Chapter 16
How Do Exposure Estimation Errors Affect Estimated Exposure-Response Relations?

Introduction

Associations between fine particulate matter (PM2.5) exposure concentrations and a wide variety of undesirable outcomes are routinely reported. Adverse outcomes associated with PM2.5 range from autism, auto theft, and COVID-19 mortality to elderly mortality, suicide, and violent crime. Many influential articles argue that reducing National Ambient Air Quality Standards for PM2.5 is desirable to reduce these outcomes; of late, it has become fashionable to explicitly interpret estimated statistical associations causally, implying that reducing PM2.5 would reduce associated adverse outcomes, typically by making untested modeling assumptions to justify interpreting association as causation. Yet, other studies have found that reducing particulate pollution dramatically, by as much as 70% and dozens of micrograms per cubic meter, has not detectably affected all-cause mortality rates even after decades, despite strong, statistically significant positive exposure concentration-response (C-R) associations between them (Zigler and Dominici 2014; see also Chap. 17).

This chapter examines whether this disconnect between association and causation might be explained in part by ignored estimation errors in estimated exposure concentrations. We use EPA air quality monitor data from the Los Angeles area of California to examine the shapes of estimated C-R functions for PM2.5 when the true C-R functions are assumed to be step functions with well-defined response thresholds. The estimated C-R functions mistakenly show risk as smoothly increasing with concentrations even well below the response thresholds, thus incorrectly predicting substantial risk reductions from reductions in concentrations that do not affect health risks. We conclude that ignored estimation errors obscure the shapes of true C-R functions, including possible thresholds, possibly leading to unrealistic predictions of the changes in risk caused by changing exposures. Instead of estimating improvements in public health per unit reduction (e.g., per 10 μg/m³ decrease)
in average PM2.5 concentrations, it may be essential to consider how interventions change the distributions of exposure concentrations.

**Interpreting PM2.5-Health Effect Associations**

Numerous influential studies have reported positive statistical associations between concentrations of fine particulate matter (PM2.5) in air and risk of adverse health effects, especially mortality. An important and common policy-relevant conclusion is that such associations suggest that substantial public health benefits might be achieved by further reducing National Ambient Air Quality Standards (NAAQS) for PM2.5. A recent high-profile paper in this tradition (Di et al. 2017) summarized the PM2.5-mortality association in a large (National Medicare) data set and its significance for national environmental policy as follows:

The US Environmental Protection Agency is required to reexamine its National Ambient Air Quality Standards (NAAQS) every 5 years, but evidence of mortality risk is lacking at air pollution levels below the current daily NAAQS in unmonitored areas and for sensitive subgroups. …Daily PM2.5 and ozone levels in a 1-km × 1-km grid were estimated… [and] daily exposures were calculated for every zip code in the United States. Each short-term increase of 10 μg/m³ in PM2.5 (adjusted by ozone) … [was] statistically significantly associated with a relative increase of 1.05% (95% CI, 0.9–1.15%) … in daily mortality rate… Absolute risk differences in daily mortality rate were 1.42 (95% CI, 1.29–1.56)… per 1 million persons at risk per day. There was no evidence of a threshold in the exposure-response relationship. In the US Medicare population from 2000 to 2012, short-term exposures to PM2.5 and warm-season ozone were significantly associated with increased risk of mortality. This risk occurred at levels below current national air quality standards, suggesting that these standards may need to be reevaluated. (Di et al. 2017)

Mortality is not the only adverse health effect that has been associated with particulate matter. As the US EPA prepares to review the PM2.5 NAAQS in 2018, there has been an outpouring of recent studies associating PM2.5 with adverse outcomes, including (but not limited to) Alzheimer’s (Calderón-Garcidueñas et al. 2016), anemia (Honda et al. 2017), asthma (Young et al. 2014), autism (Morales-Suárez-Varela et al. 2017), anxiety (Pun et al. 2017), baldness (Rajput 2015), birth defects and cleft palates (Zhou et al. 2017), bladder cancer (Yeh et al. 2017), burglaries (Mapou et al. 2017), cardiac arrest (Dennecamp et al. 2010), cardiovascular mortality and morbidity (Kim et al. 2017; Thurston et al. 2016), carpal tunnel syndrome in dialysis patients (Weng et al. 2017), cognitive impairment (Tallon et al. 2017a), coronary artery disease (McGuinn et al. 2017), COVID-19 mortality risks (Wu et al. 2020), criminal assaults (Mapou et al. 2017), dandruff (Rajput 2015), diabetes (Bai et al. 2018; Renzi et al. 2017), dementia (Chen et al. 2017), depression (Sram et al. 2017), dermatitis (Oh et al. 2018), genotoxicity in cheek cells from artisanal cashew nut roasting workers (de Oliveira Galvão et al. 2017), hair loss (Rajput 2015), heart attacks (Liu et al. 2018), congenital heart defects (Zhang et al. 2016), impotence (Tallon et al. 2017b), infections (Yadav et al. 2003), infertility (Xue and Zhang 2018), influenza (Ma et al. 2017), IQ deficits in youth (Wang et al. 2017), insomnia
or low sleep efficiency (ATS 2017), juvenile delinquency and aggression (Younan et al. 2017), kidney disease (Bowe et al. 2018), kidney cancer (Turner et al. 2017), liver cancer (Pedersen et al. 2017), liver cancer patient mortality rates (Deng et al. 2017), lung cancer (Huang et al. 2017), decreased lung function among people who feel that their neighborhoods are poorly maintained (Malecki et al. 2018), memory loss in adults (Sram et al. 2017), metabolic syndrome (Shamy et al. 2017), obesity (Mazidi and Speakman 2017), pneumonia (Yadav et al. 2003), psychiatric stress in veterans (Mehta et al. 2015), sleep-disordered breathing (Shen et al. 2018), substance abuse (Younan et al. 2017), suicide (Ng et al. 2016), theft of motor vehicles (Mapou et al. 2017), and violent crime (Herrnstadt and Muehlegger 2015).

