (4346) | ICD9 410-414 |
| 4. | respiratory disease (1871) | ICD9 460-519 |
| 5. | lung cancer (1414) | ICD9 162 |
| 6. | all cancers (6171) | ICD9 140-239 |
| 7. | others (non-cardiorespiratory) (8871) | all – ICD9 390-459 – ICD9 46 |
| 8. | others (non cancer) 2700 | all – ICD9 390-459 – ICD9 460-519 – ICD9 140-219 |

Since statistical power is proportional to the square root of sample size, we would expect to see smaller standard errors for all-causes than for lung cancer, by a factor of about 3.5. None of Jerrett et al.'s lung cancer risks are significant, which could be due to the smaller sample size or the absence of a causal association. For these reanalyses, we selected all-cause ("all"), ischemic heart disease ("IHD"), and other non-cardio-respiratory) ("other") deaths, most of which are due to cancer. This leaves 5527 deaths not considered. Although results for specific causes of death might provide clues as to possible causal mechanisms, all-cause deaths are the most relevant for policy decisions and should be used as a "gatekeeper" with respect to more detailed analyses.

**Correlations**

The Jerrett report includes correlation matrices for pollutants but not for mortality rates or for traffic indicators (road buffers). Similar pollutants are highly inter-correlated, but ozone and $NO_2$ are essentially uncorrelated. Pollutants based on individual residential addresses are only moderately correlated with those averaged over zip codes.

**Exposure Estimation**

The numbers, locations, and frequencies of pollutant measurements varied. For example, $PM_{10}$ was measured at 223 sites, $PM_{2.5}$ at 112 sites, and $NO_2$ at 138 sites. Numbers of sites were not given for $O_3$ (presumably similar to $NO_2$) or sulfate (less than or equal to $PM_{2.5}$). Various statistical methods (Table 3) were used to estimate exposures based on these measurements, either at individual subjects' residential addresses at enrollment into the ACS survey or averaged over the relevant zip codes. However, the Jerrett report does not include results for all methods for each pollutant. For example, results for an additional method referred to as "Bayesian Maximum Entropy" (BME) were only reported for ozone at the zip-code level; as a result, we did not consider this method separately.

**Table 3. Methods Used to Estimate Exposures**

Inverse distance weighting (IDW)
The statistical procedure known as kriging (KRG)
Land-use regression, based on 29 categories of land use (LUR).]
Use of remotely sensed $PM_{2.5}$ data (RS).
Bayesian Maximum Entropy (BME)

Multiple alternative protocols for estimating exposures have seldom been used in long-term studies of this type. For example, Pope et al. (1995, 2002) and Jerrett et al. (2009) assigned the same exposures to each subject in a given multi-county metropolitan statistical area, and their results have been used to set national pollution control policies.

**Restatement of the Jerret et al. Risk Estimates**

Jerrett et al. present their results in terms of relative risks (RRs) and their 95% confidence intervals (CIs), which are based on the Cox models they used. These CIs do not take into account multiple testing or multiple modeling and thus may be underestimated. However, this format is not very convenient for meta-analysis or for the examination of interrelationships. Accordingly, we used the logarithms of these values to represent the fractional risk coefficients and their standard errors.

For Model 4, which considered pollution risks in Los Angeles separately from the rest of the state, we combined those risk coefficients by adding a fraction of the Los Angeles value to the statewide value and by summing their variances. The fraction used was 0.28, as obtained from 1993 California death counts published by NCHS.

In any analysis of this type, a decision must be made as to the pollution levels for which the risks are estimated. Studies with a regulatory focus often use a fixed concentration increment like 10 $\mu\gamma/m^3$. Jerrett et al. selected the interquartile range (IQR), the difference between $75^{th}$ and $25^{th}$ percentiles, but this measure is not relevant to pollution control decisions (no one is actually exposed to the IQR). Other studies have used the mean pollution values (such estimates are known as "elasticities" in the economics literature) or "mean- minimum" values in order to account for non-zero background values. In general, using IQRs will tend to exaggerate the risks of the most widely varying pollutants; we restated the original Jerrett findings as elasticities for use in our meta-analysis. One advantage of using elasticities is the ability to compare the findings with other pollutants with which the species of interest may be correlated (Lipfert and Wyzga, 1997).

