# Cardiovascular Disease and Fine Particulate Matter

## Lessons and Limitations of an Integrated Exposure–Response Approach

C. Arden Pope III, Aaron J. Cohen, Richard T. Burnett

**Substantial evidence indicates that long-term exposure to fine particulate matter from multiple combustion sources contributes to cardiovascular disease (CVD). An integrated exposure–response (IER) approach uses evidence from exposures to air pollution, second-hand smoke, and active cigarette smoking to explore mortality exposure–risk relationships. Although there are limitations, this approach provides a useful framework to evaluate consistency and coherency of the evidence and to estimate burden of disease from air pollution.**



## Why an IER Approach?

Humans are exposed to combustion-related fine particulate matter (particles ≤2.5 μm in aerodynamic diameter), or $PM_{2.5}$, from multiple sources, including ambient air pollution, household air pollution, second-hand cigarette smoke (SHS), and active smoking. There is substantial evidence that breathing combustion-derived $PM_{2.5}$ from these sources contributes to CVD.[1] Recently, estimators of $PM_{2.5}$ relative risk (RR), termed IER functions, have been developed that integrate CVD mortality risk estimates for air pollution, SHS, and active smoking. They describe the shape of the $PM_{2.5}$–CVD mortality relationship over a broad range of exposure to $PM_{2.5}$.[2–4]

The development of IER was motivated by 2 research needs. First, the need to address the plausibility of reported CVD mortality risk estimates for air pollution and SHS relative to risk from active smoking. Exposures to $PM_{2.5}$ from air pollution and SHS are extremely small compared with that from active smoking. However, moderately elevated long-term exposures to ambient $PM_{2.5}$ (20 μg/m$^3$) and comparable exposures to SHS are associated with an ≈25% to 30% increased risk of CVD mortality[1,5,6]—estimates much larger than expected based on proportional or linear extrapolations of the effects of active smoking. Second, there was a need to develop risk functions to estimate burden of disease attributable to ambient $PM_{2.5}$ across a wide range of exposures, including areas with extremely high concentrations of air pollution but where no direct epidemiological evidence was available.[4,7]

In response to these research needs, the quantitative relationship between CVD mortality and exposure to $PM_{2.5}$ from ambient air pollution, SHS, and tobacco smoking was explored.[2,3] An IER estimator was developed to estimate the global burden of disease attributable to ambient $PM_{2.5}$.[4] Recent reports on CVD mortality risks from light cigarette smoking,[8] air pollution,[9–11] SHS,[6] and household air pollution[12] provide new evidence bearing on the validity of the IER approach. This viewpoint incorporates this new evidence, focuses on the broader implications of the IER approach to estimating the $PM_{2.5}$–CVD risk relationship, and emphasizes that the IER approach does not provide an established true estimator but is an evolving conceptual and pragmatic framework with its validity depending on integrating ongoing empirical evidence.

## Stylized Illustration of IER Approach

The Figure illustrates an IER approach using air pollution, SHS, and active smoking evidence to evaluate the $PM_{2.5}$–CVD mortality exposure–response relationship. RRs (95% confidence intervals) are plotted over estimated daily exposure of $PM_{2.5}$ and increments of cigarette smoking. Associations at low exposures are further illustrated as an inset with a magnified scale (panel A) and are also presented on the log scale (panel B). Gray and black circles represent smoking-related RR estimates for CVD-related mortality, and gray diamonds and stars represent estimates from studies of air pollution and SHS as documented previously.[2,3]

RR estimates from several important new studies are superimposed as colored symbols (red, blue, and green indicate women, men, and both sexes, respectively). Triangles represent estimates for coronary heart disease mortality associated with smoking 1, 5, and 20 cigarettes per day.[8] The green star represents the estimate for ischemic heart disease mortality associated with SHS.[6] RR estimates for CVD mortality based on 2 recent analyses of US cohorts[9,11] are represented by a green diamond and plus sign. A meta-analysis of cohort studies[5] of ambient air pollution provides the RR estimate for CVD mortality associated with 20 μg/m$^3$ of $PM_{2.5}$ (mean exposures across the cohorts ranged from 4–28 μg/m$^3$) represented by the green hex. The estimate for CVD mortality associated with 40 μg/m$^3$ of $PM_{2.5}$ (mean exposures, 43.7 μg/m$^3$) based on a large national cohort of Chinese men[10] is represented by the blue diamond. A recent RR estimate for CVD mortality from exposure to household air pollution from solid fuel use in rural China[12] is represented by the yellow square.

