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## Cardiovascular Mortality and Exposure to Airborne Fine Particulate Matter and Cigarette Smoke Shape of the Exposure-Response Relationship

C. Arden Pope III, PhD; Richard T. Burnett, PhD; Daniel Krewski, PhD; Michael Jerrett, PhD; Yuanli Shi, MD; Eugenia E. Calle, PhD; Michael J. Thun, MD

**Background**—Fine particulate matter exposure from both ambient air pollution and secondhand cigarette smoke has been associated with larger risks of cardiovascular mortality than would be expected on the basis of linear extrapolations of the relative risks from active smoking. This study directly assessed the shape of the exposure-response relationship between cardiovascular mortality and fine particulates from cigarette smoke and ambient air pollution.

**Methods and Results**—Prospective cohort data for >1 million adults were collected by the American Cancer Society as part of the Cancer Prevention Study II in 1982. Cox proportional hazards regression models that included variables for increments of cigarette smoking and variables to control for education, marital status, body mass, alcohol consumption, occupational exposures, and diet were used to describe the mortality experience of the cohort. Adjusted relative risks of mortality were plotted against estimated average daily dose of fine particulate matter from cigarette smoke along with comparison estimates for secondhand cigarette smoke and air pollution. There were substantially increased cardiovascular mortality risks at very low levels of active cigarette smoking and smaller but significant excess risks even at the much lower exposure levels associated with secondhand cigarette smoke and ambient air pollution.

**Conclusions**—Relatively low levels of fine particulate exposure from either air pollution or secondhand cigarette smoke are sufficient to induce adverse biological responses increasing the risk of cardiovascular disease mortality. The exposure-response relationship between cardiovascular disease mortality and fine particulate matter is relatively steep at low levels of exposure and flattens out at higher exposures. (*Circulation*. 2009;120:941-948.)

**Key Words:** air pollution ■ cardiovascular diseases ■ mortality ■ tobacco smoke pollution ■ smoking

Since the early 1990s, there has been growing evidence that long-term exposure to fine particulate matter air pollution contributes to the risk of all-cause and cardiovascular mortality.<sup>1-9</sup> An important issue relative to these findings is that the inhaled dose of fine particles from ambient pollution is extremely small compared with that from cigarette smoking. The cardiovascular mortality effect estimates from studies of ambient fine particulate pollution and secondhand cigarette smoke (SHS) are much higher than would be expected on the basis of extrapolations of the effects of active cigarette smoking that assume a linear dose-response relationship that goes through the origin.<sup>10-12</sup> Conversely, linear extrapolations of exposure-response functions estimated from the air pollution and SHS literature to very high levels of exposure predict cardiovascular death rates that are higher than considered plausible.<sup>13,14</sup> The present analysis explores the shape of the exposure-response relationship between cardiovascular mortality and fine particulate air pollution from cigarette smoke and ambient air pollution.

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### Methods

#### Cohort and Exposure Data

This study is largely based on data collected by the American Cancer Society (ACS) as part of the Cancer Prevention Study II (CPS-II), an ongoing prospective cohort mortality study involving >1 million adults. More detailed descriptions of this cohort are provided elsewhere.<sup>3,4,15,16</sup> Participants from throughout the United States were enrolled in the cohort in the fall of 1982. Enrollment was restricted to persons who were aged  $\geq 30$  years and who were members of households with 1 or more members aged  $\geq 45$  years. Participants completed a confidential questionnaire, which included items on age, sex, weight, height, smoking history, alcohol use, occupational exposures, diet, education, marital status, and other individual characteristics (the questionnaire can be viewed at [http://www.cancer.org/docroot/RES/RES\\_6\\_5.asp?](http://www.cancer.org/docroot/RES/RES_6_5.asp?)). As with most data collected by questionnaire, it is difficult to directly and fully verify the accuracy and validity of the research subject's responses. However, a data quality audit that utilized a sample of microfilm

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copies of the questionnaires has been conducted as part of a larger reanalysis project,<sup>3</sup> and only “minor errors” that “did not materially impact the data as published” were found.<sup>17</sup> Vital status of the study participants was ascertained by personal contact from the month of enrollment until August 1988 and thereafter through linkage with the National Death Index.<sup>16</sup> Death certificates were obtained and coded for cause of death through 1995. Beginning in 1996, cause of death codes were provided directly by the National Death Index.

Cause of death was coded according to the *International Classification of Diseases, Ninth Revision (ICD-9)*.<sup>18</sup> The present analysis used 3 ICD-9 cause of death groupings, namely, deaths due to (1) ischemic heart disease (ICD-9 410 to 414), (2) cardiovascular disease (ICD-9 401 to 459), and (3) cardiopulmonary disease (ICD-9 401 to 459 and 460 to 519). Cardiovascular and cardiopulmonary diseases have substantial common comorbidity. A potential for cross-coding and misclassification of primary causes of death is also inherent in the use of death certificate data, making it somewhat unclear which ICD-9 groupings most generally or specifically indicate death due to cardiovascular disease. For example, inflammation associated with pulmonary disease contributes to cardiovascular risk,<sup>19</sup> and individuals with chronic obstructive pulmonary disease, determined either by clinical symptoms or deficits in lung function, are much more likely to be coded as dying of cardiovascular disease on the basis of death certificate data.<sup>20–22</sup>