Particularly troubling is that associations of PM2.5 with mortality and morbidities are reported as having no safe levels or thresholds in exposure-response relations, even at concentrations at or below current standards, as noted by Di et al. (2017) for mortalities.

Associations between particulate matter (including black smoke) and mortality risk have been recognized for decades (e.g., Clancy et al. 2002). Frustratingly, some previous interventions (e.g., coal-burning bans) that attempted to reduce mortality and morbidities by reducing exposure concentrations of particulates have shown that even reducing mean air concentrations of particulate matter by up to 70% (35 μg/m³) caused no detectable change in total mortality rates after more than two decades (Dockery et al. 2013). This suggests that the relation between statistical exposure-response associations and manipulative causation that would allow responses to be reduced by reducing exposures is more subtle than was initially hoped and expected (Zigler and Dominici 2014; Harvard School of Public Health 2002). (That the bans saved lives is still mistakenly claimed in Ireland to support nation-wide extensions of regulations; see Chap. 17.) In the United States, clear, significant statistical associations between PM2.5 concentrations and mortality rates have not implied that even substantial historical reductions in PM2.5 lead to detectable reductions in mortality rates (Cox Jr and Popken 2015). Association is not causation, inviting the question: Why not? How can there be a strong, consistent, robust statistical PM2.5-mortality exposure-response relation without a causal link whereby reducing PM2.5 reduces mortality rates? The PM2.5-mortality association seems to satisfy most of the traditional Bradford Hill considerations for associative causation and is routinely presented in the abundant literature on air pollution healthy effects as if this also implied manipulative causation (Cox Jr. 2017). Why doesn’t it?

The remainder of this chapter examines in detail one possible explanation for the discrepancy between (a) statistical (association-based) exposure-response curves for mortalities or morbidities estimated from epidemiological data; and (b) causally effective exposure-response curves, for which reducing exposure reduces response as described by the curve. That explanation is unmodeled measurement or estimation error in estimates of exposure. As explained by Rhomberg et al. (2011):

It is well known among statisticians that random errors in the values of independent variables (such as exposure in exposure-response curves) may tend to bias regression results. For increasing curves, this effect tends to flatten and apparently linearize what is in truth a
steeper and perhaps more curvilinear or even threshold-bearing relationship. The degree of bias is tied to the magnitude of the measurement error in the independent variables. It has been shown that the degree of bias known to apply to actual studies is sufficient to produce a false linear result, and that although nonparametric smoothing and other error-mitigating techniques may assist in identifying a threshold, they do not guarantee detection of a threshold. The consequences of this could be great, as it could lead to a misallocation of resources towards regulations that do not offer any benefit to public health. (Rhomberg et al. 2011)

It is easy to see how a threshold-like exposure concentration-response (C-R) relation might decouple statistical associations from manipulative causation. As a trivial hypothetical example, suppose that in a certain location, coal-fired power plants are used only on days when it is unusually hot or cold and air conditioning or electric heat are being widely used. Average pollution concentrations are 24 μg/m$^3$ on days when the power plants are used and 8 μg/m$^3$ on other days. If there is an exposure concentration threshold of 10 μg/m$^3$ for adverse health responses to pollution, then cutting in half all daily exposure concentrations would not affect health responses. Although the bimodal distribution of exposure concentrations would shift leftward, neither part would cross the threshold. But if exposure estimation errors “flatten and apparently linearize” the observed (i.e., estimated) exposure-response (C-R) curve, as Rhomberg et al. describe, then the failure of the 50% reduction in mean exposure concentration to change health outcomes might appear puzzling. In reality, of course, neither a bimodal distribution of exposure concentrations nor a sharp threshold in the true (causal) population exposure concentration-response relation may be present, and yet exposure estimation error might still distort the shape of the estimated C-R curve, leading to model-predicted reductions in risk from lowering exposures quite different from what actually occurs.