**Meta-Regression Analyses**

Because of the sheer volume of the 992 results in the 16 tables of the Jerrett report and to examine them all in context, we ran ordinary least squares (OLS) regressions with elasticities as the dependent variable and Jerrett's various stratification parameters as independent variables. In our meta-analyses, we use the published risk estimates of Jerrett et al. as dependent variables (converted to elasticities), and thus their CIs are not at issue. Our analysis is simply intended to examine consistencies among these various risk estimates by considering the whole set rather than individual estimates that may or may not be statistically significant at a given *p*-value. Thus, our significance tests relate to the influences of the various stratification parameters on the relative consistency of the original risk estimates, and Jerrett et al.'s tests of whether their individual risk estimates differ from unity are not at issue.

The stratification parameters used as independent variables include:

**Model.** We used the model number (from 1 to 5) as an index of increasing complexity, as shown above.

**Exposure Method.** We chose IDW as the baseline and used dummy variables (0,1) for KRG, LUR, and RS methods. We did not consider BME because only a few results were reported by Jerrett et al.

**Spatial Scale.** Exposures were estimated for either individual addresses (base line) or for zip-code averages (dummy variable).

**Cox Model Type**. We used the standard model (SC) for the base with a dummy variable for the random effects (RE) models.

**Pollutants.** We chose $PM_{2.5}$ as the base, with dummy variables for $O_3$, $NO_2$, $PM_{10}$, $SO_4^{2-}$. and road proximity.

This protocol uses 124 observations and eleven independent variables for each of three cause-of-death categories and thus represents 372 of the published Jerrett analyses in a greatly simplified format. Intercepts of these regressions represent baseline risks for $PM_{2.5}$, for a hypothetical "Model 0." Results for Models 1-5 are obtained by adding the "model" coefficient times the model number to the intercept (Table 4a). We regard Model 2 as the most reasonable choice and also present results on this basis in Table 4(b). It is important to recognize that our coefficients for pollutants other than $PM_{2.5}$ represent incremental risks relative to $PM_{2.5}$. Thus, all the other pollutants appear to pose less IHD risk than $PM_{2.5}$ and more risk for all other causes of death. We also ran meta regressions for $PM_{2.5}$ as the only pollutant, which produced essentially the same results.

Models of increasing complexity increase the estimated risks for all-cause and for other causes, but decrease them for IHD deaths. All regression parameters are significant for IHD except model type, which is not significant for any cause of death category. Using land use regression (LUR) to estimate exposures increases risks significantly for all three cause categories. Other exposure estimation methods decrease the IHD mortality risks. Note the strong similarities among coefficient standard errors in Table 4(a) for each cause of death category. This is typical when risks are expressed as non-dimensional elasticities.

**Table 4(a) Meta-Regression Results** (coefficient, standard error)

| | **all-causes** | **IHD** | **other** |
|---|---|---|---|
| intercept ($PM_{2.5}$) | -0.0231 | **0.338** | **-0.238** |
| $R^2$ | 0.640 | 0.910 | 0.819 |
| Std error | 0.021 | 0.046 | 0.033 |
| model specification | **0.0099 (.0016)** | -0.004 (0.0035) | **0.0238 (0.0025)** |
| exposure scale | 0.0101 (0.0071) | **-0.032 (0.016)** | **0.0676 (0.0112)** |
| KRG | -0.0097 (0.0072) | **-0.050 (0.0155)** | 0.0059 (0.0113) |
| LUR | **0.0167 (0.0069)** | **0.0498 (0.0148)** | **0.0217 (0.0108)** |
| RS | -0.0123 (0.0094) | **-0.079 (0.020)** | **0.0296 (0.0147)** |
| model type | -0.001 (0.0038) | -0.000 (0.0082) | 0.0009 (0.0059) |
| $O_3$ | **-0.041 (0.0083)** | **-0.154 0.018)** | **0.0469(0.0130)** |
| $NO_2$ | 0.010 (0.0068) | **-0.037 (0.015)** | **0.0381 (0.0107)** |
| $PM_{10}$ | -0.002 (0.0094) | **-0.086 (0.015)** | **0.0366 (0.0147)** |
| $SO_4^{2-}$ | -0.005 (0.0094) | **-0.166 (0.020)** | **0.0803 (0.0147)** |
| road proximity | **0.0205 (0.0071)** | **-0.362 (0.015)** | **0.127 (0.0112)** |