Limited monitoring of ambient fine particulate matter with an aerodynamic diameter  $\leq 2.5 \mu\text{m}$  ( $\text{PM}_{2.5}$ ) was conducted for the years 1979–1983 by the US Environmental Protection Agency (EPA) as part of the Inhalable Particulate Monitoring Network. The original ACS analysis of mortality risk associated with  $\text{PM}_{2.5}$  air pollution used a subcohort of the ACS CPS-II cohort who lived in monitored areas and could be linked to air pollution data from this early monitoring network.<sup>2</sup> Because of the promulgation of the National Ambient Air Quality Standards for  $\text{PM}_{2.5}$  in 1997,<sup>23</sup> more extensive  $\text{PM}_{2.5}$  monitoring has been conducted since the late 1990s. Elevated mortality risks associated with  $\text{PM}_{2.5}$ , with the use of these additional pollution data and with subcohorts of  $\approx 320$  to 500 thousand participants in the ACS CPS-II cohort who resided in monitored areas have been estimated and reported elsewhere.<sup>2–5</sup> These analyses used longer follow-up times, and, as described elsewhere,<sup>3–5</sup> they used 3 constructed indices of exposure to  $\text{PM}_{2.5}$  that used the early  $\text{PM}_{2.5}$  exposure data near the time of enrollment (1982), mean  $\text{PM}_{2.5}$  for a period near the end of follow-up (1999–2000), and the average of the 2 in the analyses. Although there generally was a decline in pollution levels, mean  $\text{PM}_{2.5}$  levels were highly correlated over the 2 time periods, and the rank ordering of the cities by relative pollution levels remained nearly the same. As reported elsewhere,<sup>4,5</sup> similar cardiopulmonary risk estimates associated with  $\text{PM}_{2.5}$  were estimated with the use of the 3 indices. A  $10\text{-}\mu\text{g}/\text{m}^3$  elevation in  $\text{PM}_{2.5}$  was associated with adjusted relative risks for cardiopulmonary mortality equal to 1.06 (95% confidence interval [CI], 1.02 to 1.10), 1.08 (95% CI, 1.02 to 1.14), and 1.09 (95% CI, 1.03 to 1.16) for the 3  $\text{PM}_{2.5}$  exposure indices, respectively.<sup>4</sup>

The present analysis, which seeks to improve the resolution of the exposure-response relationship at the lower levels of smoking-related exposure, included the full cohort with the following exceptions: (1) individuals who smoked cigars or a pipe but not cigarettes or who had incomplete data on smoking history were excluded, and (2) to ensure the evaluation of only long-term smoking with exposure over most of their adult lifetimes, smokers who started smoking after 25 years of age were also excluded. The final analytic cohort was  $\approx 1.02$  million participants, including 217000 current smokers at time of enrollment.

## Statistical Analysis

Cox proportional hazards survival models<sup>24</sup> were estimated separately for ischemic heart, cardiovascular, and cardiopulmonary disease deaths. Deaths not in the specific cause-of-death category were censored at time of death. Survival time from the date of enrollment was used as the time axis. Because additional information on cigarette smoking and residence history was not collected after enrollment, and because changes in smoking habits can result in

increasing exposure measurement error with longer follow-up, the present analysis was based on a restricted follow-up period of  $\approx 6$  years through December 31, 1988. The baseline hazard function in the Cox regression models was stratified by 1-year age categories, sex, and race (white versus other). The models included indicator variables for smoking increments of  $\leq 3$ , 4 to 7, 8 to 12, 13 to 17, 18 to 22, and  $\geq 23$  cigarettes per day for current smokers; indicator variables using the same increments for previous smokers; and variables to control for education, marital status, body mass, alcohol consumption, occupational exposures, and diet.

In particular, 2 variables that indicated completion of high school or education beyond high school were included along with marital status variables that represented “single and other” and married. Body mass index and body mass index squared were entered as continuous variables. Alcohol consumption was represented by indicator variables for beer, liquor, and wine drinkers and nonresponders versus nondrinkers. Various variables were used to control for occupational exposures, including the following: regular occupational exposure to asbestos, chemicals/acids/solvents, coal or stone dusts, coal tar/pitch/asphalt, diesel engine exhaust, or formaldehyde, along with additional variables that indicated 7 different rankings of an occupational dirtiness index that has been developed and described elsewhere.<sup>3,25</sup> The models included quintile indicator variables for 2 diet indices that accounted for fat consumption and consumption of vegetables, citrus, and high-fiber grains.<sup>15</sup> Sensitivity to age was explored by conducting separate analyses for all ages, ages  $< 65$  years, and ages  $\geq 65$  years at time of enrollment.

## Plotting Exposure-Response Relationships

Adjusted relative risks (as estimated by the hazard ratios from the Cox proportional hazards model) for air pollution and various levels of cigarette smoking from the present ACS analysis, previous analyses of ACS- $\text{PM}_{2.5}$  cohorts, comparison  $\text{PM}_{2.5}$  risk estimates from alternative cohorts, and comparison estimates for SHS were plotted against estimated average daily inhaled doses of  $\text{PM}_{2.5}$ . Across different studies, various measures of exposure are used, including average concentrations of  $\text{PM}_{2.5}$ , cigarettes smoked per day, and different increments of SHS exposure. To evaluate exposures on a common scale, estimated average daily inhaled dose was used as the common exposure metric to plot the exposure-response relationship. The average daily dose of  $\text{PM}_{2.5}$  inhaled into the lungs was estimated by multiplying average  $\text{PM}_{2.5}$  concentrations by average daily inhalation rates ( $\text{m}^3/\text{d}$ ). Actual ventilation rates depend on age, sex, body size, activity levels, and other factors. Estimates of average daily inhalation rates for adults range from 13 to 23  $\text{m}^3/\text{d}$ .<sup>26–30</sup> For the purposes of this analysis, the baseline estimates of daily dose assume an inhalation rate of 18  $\text{m}^3/\text{d}$ , a value consistent with contemporary estimates.<sup>28–30</sup>

The dose of  $\text{PM}_{2.5}$  from cigarette smoking depends on cigarette composition and smoking patterns. The Federal Trade Commission has developed a machine-based measurement system that estimates cigarette yields according to the Federal Trade Commission protocol.<sup>31</sup> Although these yields provide estimates of potential inhaled dose by smokers, this approach is subject to certain limitations. For example, changes in cigarette composition such as reduced tar or filtered cigarettes may change machine-measured yields but not necessarily the dose because of compensatory changes in human smoking patterns or behavior. The average dose of  $\text{PM}_{2.5}$  from cigarette smoking has been estimated to be from  $\approx 7$  to 17.5 mg per cigarette. On the basis of approximate sales-weighted average delivery of particulate matter for cigarettes sold in the United States from the late 1970s to the early 1990s,<sup>31</sup> the baseline estimates of average daily dose in this analysis assume an inhaled dose of 12 mg per cigarette.