The following sections quantify the real-world distributions of errors in exposure estimates for PM2.5 concentrations using publicly available data for 10 air quality monitoring stations in Southern California. They examine the extent to which real exposure estimation errors for PM2.5 concentrations would mask or distort a threshold in the causal C-R curve if one existed in the relevant range of concentrations, as envisioned by Rhomberg et al. (2011). A goal is to understand the general relation between exposure estimation errors and estimated C-R curves when the true C-R curve has a threshold. This understanding should be equally applicable to different mortality and morbidity endpoints, from autism to violent crime.

Data

The US EPA provides data on daily average PM2.5 concentrations at many monitor locations in the US, along with their locations (latitudes and longitudes). These data are available at www.epa.gov/outdoor-air-quality-data/download-daily-data. Table 16.1 shows the first few records (rows) of data retrieved from this site for the year 2016 for Los Angeles County. Explanations of variables are provided at www.epa.gov/outdoor-air-quality-data/about-air-data-reports. The records shown in
Table 16.1 Daily PM2.5 concentrations at an air quality monitoring site (AQS) in Los Angeles county

| Date       | AQS_site_ID | POC | Daily mean PM2.5 concentration | Units   | Daily_AQI_value | Daily_OBS_count | Percent_complete | AQS_Parameter_code | AQS_parameter_desc | CBSA_code | CBSA_name   | State_code | State | County_code | County | Site_latitude   | Site_longitude |
|------------|-------------|-----|--------------------------------|---------|-----------------|-----------------|-----------------|-------------------|--------------------|------------|-------------|------------|-------|-------------|--------|----------------|----------------|
| 1/1/2016   | 60370002    | 1   | 6                              | ug/m³   | 25              | 1               | 100             | 88101             | -Local Con        | 31080      | Long Beach  | 6          | California | 37       | Los Angeles     | -117.92391 |
| 1/4/2016   | 60370002    | 1   | 8.7                            | ug/m³   | 36              | 1               | 100             | 88101             | -Local Con        | 31080      | Long Beach  | 6          | California | 37       | Los Angeles     | -117.92391 |
| 1/7/2016   | 60370002    | 1   | 0.7                            | ug/m³   | 3               | 1               | 100             | 88101             | -Local Con        | 31080      | Long Beach  | 6          | California | 37       | Los Angeles     | -117.92391 |
| 1/10/2016  | 60370002    | 1   | 12.2                           | ug/m³   | 51              | 1               | 100             | 88101             | -Local Con        | 31080      | Long Beach  | 6          | California | 37       | Los Angeles     | -117.92391 |
| 1/13/2016  | 60370002    | 1   | 11                             | ug/m³   | 46              | 1               | 100             | 88101             | -Local Con        | 31080      | Long Beach  | 6          | California | 37       | Los Angeles     | -117.92391 |
| 1/16/2016  | 60370002    | 1   | 16                             | ug/m³   | 59              | 1               | 100             | 88101             | -Local Con        | 31080      | Long Beach  | 6          | California | 37       | Los Angeles     | -117.92391 |
| 1/19/2016  | 60370002    | 1   | 14.4                           | ug/m³   | 56              | 1               | 100             | 88101             | -Local Con        | 31080      | Long Beach  | 6          | California | 37       | Los Angeles     | -117.92391 |

Source: [www.epa.gov/outdoor-air-quality-data/download-daily-data](http://www.epa.gov/outdoor-air-quality-data/download-daily-data)

Lower quartiles range from 6 μg/m³ for site 1–9.15 for site 3. Upper quartiles range from 11 μg/m³ for site 6–16 μg/m³ for site 3.
Table 16.1 are for a specific air quality monitoring site (AQS) (ID 60370002) at the location shown in the latitude and longitude columns at the right of the table.

We select the LA area because publicly available data show both (a) A clear, positive, statistically significant exposure concentration-response (C-R) association between PM2.5 and daily elderly mortality rates for the corresponding air basin (e.g., a significant positive regression coefficient in a Poisson regression model for daily mortality count as a function of daily high and low temperatures, humidity, and PM2.5 concentrations); and yet (b) No detectable predictive causal relation between changes in PM2.5 and changes in mortality (Cox Jr. 2017). We use data from the LA area to examine what role exposure estimation error might play in creating a strong statistical C-R association in the absence of a strong causal impact of changes in exposure on changes in response.

Figure 16.1 shows the locations (latitudes and longitudes) of AQS monitoring sites in the “Los Angeles-Long Beach-Anaheim, CA” core-based statistical area (CBSA). Ten AQS sites, indicated by a black rectangle enclosing them in Fig. 16.1, are clustered relatively closely together. Figure 16.2 shows a closer view of these ten locations and assigns them numbers 1–10 for future reference. Data from these sites will be used next to quantify errors from imputing to each location the PM25 concentrations measured at nearby monitors.

Table 16.2 shows the layout of the data. For each site (column), and for each day (row) in 2016 on which data were collected for that site, the daily average PM2.5 concentration recorded for that site is shown in the table. Not all sites record PM2.5 concentrations every day, as indicated by the missing values in the table.