Table 4(b) was created to represent risks according to Model 2, with individual exposure estimation by land use regression (LUR). This protocol represents an average upper limit for models (Models 1 and 2) that do not single out Los Angeles as a special case and for the exposure method that yields the strongest positive estimates. Risks for each other pollutant were estimated by adding its coefficient to the $PM_{2.5}$ baseline. Road proximity has the largest risk for all-cause and other mortality; $PM_{2.5}$ posed the largest

risk for IHD deaths. There is a nearly inverse relationship between estimated risks for IHD and for other causes (causes of death are mutually exclusive for individuals).

**Table 4(b) Relative Risks for Model 2 and individual exposures by land-use regression**

| | all-causes | IHD | other non-CVD |
|---|---|---|---|
| $PM_{2.5}$ | 0.997 | **1.28** | **0.89** |
| $O_3$ | **0.957** | **1.10** | **0.93** |
| $NO_2$ | 1.007 | **1.23** | **0.92** |
| $PM_{10}$ | 0.994 | **1.18** | **0.92** |
| $SO_4^{2-}$ | 0.991 | **1.08** | 0.96 |
| Roads | 1.017 | **0.89** | 1.01 |
| Average | 0.994 | 1.13 | 0.94 |
| 95% CIs | 0.942-1.045 | 0.77-1.49 | 0.83-1.05 |

When considered as a group, Table 4 indicates that there are no significant differences among these six risk predictor variables for any of the causes of death considered, either for all models (Table 4a) or for the exposure method yielding the largest positive risks (Table 4b).

**Concluding Discussion**

The objective of the above meta-analysis is to present a comprehensive picture of the entire Jerrett analysis, focusing on all-cause mortality and two non-overlapping specific cause of death categories. There are important similarities and differences among these meta-analysis results for different causes of death.

**What Does the Meta-Analysis Show?**

The model type (SC vs. RE) variable was essentially zero for all three cause categories (Figure 1), implying no difference between these two types of Cox models. This also implies that 50% of the model runs were redundant. Exposures based on land-use regressions produced higher risk estimates for all three causes, for reasons that were not discussed. Differences in model specifications (models 1-5) were important for all and for other causes but not for IHD.

Exposure scale (individual vs. zip code) was not important for all causes, negative for IHD, and positive for other causes; a positive effect would have been expected because of the greater precision implied for individual exposures. Effects of the various methods used to estimate exposures were inconsistent across causes of death. Further, exposures were based on residence locations, and no attempts were made to account for either individual mobility or temporal changes in conjunction with latency periods. These uncertainties are common to all pollutants and may have contributed to the inability to distinguish among them.

Averages of the standard errors of elasticities were the same for all diseases after correcting for sample size (Figure 2). This implies no differences in relative model fits for these three cause-of-death categories.

As shown in Table 4(b), only ozone had a significant relationship with all-cause mortality, and it was *negative*, implying beneficial effects. Road proximity had the largest (but not significant) *positive* association with all-cause mortality. However, when

considered as averages based on land-use-regression exposure estimates, there are no significant differences among the 6 pollutants.