For comparison purposes, excess cardiovascular mortality risk estimates from the 2006 Surgeon General’s report<sup>32</sup> for low to moderate SHS exposure (1 to 14 or 1 to 19 cigarettes per day) and for moderate to high exposure ( $\geq 15$  or  $\geq 20$  cigarettes per day) are included in the plots. Additionally, risk estimates for acute myocardial infarction from the INTERHEART study<sup>33</sup> of 52 countries associated with 1 to 7 hours per week of SHS exposure or exposure

**Table 1. Selected Summary Statistics for the Primary ACS CPS-II Analytic Cohorts Used in the Analysis**

Statistic	Full Cohort Used to Estimate Active Smoking Effects	PM <sub>2.5</sub> Subcohort Used to Estimate Pollution Effects*
n, millions	1.02	0.50
Age at enrollment, mean (SD), y	57 (11)	57 (11)
Body mass index, mean (SD)	25 (4)	25 (4)
Percentage of cohort		
Female	56	57
White	95	94
With high school education	32	31
With more than high school education	54	57
Current smoker	21	22
Former smoker	25	30
Percentage of current smokers who smoked		
≤3 cigarettes per day	3	3
4–7 cigarettes per day	6	7
8–12 cigarettes per day	13	13
13–17 cigarettes per day	7	8
18–22 cigarettes per day	34	33
≥23 cigarettes per day	37	36

\*Subcohorts of various sizes from ≈0.30 to 0.50 million subjects were used in various studies<sup>2–5</sup> depending on the specific PM<sub>2.5</sub> pollution index used. Similar summary statistics were observed for each of the PM<sub>2.5</sub> subcohorts.

from living with a spouse who smoked are included. Long-term average PM<sub>2.5</sub> exposure is estimated to be 20 μg/m<sup>3</sup> for low to moderate SHS exposure (including 1 to 7 hours per week), 50 μg/m<sup>3</sup> for moderate to high exposure, and 30 μg/m<sup>3</sup> for living with a spouse who smokes, on the basis of limited studies that have sampled SHS exposure over time to characterize long-term exposure.<sup>32,34–38</sup>

## Results

Table 1 presents selected summary statistics for the primary ACS CPS-II analytic cohorts used in the analysis, including the larger cohort used to estimate smoking effects and the subcohorts with air pollution data used to estimate air pollution effects. Table 2 presents adjusted relative cardiovascular risk estimates and estimated daily dose of PM<sub>2.5</sub> for various increments of exposure from cigarette smoking, SHS, and ambient air pollution from the present analysis and the selected comparison studies. Figure 1 presents the adjusted relative risks of ischemic heart disease, cardiovascular disease, and cardiopulmonary disease mortality plotted against estimated daily dose of PM<sub>2.5</sub> from different increments of current cigarette smoking (relative to never smokers). Diamonds represent comparable mortality risk estimates for PM<sub>2.5</sub> from air pollution. Stars represent comparable pooled relative risk estimates associated with SHS exposure from the 2006 Surgeon General's report<sup>32</sup> and from the INTERHEART 52-country study of acute myocardial infarction.<sup>33</sup> The 2 dotted lines represent linear fits through the active smoking estimates, with 1 being constrained to pass through the origin. The solid line represents a nonlinear fit through all of the estimates (including active smoking, SHS, ambient PM<sub>2.5</sub>) with the use of a simple nonlinear power function

[relative risk = 1 + 0.2968(dose)<sup>0.2107</sup>] fit with the use of iterative nonlinear regression.

Figure 1 reveals several important findings. (1) The estimated daily dose of PM<sub>2.5</sub> from typical long-term exposure to SHS or ambient air pollution is extremely small compared with the estimated dose from active cigarette smoking. (2) The estimated relative risks from active cigarette smoking, even at relatively light smoking levels, are substantially larger than the relative risks from ambient air pollution or SHS. (3) A linear fit constrained to pass through the origin does not describe the empirical evidence very well, substantially underestimating the effects at low levels of exposure and overestimating the effects at high levels of exposure. (4) An unconstrained linear fit to the active smoking data does not pass through the origin and predicts substantially elevated relative risks even at extremely low doses of PM<sub>2.5</sub> that are higher than the estimated relative risks from air pollution and SHS. (5) The observed patterns of relative risk across the full range of exposure suggest a nonlinear exposure-response function that is relatively steep at low exposures and levels off at higher exposures.

Figure 2 presents the adjusted relative risks plotted over baseline estimated daily doses of PM<sub>2.5</sub> similar to Figure 1 but with the use of a log scale for dose. Risk estimates from 3 major US prospective cohorts that have been used to study the mortality effects of long-term exposure to PM<sub>2.5</sub> are included.<sup>1,2,4,5,7,8</sup> An exposure gap between active cigarette smoking and air pollution or SHS limits our ability to estimate the exposure-response function with high resolution. Nevertheless, a pattern of increasing risk with increasing exposure is generally observed. Daily dose estimates using reasonable alternative assumptions about inhalation rates and inhaled dose from cigarette smoking did not change the basic shape of the exposure-response relationship (plots not shown).

Figure 3 presents adjusted relative risks plotted over different increments of cigarette smoking for participants who were <65 and ≥65 years of age at time of enrollment. Linear fits through the relative risk estimates for cardiovascular disease along with log-linear fits for low exposure levels (≤100 mg) are presented as potential monotonic exposure-response functions. Similarly shaped exposure-response relationships were observed for both men and women. Relative risks of cigarette smoking were larger for younger and middle-aged individuals than for the elderly. Stratifying the data by age groups and estimating relative risks for narrow increments of cigarette smoking result in some statistical noise relative to the shape of the exposure-response function for different age groups at these low levels of smoking. However, for both age groups, there was substantial excess risk associated with even very light smoking and an apparent flattening out of the exposure-response relationship at higher levels of smoking.