![Air quality monitor locations](image)

**Fig. 16.1** AQS station locations and 10 stations selected for analysis
Methods

Two ways to estimate individual exposures to air pollutants are to assign to each individual on each day either the average daily concentration measured at the nearest monitoring site to the individual’s residence, or the average daily concentration for a surrounding geographic area (e.g., a county, zip code, SMSA, etc.) estimated by averaging measurements from several monitors included within its boundaries. To understand the quantitative distribution of errors in the imputed exposure values produced by these methods, we use them to estimate PM2.5 concentrations at different AQS monitoring sites and then compare the estimated values to the true values recorded at those sites. Basic non-parametric descriptive analytics methods (scatter plots, interaction plots, and non-parametric (smoothing) regression) and correlations characterize how informative exposure concentration measurements at one location are about exposure concentrations at other locations.

To see how exposure estimation errors distort estimated exposure-response curves, we first consider their effects on estimation of a sharp exposure-response threshold function—that is, a step function that has probability 0 of response for daily exposure concentrations below a threshold, such as 10 $\mu$g/m$^3$, and probability 1 of response for daily exposures concentrations at or above that threshold value. (The response in this case would have to be a morbidity, rather than mortality, to

**Fig. 16.2** Locations of ten AQS monitoring sites in Los Angeles County used in subsequent data analyses. This is an expansion of the 45 mile x 30 mile rectangle in Fig. 16.1
Table 16.2  Layout of the daily PM2.6 concentrations data for the 10 AQS sites in Los Angeles County in Fig. 16.2

| 1 Month | 2 Day | 3 PM2.5 site 1 | 4 PM2.5 site 2 | 5 PM2.5 site 3 | 6 PM2.5 site 4 | 7 PM2.5 site 5 | 8 PM2.5 site 6 | 9 PM2.5 site 7 | 10 PM2.5 site 8 | 11 PM2.5 site 9 | 12 PM2.5 site 10 |
|---------|-------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|----------------|
| 1       | 1     | 6.0           | 8.9           | 11.9          | 28.0          | 17.6          | 17.7          | 22.0          | 30.8          | 26.5          | 7.1            |
| 1       | 2     | 10.5          | 12.6          | 12.6          | 23.5          | 22.4          | 23.8          | 17.1          | 30.2          | 17.1          |                |
| 1       | 3     | 10.5          | 19.0          | 25.6          | 25.1          | 30.2          | 17.1          |                |                |                |                |
| 1       | 4     | 8.7           | 13.4          | 10.9          | 13.2          | 14.3          | 10.0          | 10.5          | 11.7          | 12.8          | 9.4            |
| 1       | 5     | 11.2          | 7.8           | 5.1           | 6.6           | 7.2           | 5.8           |                |                |                |                |
| 1       | 6     | 7.5           | 5.4           | 6.1           | 5.4           | 8.3           | 8.3           |                |                |                |                |
| 1       | 7     | 0.7           | 4.5           | 4.4           | 5.2           | 2.7           | 4.5           | 3.9           | 5.4           | 5.6           |                |
| 1       | 8     | 9.7           | 7.0           | 11.2          | 9.7           | 13.6          | 14.2          |                |                |                |                |
| 1       | 9     | 12.7          | 10.8          | 12.5          | 10.2          | 15.1          | 11.8          |                |                |                |                |
| 1       | 10    | 12.2          | 14.1          | 15.6          | 16.9          | 17.5          | 7.2           | 7.2           | 9.2           | 11.8          |                |

Lower quartiles range from 6 μg/m³ for site 1–9.15 for site 3. Upper quartiles range from 11 μg/m³ for site 6–16 μg/m³ for site 3.
avoid killing everyone when a response occurs.) Next, less extreme cases are considered for which exposure concentrations in excess of a threshold increases risk above its non-zero background level. In reality, of course, different individuals might have different thresholds (or, more generally, different sigmoid individual exposure-response curves), but understanding how exposure estimation error affects estimates of these known step-function exposure-response curves illuminates more general cases in which mixtures of individual step-function responses are affected.

The statistical analyses and visualizations reported here were performed using the Statistica 12 commercial statistics package, R, and the free R-based Causal Analytics Toolkit (CAT) software (https://cox-associates.com/).

Results

Variability Around Average Exposure Concentration Values

Based on mutual proximity, the monitoring sites in Fig. 16.2 can be partitioned into the following clusters: \{1, 2\}, \{3, 5, 6\}, \{4, 7, 8, 9\}, and \{10\}. Figure 16.3 shows how average PM2.5 concentrations vary throughout the year for each of these sites. The three panels in Fig. 16.3 correspond to the first three spatial clusters. Site 10 is added to the cluster \{4, 7, 8, 9\} because its monthly PM2.5 values are similar to theirs.

The vertical axes in these interaction plots represent the monthly averages of the daily concentrations of PM2.5 recorded for each site. Time is aggregated by months, so that each data point (1/month) represents the average of 1 month of daily values, except for the scatterplot in the lower right, where each dot represents a value for 1 day and site. (Several dots may be superimposed.) The vertical bars around the monthly averages in the other three plots represent approximate 95% confidence intervals (monthly mean concentration plus or minus 1.96 sample standard deviations). In the lower right panel, a non-parametric (loess smooth) curve is fit through the scatterplot, and the vertical scatter around it indicates the spread of values among days and sites around the monthly average value.