**How Do the Results of Jerrett et al. Compare with Those of Previous Studies?**

A number of other studies of California mortality and air pollution have been published, for both long-term (spatial) and daily (time-series) analyses. The all-cause risk levels reported by Jerrett et al. (2011) are consistent with those of Enstrom (2005, whole state, n=35000) and of Jerrett et al. (2005, Los Angeles, n=5800), but not with those of Ostro et al. (2010, whole state, n=540). Abbey et al. (1999) showed a $PM_{10}$ threshold relationship for 6338 nonsmokers. In addition, some of the national long-term mortality studies using this ACS cohort are relevant (Pope et al.,1995; Pope et al., 2002). Zeger et al.(2008) found $PM_{2.5}$ all-cause mortality risks in the eastern and central portions of the US but not in the west (n=3.1 million). The Veterans Cohort Study (Lipfert et al., 2000) indicated Los Angeles as a "hot spot" for excess all-cause mortality.

By cause of death, Jerrett et al. (2005) found elevated but non-significant risks for all causes of deah in Los Angeles, based on fully-adjusted regression models. Pope et al. (2002) found significantly elevated national risks for cardiovascular diseases and lung cancer, with non-significant risks for all other causes.

The results of Jerrett al. (2011)s are similar to the findings of time-series studies of California daily mortality (Kinney and Ozkaynak, 1991; Fairley, 1998; Moogavkar, 2000, 2003; Ostro et al., 2000, 2006). However, many of these studies suffer from the same problems noted for Jerrett et al., such as failure to account for latency of pollution exposures.

**What Other Issues Remain?**

There may also be issues of timing and of space-time interactions. Mortality follow-up was from1982-2000 but most of the air quality data (especially $PM_{2.5}$) are from ca. 2000. Jerrett et al., do not discuss this discrepancy. Other studies (Lipfert et al. 1998, 2002) show that ambient air quality has improved by about a factor of 2 during this period, but mainly in urbanized areas. Thus, there may be different exposure biases between urban and rural areas. Such biases would also be affected by latency periods between exposure and response. If the responses were really due to previous much higher exposures, Jerrett's pollution response functions (deaths per unit pollution) would be biased high, more so in urban areas. It is perhaps noteworthy that the Jerrett report devotes almost 40 pages to the estimation of the spatial distributions of exposures (without mentioning temporal trends) and a total of only 5 pages to discuss of all of the findings and conclusions.

Explanations of the differences in the 5 methods of estimating exposures were not offered. Since all of them dealt with outdoor air quality and none of them considered indoor or personal levels, exposure errors common to all of them may be involved. Extensive measurements of personal exposures were conducted in Riverside, CA (Ozkaynak et al., 1996) which should at least have been mentioned.

All of the pollutant associations with IHD were significant, with similar risks for $PM_{2.5}$ and $NO_2$ and a *beneficial* relationship with road proximity. However, none of these results appear to be credible; the hypothesis that almost 30% of IHD deaths could be due to these modest levels of $PM_{2.5}$ seems implausible in the light of much higher pollution levels in other countries and previously in Los Angeles. The opposite situation is seen with "other" causes of death, which are mainly from cancer. It is equally implausible that an 11% *decrease* in cancer mortality could result from exposure to $PM_{2.5}$. Even if all of

these estimates were biased high because of trends in ambient air quality, the inexplicable differences in sign between IHD and cancer mortality associations would remain.

Explanations for these two sets of implausible results must lie with either biased diagnoses or uncontrolled confounding. It is not clear whether the Jerrett analysis properly controls for individual Hispanic ethnicity, for example. It also appears that controls are lacking for individual income, medical status at enrollment, and climate. By contrast, studies of a national cohort of US military veterans controlled for individual initial blood pressure and for climate, both of which were highly significant (Lipfert et al., 2000, 2003), while $PM_{2.5}$ was not. Also, since cardiovascular mortality typically occurs in younger age groups and respiratory deaths in the elderly, age-stratified regressions may have produced more rational results.