## Discussion

Active cigarette smoking has been established as a major independent cause of cardiovascular disease since at least 1983 on the basis of extensive epidemiological, clinical, and experimental data.<sup>39,40</sup> Declining smoking-related relative risks for more elderly participants, potentially because of



**Table 2. Adjusted Relative Cardiovascular and Cardiopulmonary Risk Estimates for Various Increments of Exposure From Cigarette Smoking, Secondhand Cigarette Smoke, and Ambient Air Pollution From the Present Analysis and Selected Comparison Studies**

Source of Risk Estimate	Increments of Exposure	Adjusted Relative Risk (95% CI)			Estimated Daily Dose of PM <sub>2.5</sub> , mg	
		Ischemic Heart Disease	Cardiovascular Disease	Cardiopulmonary Disease	Baseline*	Alternative†
Cigarette smoking estimates based on ACS CPS-II cohort						
ACS full cohort, present analysis	≤3 (1.5) cigarettes/day	1.63 (1.36–1.96)	1.64 (1.42–1.89)	1.72 (1.50–1.96)	18.0	10.5
ACS full cohort, present analysis	4–7 (5.5) cigarettes/day	1.54 (1.34–1.77)	1.61 (1.45–1.78)	1.65 (1.50–1.82)	66.0	38.5
ACS full cohort, present analysis	8–12 (10) cigarettes/day	1.85 (1.69–2.02)	1.79 (1.67–1.93)	1.87 (1.75–2.00)	120.0	70.0
ACS full cohort, present analysis	13–17 (15) cigarettes/day	1.79 (1.59–2.02)	1.67 (1.52–1.85)	1.75 (1.60–1.92)	180.0	105.0
ACS full cohort, present analysis	18–22 (20) cigarettes/day	1.98 (1.87–2.10)	2.02 (1.93–2.11)	2.09 (2.01–2.18)	240.0	140.0
ACS full cohort, present analysis	≥23 (27) cigarettes/day	1.97 (1.86–2.10)	2.03 (1.93–2.13)	2.17 (2.08–2.27)	324.0	189.0
Ambient air pollution estimates based on ACS CPS-II cohort						
ACS PM <sub>2.5</sub> subcohort, original <sup>2</sup>	24.5 μg/m <sup>3</sup> ambient PM <sub>2.5</sub>	...	...	1.31 (1.17–1.46)	0.44	0.56
ACS PM <sub>2.5</sub> subcohort, extended <sup>4,5</sup>	10 μg/m <sup>3</sup> ambient PM <sub>2.5</sub>	1.18 (1.14–1.23)	1.12 (1.08–1.15)	1.09 (1.03–1.16)	0.18	0.23
Comparison ambient air pollution estimates based on alternative cohorts						
Harvard Six Cities original <sup>1</sup>	18.6 μg/m <sup>3</sup> ambient PM <sub>2.5</sub>	...	...	1.37 (1.11–1.68)	0.33	0.42
Harvard Six Cities extended <sup>7</sup>	10 μg/m <sup>3</sup> ambient PM <sub>2.5</sub>	...	1.28 (1.13–1.44)	...	0.18	0.23
Women's Health Initiative <sup>8</sup>	10 μg/m <sup>3</sup> ambient PM <sub>2.5</sub>	...	1.24 (1.09–1.41)‡	...	0.18	0.23
Comparison SHS estimates						
Surgeon General's report <sup>32</sup>	Low-moderate SHS exposure	...	1.16 (1.03–1.32)	...	0.36	0.46
Surgeon General's report <sup>32</sup>	Moderate-high SHS exposure	...	1.26 (1.12–1.42)	...	0.90	1.15
INTERHEART study <sup>33</sup>	1–7 h/wk SHS exposure	1.24 (1.17–1.32)§	...	...	0.36	0.46
INTERHEART study <sup>33</sup>	Live with smoking spouse	1.28 (1.12–1.47)§	...	...	0.72	0.92

\*The baseline estimated daily dose assumes an inhalation rate of 18 m<sup>3</sup>/d and a dose of 12 mg per cigarette.

†The alternative estimated daily dose assumes an inhalation rate of 23 m<sup>3</sup>/d and a dose of 7 mg per cigarette.

‡First cardiovascular disease event.

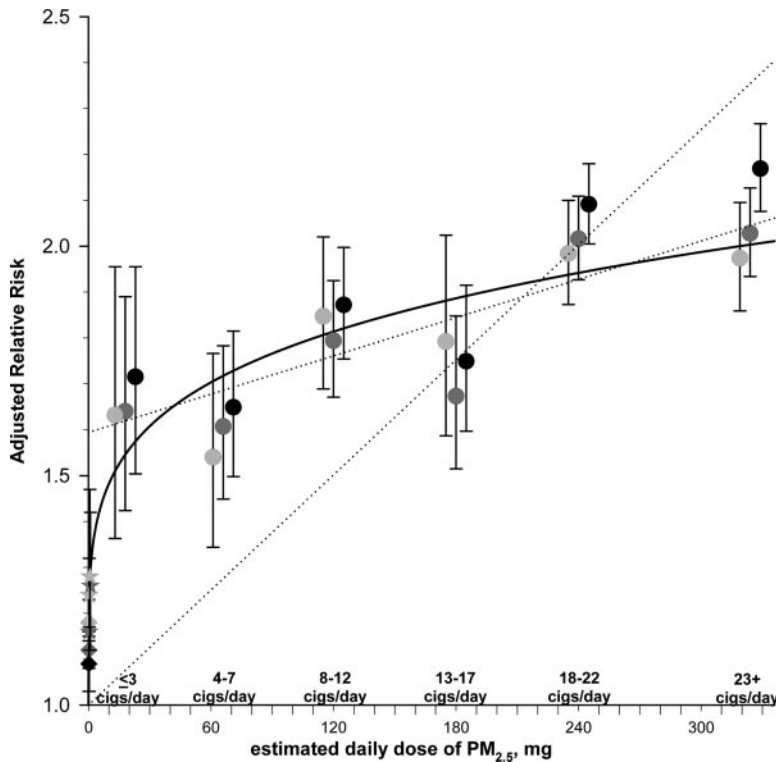
§Myocardial infarction.