These plots reveal systematic relations between values measured at different locations. In the upper left panel, average PM2.5 concentrations are less for site 1 than for site 2 in January-May, and are greater for site 1 than for site 2 during the rest of the year. These differences are statistically significant for some individual months (April, October), as indicated by non-overlapping confidence intervals. In the upper right panel, site 3 has higher average PM2.5 values than site 6 throughout the year. The lower left panel shows many significant differences between monthly concentrations at different sites (e.g., between sites 4 and 9). The lower right panel indicates that there are wide scatters of PM2.5 values at different sites and on different days around the monthly averages. Figure 16.4 makes the same point using days instead of months as the time steps. Each dot represents a PM2.5 value for an
individual AQS monitoring site on a specific day, and the numbers on the horizontal axis indicate month and day using the code 100*Month + day, so that 412, for example, would be the 12th day of the 4th month of the year, i.e., April 12. The wide scatter of recorded PM2.5 values around the daily average (indicated approximately by the smooth curve) is clear, as is the fact that it varies throughout the year: PM2.5 values in excess of 30 $\mu$g/m$^3$ occur frequently in December-March, for example (when elderly mortality rates are also highest in this area (Cox Jr. 2017)), but not at all in August-November (when elderly mortality rates are also lower). Such distributional details are lost when only average concentrations are considered.

That some sites have systematically higher PM2.5 values than others suggests that discussions of how risk varies with average PM2.5 values may have limited relevance to understanding health risks. For example Di et al. (2017) emphasize that “short-term exposures to PM2.5 and warm-season ozone were significantly associated with increased risk of mortality. This risk occurred at levels below current national air quality standards, suggesting that these standards may need to be reevaluated.” However, the claim that “This risk occurred at levels below current national air quality standards” refers only to estimated average levels of exposure concentrations (averaged at the level of zip codes), not to the variable actual levels of exposure concentrations that individuals received. In light of the variability illustrated in

Fig. 16.3 Monthly average PM2.5 concentrations ($\mu$g/m$^3$), by AQS site and month. Lower quartiles range from 6 $\mu$g/m$^3$ for site 1–9.15 for site 3. Upper quartiles range from 11 $\mu$g/m$^3$ for site 6 to 16 $\mu$g/m$^3$ for site 3
Fig. 16.4, it seems plausible that on a day when a zip code has an estimated average PM2.5 concentration “below current national air quality standards,” there might well be many sub-areas with concentrations 3 or 4 times greater than the average value, well above the current standards. The lower right panel of Fig. 16.3 shows a similar finding on a monthly time scale. How deaths would change if no areas had concentrations above the current NAAQS on any given day or month is not clear from such variable data. In short, substantial variability among measured concentrations at different sites on the same day implies that estimated average daily concentrations for an entire area do not reveal either the relatively high exposure concentrations that occur within the area or the full distribution of concentrations, which may be needed to understand causal exposure-response functions.

**Effects of Using Average Concentrations or Concentrations at One Location as Surrogates for Concentrations at Nearby Locations**

PM2.5 concentrations on the same day are generally strongly and positively correlated with each other across AQS sites, although the sizes of correlations vary considerably for different pairs of sites. Figure 16.5 shows the numerical correlations
(numbers above the main diagonals) and corresponding scatter plots and superimposed smooth regression curves (plots below the main diagonals) for sites 1–4 (left panel) and 5–10 (right panel). The frequency histograms of concentrations on the main diagonals show long right tails. For completeness, Table 16.3 shows all pairwise Pearson’s correlations between daily PM2.5 concentrations at different sites. All correlations are for days with PM2.5 measurements at all AQS sites.

Spatial proximity is a useful but imperfect predictor of strength of correlation. For example, concentrations at site 1 are correlated more strongly with concentrations at sites 6 and 3, some distance away, than with concentrations at the nearby site 2, which is relatively poorly correlated with other sites. Correlation is only part of the story, however: shifting a monitor’s concentrations up or down by any fixed amount does not change the correlation numbers, but may greatly affect how well its concentrations approximate concentrations at other locations.