Finally, as voluminous as the Jerrett report is, it does not tell the whole story. Other important pollutants were not considered: CO, $SO_2$, PM constituents like metals and carbon. Multi-pollutant models were not evaluated. The apparent excess rural mortality with respect to urban areas was not explained. The rationale for the "best" exposure model was not discussed. No information is provided on the performance of the various covariate confounders, such as education, body-mass, smoking status, neighborhood socioeconomic status, etc. It would be helpful to see whether the effects of these important variables are consistent for each cause of death and for both urban and rural areas. The apparent inconsistent application of the various exposure methods to all pollutants raises questions about possible selective presentation of results. There are also questions of exposure timing, previous and historical pollutant concentrations were substantially higher as were urban-rural gradients (Lipfert, 1998; Lipfert and Morris, 2002). This has the effect if inflating risks based on current concentrations. Most of these questions can only be resolved through a complete reanalysis of the original data, free from regulatory pressures. Requests for the data set used in the Jerrett report for such reanalyses have been declined.

## Conclusions

Based on meta-analysis of the entire body of results of Jerrett et al. (2011), we find no relationship between $PM_{2.5}$ exposures as estimated in various ways and all-cause mortality in California from 1982-2000. Our results are consistent with those of most other investigators. We also find no significant differences among the risks associated with different pollutants. Our results are not affected by uncertainties in the confidence intervals reported by Jerrett et al. that may have been affected by multiple testing. The opposing and near-canceling risk estimates for heart disease and other diseases remain unexplained.