competing risks and selection bias, have also been observed previously.<sup>40</sup> The causal relationship between SHS and cardiovascular disease has been recognized by scientific consensus reviews beginning in the early 1990s.<sup>32,41</sup> There is growing evidence that ambient air pollution is also a risk factor for cardiovascular disease.<sup>42,43</sup> Previous studies, including those using the ACS CPS-II cohort data, have observed that ambient PM<sub>2.5</sub> is associated with cardiopulmonary disease mortality but not with non-cardiopulmonary disease mortality.<sup>1–7</sup>

The present analysis combined exposure and risk information for active and passive cigarette smoking and air pollution. The results indicate that it is fundamentally implausible that the relationship between cardiovascular mortality and fine particulate pollution from cigarette smoke and ambient air pollution can be characterized as linked by a simple linear dose-response relationship. The exposure-response relationship between long-term exposure to PM<sub>2.5</sub> and risk of cardiovascular disease mortality is not a linear function that passes through the origin. Rather, our results suggest that the exposure-response function is relatively steep at very low levels of exposure, flattening out at high exposure levels. An

analysis of the PM<sub>2.5</sub>-mortality exposure-response relationship suggests that effect estimates from the studies of ambient air pollution and SHS are not necessarily higher than would be expected on the basis of extrapolations of effects of active cigarette smoking. Even the lowest levels of cigarette smoking are associated with excess risk that exceeds those observed in studies of ambient air pollution and SHS.

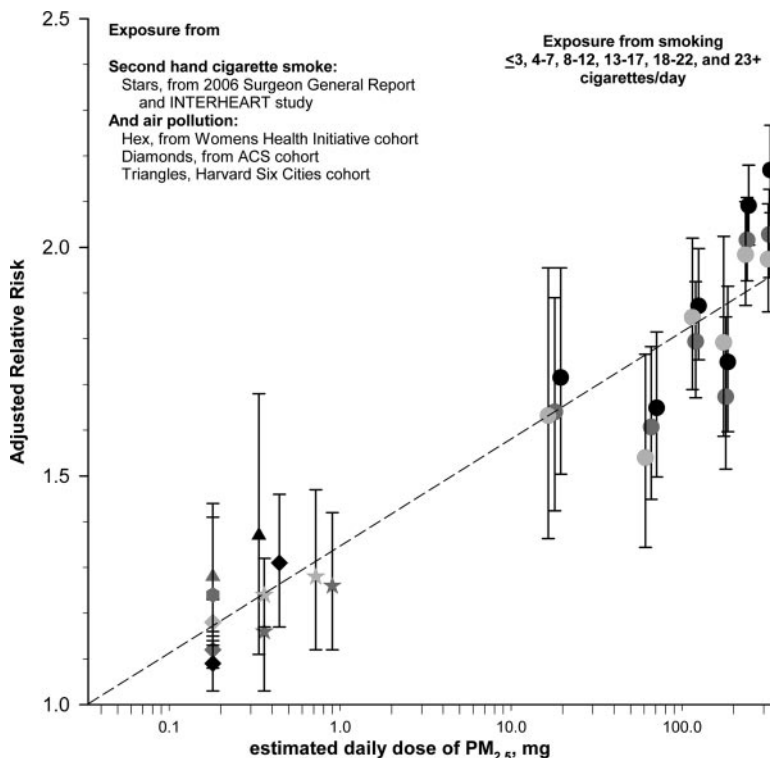
This analysis has several limitations, particularly the large exposure gap between ambient air pollution, SHS, and active smoking. There are no prospective cohort or related studies of long-term exposure across the range of exposure that substantively help to fill this gap. However, historical time-series data from London are instructive.<sup>44,45</sup> Figure 4 presents daily mortality in London for the winters of 1958–1972 plotted over concentrations of particulate pollution and estimated daily dose. The dots represent daily means for 20 adjacent values after sorting by pollution concentrations, as similarly presented previously.<sup>45</sup> The range of air pollution concentrations results in estimated inhaled doses that are approximately between contemporary levels of air pollution and very light active smoking (1 or 2 cigarettes per day). The use of different measures of particulate pollution and different time



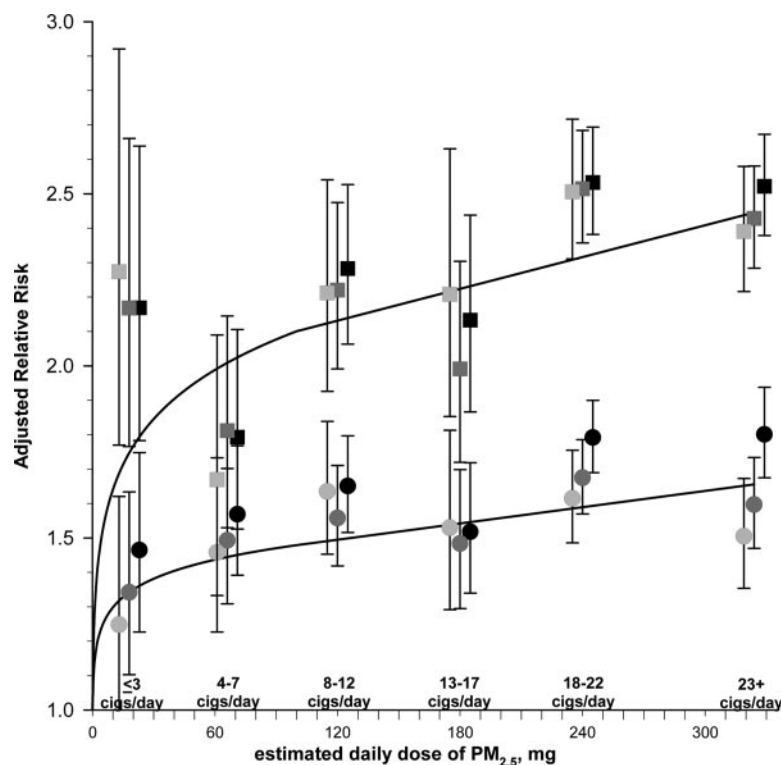
**Figure 1.** Adjusted relative risks (and 95% CIs) of ischemic heart disease (light gray), cardiovascular disease (dark gray), and cardiopulmonary disease (black) mortality plotted over baseline estimated daily dose of  $PM_{2.5}$  from different increments of current cigarette (cigs) smoking (relative to never smokers). Diamonds represent comparable mortality risk estimates for  $PM_{2.5}$  from air pollution. Stars represent comparable pooled relative risk estimates associated with SHS exposure from the 2006 Surgeon General's report and from the INTERHEART study. The solid and dotted lines are fitted linear and nonlinear lines illustrating alternative monotonic exposure-response relationships.