To understand the effects on estimated exposure concentration-response (C-R) functions of using PM2.5 concentrations from nearby monitors, or the average value of PM2.5 over all monitors in the areas, as proxies for the concentrations at a given location, we will first consider the extreme case of a step-function C-R function, the same for all individuals, with a response probability of 0 for days with average PM2.5 concentrations no greater than 10 micrograms per cubic meter and a response probability of 1 for days with average PM2.5 concentrations above 10. This is not intended to be realistic—e.g., it leaves out delays between exposure and response and gradual increases of response probability with increasing exposure concentrations—but is meant only to clarify the effect of exposure estimation error on reconstruction of a C-R function having a simple known form. Figure 16.6 shows the C-R functions estimated for each of the 10 AQS monitoring locations when average daily PM2.5 exposure concentration, averaged over all ten locations, is used as the exposure variable on the x axis and the daily response probability on the y axis.
Table 16.3  Correlations among PM2.5 daily concentrations at different sites

| Variable  | Means | Std. dev. | PM2.5 site 1 | PM2.5 site 2 | PM2.5 site 3 | PM2.5 site 4 | PM2.5 site 5 | PM2.5 site 6 | PM2.5 site 7 | PM2.5 site 8 | PM2.5 site 9 | PM2.5 site 10 | PM2.5 average |
|-----------|-------|-----------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|----------------|
| PM2.5 site 1 | 10.1  | 5.6       | 1.00         | 0.80         | 0.80         | 0.44         | 0.78         | 0.87         | 0.48         | 0.39         | 0.42         | 0.67         | 0.82          |
| PM2.5 site 2 | 10.5  | 5.6       | 1.00         | 0.80         | 0.67         | 0.23         | 0.50         | 0.66         | 0.39         | 0.35         | 0.31         | 0.54         | 0.59          |
| PM2.5 site 3 | 13.4  | 6.5       | 0.80         | 0.67         | 1.00         | 0.69         | 0.90         | 0.89         | 0.72         | 0.65         | 0.66         | 0.78         | 0.91          |
| PM2.5 site 4 | 11.0  | 5.6       | 0.44         | 0.23         | 0.69         | 1.00         | 0.84         | 0.66         | 0.93         | 0.90         | 0.95         | 0.73         | 0.86          |
| PM2.5 site 5 | 11.7  | 5.7       | 0.78         | 0.50         | 0.90         | 0.84         | 1.00         | 0.87         | 0.81         | 0.74         | 0.80         | 0.85         | 0.96          |
| PM2.5 site 6 | 9.5   | 4.8       | 0.87         | 0.66         | 0.89         | 0.66         | 0.87         | 1.00         | 0.65         | 0.58         | 0.61         | 0.69         | 0.90          |
| PM2.5 site 7 | 10.3  | 4.4       | 0.48         | 0.39         | 0.72         | 0.93         | 0.81         | 0.65         | 1.00         | 0.93         | 0.97         | 0.82         | 0.88          |
| PM2.5 site 8 | 10.5  | 4.7       | 0.39         | 0.35         | 0.65         | 0.90         | 0.74         | 0.58         | 0.93         | 1.00         | 0.93         | 0.79         | 0.82          |
| PM2.5 site 9 | 12.0  | 4.8       | 0.42         | 0.31         | 0.66         | 0.95         | 0.80         | 0.61         | 0.97         | 0.93         | 1.00         | 0.77         | 0.86          |
| PM2.5 site 10| 11.1  | 5.2       | 0.67         | 0.54         | 0.78         | 0.73         | 0.85         | 0.69         | 0.82         | 0.79         | 0.77         | 1.00         | 0.87          |
| PM2.5 average| 11.2  | 4.6       | 0.82         | 0.59         | 0.91         | 0.86         | 0.96         | 0.90         | 0.88         | 0.82         | 0.86         | 0.87         | 1.00          |
is either 1 or 0 at each location, depending on whether the true (site-specific and
day-specific) concentration there is or is not greater than 10. The estimated C-R
functions in Fig. 16.6 are obtained by fitting nonparametric smooth (loess) regres-
sion curves to the average PM2.5 concentration from all ten sites on each day and
the corresponding site-specific and day-specific response probabilities (0 or 1) for
each site. Non-parametric smoothing is used to avoid potential parametric model
specification errors or model selection biases. There are between 115 days of data
(for Site 4) and 366 days of data (for sites 3 and 8) for each site, depending on moni-
toring frequency.

In the absence of exposure estimation errors, all ten curves in Fig. 16.6 would be
the same: they would all jump from 0 for PM2.5 less than 10 to 1 for PM2.5 greater
than 10. But because of the differences between the true concentrations and the
imputed (average) concentrations, the estimated C-R functions at a large fraction of
the sites fall far from this ideal. The estimated C-R curve for site 2 provides an
especially poor approximation to the correct C-R curve, increasing gradually over
the entire range from about 2–30 μg/m^3, consistent with the warnings of Rhomberg
et al. (2011). In addition, many of the estimated C-R functions, while providing bet-
ter approximations to step functions, are shifted rightward or leftward with respect
to the true test C-R function, i.e., they increase from 0 to 1 at concentrations ranging
roughly from 8 to 18 μg/m^3 instead of jumping at the correct value of 10 μg/m^3.
Figure 16.7 shows the composite estimated C-R function obtained from the site-specific estimated C-R functions in Fig. 16.6 by plotting the fraction of the population responding on a given day as a function of the average PM2.5 concentration for that day (averaged over all 10 sites), assuming that 10% of the total population is located at each AQS site. As suggested by Rhomberg et al. (2011), this estimated C-R function is a smoothly increasing sigmoid curve, even though the underlying true C-R function that it is estimating is a sharp threshold (step) function. The estimated C-R function starts increasing at about 5 $\mu$g/m$^3$ even though the true C-R function does not increase until 10 $\mu$g/m$^3$, and the estimated C-R function is still well below 1 at 15 $\mu$g/m$^3$, even though the true C-R function jumps to 1 at 10 $\mu$g/m$^3$.