The maroon curve illustrates an IER function, with the mathematical form used in global burden of disease estimates as documented elsewhere.[4,7]

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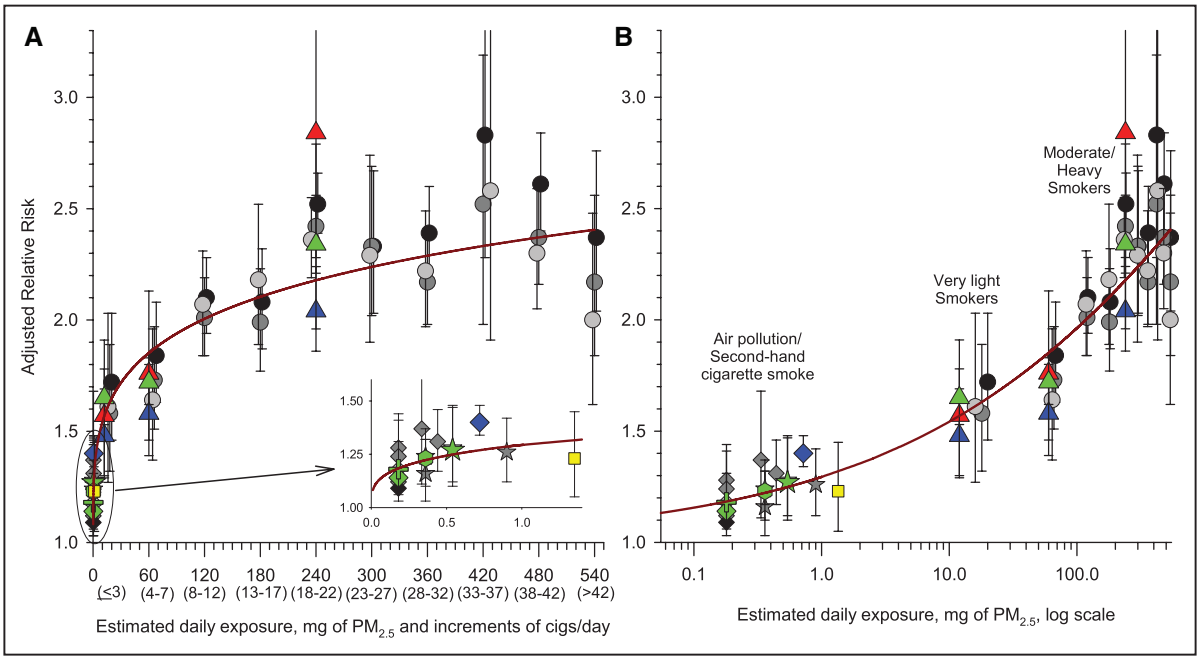


**Figure. Illustration of the integrated exposure–response (IER) approach to evaluate the $PM_{2.5}$ cardiovascular disease (CVD) mortality exposure–response relationship.** Relative risks (95% confidence intervals) of CVD-related mortality plotted over estimated daily exposure of $PM_{2.5}$ and increments of cigarette smoking in linear (**A**) and log (**B**) scales. An IER function is fit through the data. Details provided in Stylized Illustration of IER Approach subsection of text.

## Lessons Learned

The integrated evidence on the CVD–$PM_{2.5}$ mortality risk relationship from air pollution, SHS, and active smoking is remarkably coherent (Figure). Breathing combustion-related $PM_{2.5}$ seems to contribute to CVD mortality risk in a way that is largely exposure dependent, but nonlinear. The exposure–response is steep at low exposures and levels off at higher exposures. The IER approach illustrates why reducing CVD mortality risk from cigarette smoking is more effectively accomplished by complete smoking cessation, even among light smokers, rather than smoking reduction.

The IER approach is also instructive in making informed estimates of burden of disease and exploring plausible biological mechanisms. Evidence indicates that $PM_{2.5}$ exposures from cigarette smoke or air pollution affect multiple physiological pathways[1] and is suggestive of a saturation phenomenon, where relatively low exposures to $PM_{2.5}$, either from light smoking or even from SHS and air pollution, seem sufficient to induce adverse biological responses and increase the risk of CVD.