scales of exposure makes direct comparisons with Figure 1 problematic, but these results are also suggestive of a non-linear response relationship with declining marginal effects at higher concentrations. The response relationship is relatively steep and nearly linear at the low range of exposure, consistent with more contemporary daily time-series studies with lower levels of air pollution and substantially narrower ranges of exposure.<sup>43</sup>

This study is also subject to uncertainty arising from measurement error in  $PM_{2.5}$  exposure estimates. After enrollment, additional information on cigarette smoking and residence history was not collected. Changes in smoking habits, including quitting smoking, would likely result in underestimation of the exposure effects. Furthermore, changes in composition of cigarettes and smoking habits may have changed the inhaled dose of  $PM_{2.5}$  per cigarette. Reasonable



**Figure 2.** Adjusted relative risks (and 95% CIs) of ischemic heart disease (light gray), cardiovascular disease (dark gray), and cardiopulmonary disease (black) mortality plotted over baseline estimated daily dose (using a log scale) of  $PM_{2.5}$  from current cigarette smoking (relative to never smokers), SHS, and air pollution.

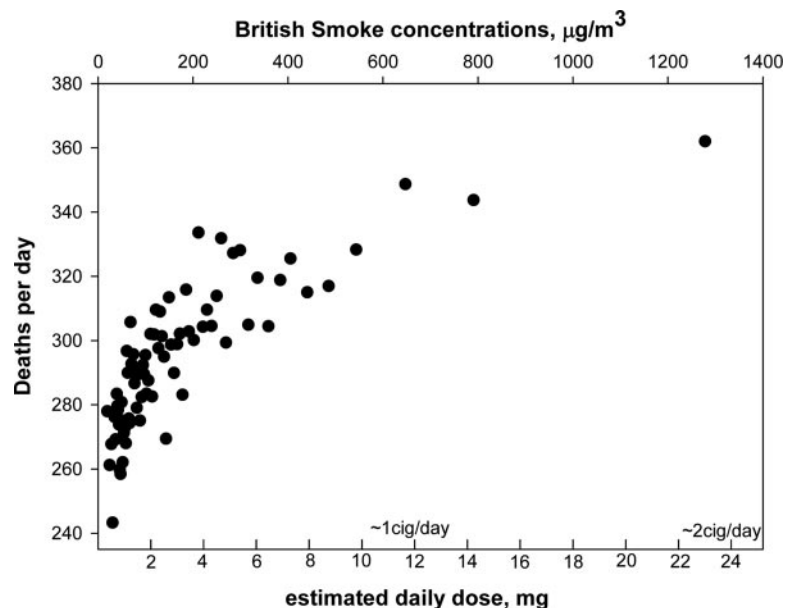


**Figure 3.** Adjusted relative risks (and 95% CIs) of ischemic heart disease (light gray), cardiovascular disease (dark gray), and cardiopulmonary disease (black) mortality plotted over baseline estimated daily dose of  $PM_{2.5}$  from different increments of current cigarette (cigs) smoking (relative to never smokers) for participants who were aged <65 years (squares) and those who were aged  $\geq 65$  years (circles).

changes in assumptions used to calculate doses (such as ventilation rates and yields of  $PM_{2.5}$  per cigarette) can affect the size of the exposure gap between active cigarette smoking and SHS or air pollution exposures. In addition, it may be possible that very light smokers inhale more often or more deeply and have larger doses per cigarette than those who smoke more. However, even doubling the estimated dose for those who smoke  $\leq 3$  cigarettes per day from 18 to 36 mg (which in Figures 1 and 2 would move the estimated relative risks for the lightest smokers to the right by 18 mg) does not fundamentally change the overall shape of exposure-response relationship. Reasonable changes in assumptions about ven-

tilation rate and dose per cigarette do not alter the principal observation that the exposure-response function is much steeper at lower exposures than at higher exposures.

Another limitation of this study is that it uses  $PM_{2.5}$  as the metric of exposure from different sources. There may be important differences in health effects due to differences in the composition of fine particles from active smoking, SHS, and air pollution from various sources. Components or combinations of components of fine particulates from cigarette smoke and other combustion sources and the mechanisms responsible for the observed adverse cardiovascular health effects have yet to be elucidated fully. However,



**Figure 4.** Daily mortality in London for the winters of 1958–1972 plotted over concentrations of particulate air pollution (British smoke,  $\mu g/m^3$ ) and estimated daily dose. Points represent daily means for 20 adjacent values, after sorting by pollution concentrations.

reviews of the evidence suggest that long-term exposures to PM<sub>2.5</sub> from cigarette smoke and ambient air pollution affect multiple physiological pathways and that relatively low levels of exposure from SHS and ambient air pollution are adequate to contribute substantively to adverse biological responses, including pulmonary and systemic oxidative stress, inflammatory vascular dysfunction, increased platelet activation and blood viscosity, atherosclerosis, ischemic heart disease, and altered cardiac autonomic function.<sup>32,42,43,46</sup> Ambrose and Barua,<sup>46</sup> in an evaluation of the pathophysiology of cigarette smoke and cardiovascular disease, discuss the plausibility of a nonlinear response relationship for cardiovascular health and suggest that this nonlinear response may be caused by underlying biochemical and cellular processes becoming saturated with small doses of toxic components.