Figures 16.6 and 16.7 show the distorted C-R function created by exposure estimation errors when the exposure estimated for each location is the average PM2.5 concentration for the whole area, i.e., the average concentration over all 10 AQS sites.

Similar distortions occur when the PM2.5 concentrations measured at one monitoring site are used as surrogates for the concentrations at other locations. Figure 16.8 shows an example very similar to Fig. 16.7 except that the estimated concentration is now the concentration at site 5 (the most centrally located site of the 10 sites in Fig. 16.2) instead of the average concentration over all sites. The resulting sigmoid estimated C-R function is similar to that in Fig. 16.7, but somewhat wider; again, it is not a very close approximation to the underlying true C-R function, which steps from 0 to 1 at 10 $\mu$g/m$^3$.

**Fig. 16.7** Estimated C-R function if all ten AQS sites are weighted equally and average PM2.5 concentration for all AQS sites is used as an exposure surrogate. Lower quartiles range from 6 $\mu$g/m$^3$ for site 1–9.15 for site 3. Upper quartiles range from 11 $\mu$g/m$^3$ for site 6–16 $\mu$g/m$^3$ for site 3
The step function used so far is extreme, representing an all-or-nothing response threshold. A more realistic test function for elderly mortality would have a non-zero background mortality rate on the order of 0.001 expected deaths per day for a person with a remaining life expectancy of a few years. Suppose that exposure to 10 μg/m$^3$ or more were to increase this rate by 2%, to 0.00102/person/year. Figure 16.9 shows an estimated C-R function fit to simulated data from a population of ten million people, one million at each of the 10 AQS sites, where the number of deaths at each site on any given day has a binomial distribution with parameters $n = 1,000,000$ and $p = 0.001$ if the daily PM2.5 concentration recorded for that site does not exceed 10μg/m$^3$, and has a binomial distribution with parameters $n = 1,000,000$ and $p = 0.00102$ otherwise. A nonparametric (loess) regression curve is fit to the simulated data (using the scatter.smooth function in R; for replication, the random number generator for the simulation was initialized using set.seed(1234)). The effect of exposure estimation errors in this case is to obscure the threshold at 10 μg/m$^3$. Instead, the estimated C-R function appears to increase smoothly and approximately linearly with concentration, starting at the lowest exposure levels, with no evidence of a threshold.

This pattern is consistent with the warning by Rhomberg et al. (2011) that “It has been shown that the degree of bias known to apply to actual studies is sufficient to produce a false linear result, and that although nonparametric smoothing and other error-mitigating techniques may assist in identifying a threshold, they do not guarantee detection of a threshold.” It is also consistent with the report by Di et al. (2017) that “[R]esponses were almost linear, with no indication of a mortality risk threshold

Fig. 16.8  Estimated C-R function if all ten AQS sites are weighted equally and PM2.5 concentration at site 5 is used as an exposure surrogate
at very low concentrations,” bearing in mind that the “very low concentrations” referred to are only estimates based on zip code-level average values, and that the distributions of true concentrations—some of which were probably much higher than the averages, as illustrated in Fig. 16.4—were not considered.

**Possible Implications for Differences between Associational and Causal C-R Functions**

A C-R function based on average values, such as each of the curves in Figs. 16.7, 16.8, and 16.9, might seem to suggest that changing the average PM2.5 concentration would cause the response rate to change as described by the curve. This causal interpretation is often made, but it is unjustified in general: drawing a regression curve through a scatterplot has no necessary implications for how changing one variable would change the other (Cox Jr. 2017). The effects of measurement errors illustrated in Figs. 16.6, 16.7, 16.8, and 16.9 raise a distinct but related methodological point: without specifying how a pollution control measure affects the distribution of exposure concentrations, rather than just the average exposure concentration, it may be impossible, even in principle, to determine what change in
responses (if any) the intervention will cause. This is because the same change in average concentration may correspond to very different changes in distributions of concentrations that have very different implications for changes in responses.