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**Figures**

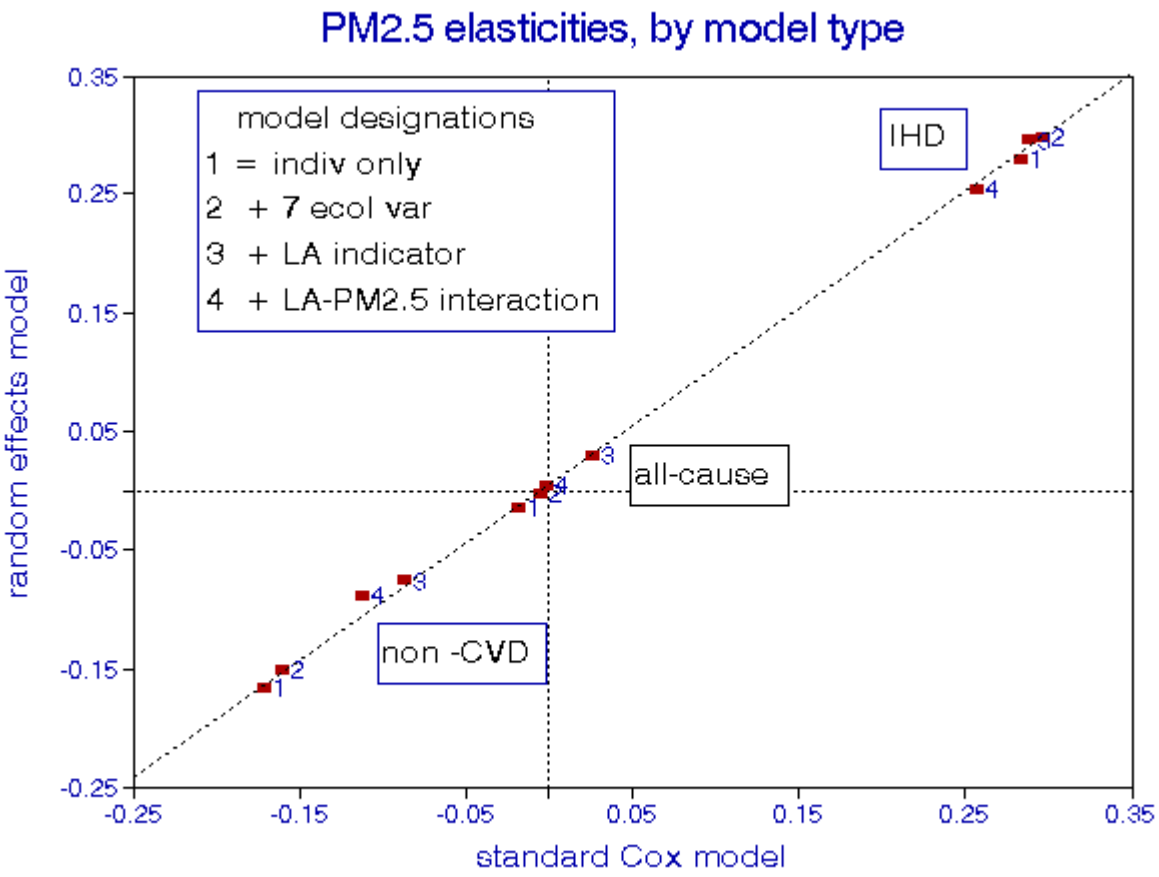


Figure 1. $PM_{2.5}$ elasticities are compared for the standard Cox and the random effects models, by cause of death and model specification.

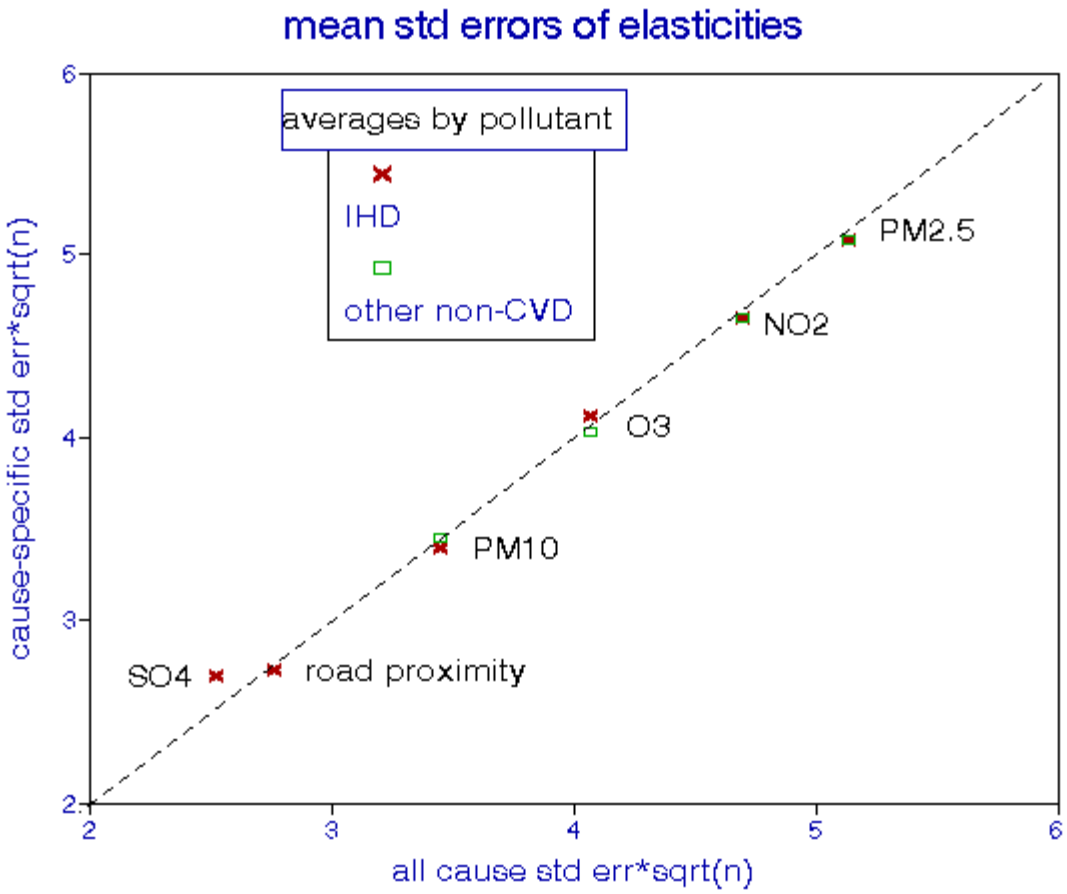


Figure 2. Mean standard errors of elasticities are compared by cause of death and pollutant, after adjustment for sample size.