Cumulative exposure depends on both the intensity and duration of exposure. A recent analysis explored the dynamic exposure-response relationship between particulate pollution exposure and mortality risk by integrating evidence from different time scales of exposure.<sup>47</sup> Interestingly, the dynamic exposure-response to duration of exposure was also not linear but nearly log-linear, with relatively recent exposures having the largest health impacts. Overall, these results suggest a nonlinear exposure-response association with both dimensions of cumulative exposure, the level of ongoing contemporaneous exposure and the duration of exposure.

The empirical findings of this analysis have important public health implications. For example, cohort studies of the effects on cardiovascular mortality of long-term exposure to PM<sub>2.5</sub> have been conducted in areas where annual average concentrations rarely exceed 30  $\mu\text{g}/\text{m}^3$ . However, average concentrations of particulate air pollution in major population centers of China, India, and other developing countries are often much higher, exceeding 100  $\mu\text{g}/\text{m}^3$  according to recent estimates.<sup>48</sup> Although estimates of the burden of disease attributable to air pollution are highly sensitive to the modeling of the shape of the exposure-response relationship, a compelling empirical rationale for the choice of a linear, log linear, or alternative model has not been presented.<sup>13,14</sup> Our analysis contributes much-needed empirical evidence on the shape of the exposure-response relationship of the health impacts of fine particulate matter exposure from cigarette smoke and combustion-related ambient air pollution.

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### References

1. Dockery DW, Pope CA III, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, Speizer FE. An association between air pollution and mortality in six U.S. cities. *N Engl J Med*. 1993;329:1753–1759.
2. Pope CA III, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, Heath CW Jr. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *Am J Respir Crit Care Med*. 1995;151:669–674.
3. Krewski D, Burnett RT, Goldberg MS, Hoover K, Siemiatycki J, Jerrett M, Abrahamowicz M, White WH. *Reanalysis of the Harvard Six Cities Study and the American Cancer Society Study of Particulate Air Pollution and Mortality: Special Report*. Cambridge, Mass: Health Effects Institute; 2000.
4. Pope CA III, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, Thurston GD. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA*. 2002;287:1132–1141.
5. Pope CA III, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation*. 2004;109:71–77.
6. Jerrett M, Burnett RT, Ma R, Pope CA III, Krewski D, Newbold KB, Thurston G, Shi Y, Finkelstein N, Calle EE, Thun MJ. Spatial analysis of air pollution and mortality in Los Angeles. *Epidemiology*. 2005;16:727–736.
7. Laden F, Schwartz J, Speizer FE, Dockery DW. Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities Study. *Am J Respir Crit Care Med*. 2006;173:667–672.
8. Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, Kaufman JD. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med*. 2007;356:447–458.
9. Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ, Jerrett M, Hughes E, Armstrong B, Brunekreef B. Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR Study). *Environ Health Perspect*. 2008;116:196–202.
10. Law MR, Morris JK, Wald NJ. Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. *BMJ*. 1997;315:973–980.
11. Howard G, Thun MJ. Why is environmental tobacco smoke more strongly associated with coronary heart disease than expected? A review of potential biases and experimental data. *Environ Health Perspect*. 1999;107(suppl 6):853–858.
12. Gamble JF, Nicolich MJ. Comparison of ambient PM risk with risks estimated from PM components of smoking and occupational exposures. *J Air Waste Manag Assoc*. 2000;50:1514–1531.
13. Cohen AJ, Anderson HR, Ostro B, Pandey KD, Krzyzanowski M, Kuenzli N, Gutschmidt K, Pope CA, Romieu I, Samet JM, Smith KR. Mortality impacts of urban air pollution. In: Ezzati M, Lopez AD, Rodgers A, Murray CJL, eds. *Comparative Quantification of Health Risks: Global and Regional Burden of Disease Due to Selected Major Risk Factors*. Vol 2. Geneva, Switzerland: World Health Organization; 2004.
14. Ostro B. *Outdoor Air Pollution: Assessing the Environmental Burden of Disease at National and Local Levels*. Geneva, Switzerland: World Health Organization; 2004. WHO Environmental Burden of Disease Series, No. 5.
15. Chao A, Thun MJ, Jacobs EJ, Henley SJ, Rodriguez C, Calle EE. Cigarette smoking and colorectal cancer mortality in the Cancer Prevention Study II. *J Natl Cancer Inst*. 2000;92:1888–1896.
16. Calle EE, Terrel DD. Utility of the National Death Index for ascertainment of mortality among Cancer Prevention Study II participants. *Am J Epidemiol*. 1993;137:235–241.
17. Hoover BK, Foliant DE, White WH, Cohen AJ, Calisti LJ, Krewski D, Goldberg MS. Retrospective data quality audits of the Harvard Six Cities and American Cancer Society studies. *J Toxicol Environ Health*. 2003;66:1553–1562.
18. World Health Organization. *International Classification of Diseases: Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Ninth Revision*. Geneva, Switzerland: WHO; 1977.
19. van Eeden SF, Yeung A, Quinlan K, Hogg JC. Systemic response to ambient particulate matter: relevance to chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2005;2:61–67.
20. Speizer FE, Fay ME, Dockery DW, Ferris BG Jr. Chronic obstructive pulmonary disease mortality in six U.S. cities. *Am Rev Respir Dis*. 1989;140:S49–S55.
21. Sin DD, Man SFP. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc*. 2005;2:8–11.