The IER approach provides a framework to evaluate the consistency and coherency of evidence on the contribution of $PM_{2.5}$ exposure to CVD risk. Recent meta-analytic RR estimates of smoking 1, 5, and 20 cigarettes[8] are consistent with earlier reported results[2,3] and provide additional corroboration of the overall shape of the exposure–response relationship. The effect of smoking a single cigarette narrows the evidence gap between active smoking and ambient air pollution and seems consistent with the IER function. The recent China cohort study[10] also helps narrow the evidence gap but does not fit the IER as well, suggesting that the IER may be underestimating effects at the high concentrations in China. The household air pollution study in rural China[12] is also informative. Given the uncertainty in estimates of RR and average differential $PM_{2.5}$ exposures specific to solid fuel use versus clean fuel (tentatively ≈75 μg/m$^3$), the estimates are reasonably consistent.

## Limitations

Despite its utility as both a conceptual framework and a practical approach for risk estimates for $PM_{2.5}$ from diverse combustion sources, neither specific IER estimators nor the IER approach more generally provides a unified $PM_{2.5}$ mass risk model that fully and accurately defines risk relationships between CVD and $PM_{2.5}$ from all sources and under all circumstances. This approach has been constantly evolving, and specific estimated IER functions change with new empirical evidence.

One limitation of the IER approach is that it requires uncertain assumptions on scaling exposures to $PM_{2.5}$ from different sources. In the Figure, for active smoking, daily inhaled exposure is 12 mg $PM_{2.5}$ per cigarette. For air pollution and SHS, daily average inhaled exposure is estimated as $PM_{2.5}$ concentrations (mg/m$^3$) multiplied by average daily inhalation rates (18 m$^3$/d) as discussed elsewhere.[2,3] However, changes in cigarette design and compensatory smoking behavior make estimates of $PM_{2.5}$ exposure per cigarette smoked uncertain. Scaling of exposure estimates requires assumptions on ventilation rates, yields of $PM_{2.5}$ per cigarette, and estimates of average concentrations from air pollution and SHS.

Another limitation is the assumption that health impacts are dependent on $PM_{2.5}$ mass exposure without allowance for variations in toxicity that depend on source, chemical composition, or other characteristics. Even when excluding air pollution evidence, however, and only using evidence from exposure to cigarette smoke, the nonlinear exposure–response function illustrated in the Figure is nearly identical. The range of exposures associated with active smoking alone results in an exposure–response function that is not linear passing through the origin (Figure [A]). Assuming no excess risk

at zero exposure, a monotonic exposure–response function would require a nonlinear function that is steeper at low exposures and flattens out at high exposures. The nonproportional excess risk associated with SHS provides further evidence of an exposure–response curve that is relatively steep at low exposures.

The assumption of equivalent toxicity across sources is more problematic when exposures to air pollution from multiple sources are included. Differential toxicity of $PM_{2.5}$ from different combustion sources remains poorly understood. Recent observations suggest that particles from fossil fuel combustion are more toxic than particles from other sources, such as biomass burning.[13] The IER approach might underestimate $PM_{2.5}$ health effects in areas with extensive burning of coal and other fossil fuels—one possible explanation for the discrepancy between IER predictions and the results of the recent cohort study from China noted above.[10] However, there is currently insufficient evidence to clearly differentiate toxicity by physical, chemical, or source characteristics.[4,14] Furthermore, similar exposures to particles from SHS and ambient air pollution are associated with approximately comparable elevated risks of CVD mortality.

Another limitation of the IER illustrated in the Figure is that it does not allow for a sigmoidal shape. When applying the IER function to estimate global burden of disease, excess risk has been estimated in contrast to a small, but nonzero, counterfactual level of pollution exposure—implicitly assuming no effects below the counterfactual level.[7] As the number of cohort studies of long-term exposure to air pollution grow, meta-analytic methods that more flexibly estimate the shape of the exposure–response function using only studies of ambient air pollution are becoming possible.

Finally, the IER approach assumes that excess risk from one source of $PM_{2.5}$ exposure is not dependent on another source. The evidence, however, suggests that smokers are also affected by exposure to air pollution, indicating interaction between smoking and air pollution not accounted for by this approach.[15]

## Conclusions

Despite its limitations, the IER approach has been useful in estimating the size and shape of the $PM_{2.5}$–CVD mortality risk–exposure relationship. Evidence provided by the IER approach provides evidence that breathing combustion-related fine particulate matter, from multiple sources, contributes to CVD risk.

The IER approach has been useful in making informed estimates of burden of disease from ambient air pollution and in exploring biological mechanisms. An important feature of the IER development is that it has been ongoing, with emerging evidence being integrated into the estimates of the exposure–response functions. The IER approach provides context, and helps evaluate plausibility, consistency, and coherency of the overall evidence.

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## Disclosures

None.

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