22. Sin DD, Wu L, Man SFP. The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. *Chest*. 2005;127:1952–1959.
23. Environmental Protection Agency. Revised requirements for the designation of reference and equivalent methods for PM<sub>2.5</sub> and ambient air quality surveillance for particulate matter: final rule. *Fed Regist*. 1997; 62:5725–5726.
24. Fleming TR, Harrington DP. *Counting Processes and Survival Analysis*. New York, NY: John Wiley & Sons; 1991.
25. Siemiatycki J, Nadon L, Lakhani R, Beegin D, Geerin M. Exposure assessment. In: Siemiatycki J, ed. *Risk Factors for Cancer in the Workplace*. Baton Rouge, La: CRC Press; 1991:45–114.
26. Layton DW. Metabolically consistent breathing rates for use in dose assessments. *Health Phys*. 1993;64:23–36.
27. US EPA. *Exposure Factors Handbook*. Washington, DC: Office of Research and Development; 1997. EPA/600/C-99/001.
28. Brochu P, Ducré-Robitaille J, Brodeur J. Physiological daily inhalation rates for free-living individuals aged 1 month to 96 years, using data from doubly labeled water measurements: a proposal for air quality criteria, standard calculations and health risk assessment. *Hum Ecol Risk Assessment*. 2006;12:675–701.
29. Stifelman M. Using doubly-labeled water measurements of human energy expenditure to estimate inhalation rates. *Sci Total Environ*. 2007;373: 585–590.
30. Allan M, Richardson GM, Jones-Otazo H. Probability density functions describing 24-hour inhalation rates for use in human health risk assessments: an update and comparison. *Hum Ecol Risk Assessment*. 2008;14: 372–391.
31. National Cancer Institute. *The FTC Cigarette Test Method for Determining Tar, Nicotine, and Carbon Monoxide Yields of US Cigarettes: Report of the NCI Expert Committee*. Bethesda, Md: National Institutes of Health; 1996.
32. US Department of Health and Human Services. *The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General*. Atlanta, Ga: US Dept of Health and Human Services, Center for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2006.
33. Teo KK, Ounpuu S, Hawken S, Pandey MR, Valentin V, Hunt D, Diaz R, Rashed W, Freeman R, Jiang LX, Zhang XF, Yusuf S. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet*. 2006;368:647–658.
34. Dockery DW, Spengler JD. Indoor-outdoor relationships of respirable sulfates and particles. *Atmos Environ*. 1981;15:335–343.
35. Spengler JD, Treitman RD, Tosteson TD, Mage DT, Soczek ML. Personal exposures to respirable particulates and implications for air pollution epidemiology. *Environ Sci Technol*. 1985;19:700–707.
36. Spengler JD. *Indoor Air Pollution: A Health Perspective*. Baltimore, Md: Johns Hopkins University Press; 1991:33–67.
37. Leaderer BP, Hammond SK. Evaluation of vapor-phase nicotine and respirable suspended particle mass as markers for environmental tobacco smoke. *Environ Sci Technol*. 1991;25:770–777.
38. Jenkins RA, Palausky A, Counts RW, Bayne CK, Dindal AB, Guerin MR. Exposure to environmental tobacco smoke in sixteen cities in the United States as determined by personal breathing zone air sampling. *J Exposure Anal Environ Epidemiol*. 1996;6:473–502.
39. US Department of Health and Human Services. *The Health Consequences of Smoking: Cardiovascular Disease: A Report of the Surgeon General*. Rockville, Md: US Dept of Health and Human Services, Office of Smoking and Health; 1983.
40. US Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta, Ga: US Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office of Smoking and Health; 2004.
41. US Department of Health and Human Services. *Women and Smoking: A Report of the Surgeon General*. Rockville, Md: US Dept of Health and Human Services, Public Health Service, Office of the Surgeon General; 2001.
42. Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, Luepker R, Mittleman M, Samet J, Smith SC Jr, Tager I. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation*. 2004;109:2655–2671.
43. Pope CA III, Dockery DW. Health effects of fine particulate air pollution: lines that connect. *J Air Waste Manage Assoc*. 2006;56:709–742.
44. Ostro BA. Search for a threshold in the relationship of air pollution to mortality: a reanalysis of data on London winters. *Environ Health Perspect*. 1984;58:397–399.
45. Schwartz J, Marcus A. Mortality and air pollution in London: a time series analysis. *Am J Epidemiol*. 1990;131:185–194.
46. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease. *J Am Coll Cardiol*. 2004;43:1731–1737.
47. Pope CA III. Mortality effects of longer term exposures to fine particulate air pollution: review of recent epidemiological evidence. *Inhalation Tox*. 2007;19(suppl 1):33–38.
48. Sivertsen B. Global ambient air pollution concentrations and trends. In: *Air Quality Guidelines: Global Update 2005*. Copenhagen, Denmark: World Health Organization Regional Office for Europe; 2006.

### CLINICAL PERSPECTIVE

Active cigarette smoking is well established as a major independent cause of cardiovascular disease on the basis of extensive epidemiological, clinical, and experimental data. Compared with active cigarette smoking, passive exposure to secondhand cigarette smoke and ambient air pollution results in extremely small estimated daily doses of inhaled fine particulate and related pollutants. Yet there is substantial and growing evidence that secondhand cigarette smoke and ambient air pollution also contribute to cardiovascular disease, with risk estimates much higher than predicted on the basis of simple extrapolations of the effects of active smoking that assume a linear exposure-response function. The present study empirically explores the shape of the exposure-response relationship by integrating analyses of data from a prospective cohort mortality study of >1 million adults (collected by the American Cancer Society as part of the Cancer Prevention Study II) and exposure and risk information from comparison studies of air pollution and secondhand cigarette smoke. With the use of estimated average daily inhaled dose of fine particulate as the common exposure metric, the exposure-response relationship appears to be relatively steep at low levels of exposure. The largest marginal increases in cardiovascular risk occur at remarkably low levels of exposure. Therefore, much of the excess cardiovascular risk from active smoking occurs even at very low levels of smoking, and smaller but substantive excess risks are also associated with passive exposure to secondhand smoke and ambient air pollution.