As a simple example, consider again the case of a bimodal distribution with half of days exposing people to 24 μg/m³ and the other half exposing them to 8 μg/m³, for an average of 16 μg/m³. Now suppose that average exposure is reduced by 5 μg/m³, from 16 μg/m³ to 11 μg/m³, and that the true C-R function is a step function at 10 μg/m³. What will be the effect of this reduction on health risks? The correct answer depends on how the distribution of concentrations has changed. It cannot be uniquely determined from the information given. If the reduction is accomplished by reducing each day’s concentration by 5 μg/m³, then there is no impact on health risks, as previously noted: a reduction from 24 to 19 leaves exposures above 10, and a reduction from 8 to 3 leaves exposure below 10, so neither reduction affects health risks described by a C-R step function at 10 μg/m³ (or anywhere else strictly between 8 and 19 μg/m³ or above 24 μg/m³ or below 3 μg/m³). On the other hand, if the same reduction in average concentration is accomplished by reducing the exposure for half of the high-exposure days from 24 μg/m³ to 4 μg/m³ (giving an average of 0.25*24 + 0.25*4 + 0.5*8 = 11 μg/m³), then risk on these days will be reduced from the high (above-threshold) to the low (below-threshold) level. If the reduction is accomplished by increasing the concentrations on low-exposure days from 8 μg/m³ to 11 μg/m³, then the reduction in average exposure concentration from 16 μg/m³ to 11 μg/m³ will be accompanied by an increase in risk, with twice as many people experiencing the higher risk level after the reduction. Thus, the same 5 μg/m³ reduction in average exposure concentration can create an increase, decrease, or no change in health risk, depending on how the underlying distribution of concentrations changes. Such examples illustrate that using only average PM2.5 concentrations can lose essential information, and that the overall shape of the frequency distribution of PM2.5 exposure concentrations must be considered (e.g., using a few quantiles, such as the deciles) to accurately understand and interpret population concentration-response data.

Many papers express their main findings in the form of predictions that each reduction of exposure concentration by a certain amount (customarily 10 μg/m³ for PM2.5) would produce a certain change in health risks (e.g., Schwartz et al. 2008; Shi et al. 2016; Wang et al. 2016; Di et al. 2017). Such papers typically do not specify how the underlying distribution of concentrations is assumed to change when the average exposure is decreased. Hence they fail to engage with the fact that this change in distribution drives change in risk, and that the same average reduction in exposure concentration can have a wide range of implications for changes in risk, perhaps including increases, decreases, and no change. The usual justification is that estimated C-R functions are approximately linear and non-threshold; if the true C-R function is also linear and non-threshold, then average change in response is simply proportional to average change in exposure concentration, and hence there is no need to be explicit about how the underlying distribution of concentrations changes.

The significance of the findings in Figs. 16.6, 16.7, 16.8, and 16.9 is that true C-R
functions need not resemble estimated C-R functions that ignore exposure estimation errors. A linear no-threshold model for an estimated C-R function can correspond to a highly nonlinear (step function) true C-R function. The literature that conflates true and estimated C-R functions leaves unaddressed the true shape of the C-R function and the possibly crucial effects of proposed interventions on the shapes of concentration distributions.

Discussion and Conclusions

It is common practice in air pollution health effects research, as in many other areas of applied epidemiology (e.g., occupational health studies using job exposure matrices), to use surrogate measures or estimates for unknown individual-level exposure concentrations and to analyze and refer to the surrogate measures or estimates as if they were accurate measures of true concentrations. Common surrogate measures include concentrations at nearby monitors and averaged concentrations from multiple monitors in an area. Although we have focused on the recent paper of Di et al. (2017) as a motivating example, many other influential papers present estimated exposures as if they were true exposures. For example,

- Shi et al. (2016) state that “PM2.5 was associated with increased mortality. … [We] estimated significant acute and chronic effects of PM2.5 exposures below current EPA standards. These findings suggest that improving air quality below current standards may benefit public health.” Shi et al. refer to estimates of average PM2.5 concentrations (in this case, predicted via a model from satellite aerosol optical depth estimates on a 1 km × 1 km grid) as simply “PM2.5 exposures” without differentiating between estimated and true PM2.5 exposures and without modeling the errors in the estimates or the uncertainties and variability in the true values. Other research has estimated a root mean squared prediction error of about 5.5 μg/m³ for such estimates in Mexico City (Just et al. 2015), but aerosol optical depth appears to contribute little predictive power to accurate estimation of PM2.5 on urban or sub-regional scales in the eastern United States (Paciorek et al. 2012). Shi et al. do not quantify what fraction of people experienced exposure concentrations above current standards on days when the estimated average was below current standards, but the long tails of concentration distributions in our Fig. 16.4 suggest the importance of such distributional considerations.

- Wang et al. (2016) state that “We estimated the causal effects of long-term PM2.5 exposure on mortality.” Again, the “PM2.5 exposure” referred to is not actual exposure, but the output of “A 3-stage statistical modeling approach for predicting daily PM2.5” containing unknown errors. (The authors address model quality using correlation coefficients, but correlation coefficients are insensitive to even very large biases.)

- A decade earlier, Schwartz et al. (2008) wrote that “Understanding the shape of the concentration–response curve for particles is important for public health, and
lack of such understanding was recently cited by U.S. Environmental Protection Agency (EPA) as a reason for not tightening the standards. Similarly, the delay between changes in exposure and changes in health is also important in public health decision making. We addressed these issues using an extended follow-up of the Harvard Six Cities Study. … We found that the concentration–response curve is linear, clearly continuing below the current U.S. standard of 15 μg/m³, and that the effects of changes in exposure on mortality are seen within 2 years.” However, the PM2.5 concentrations referred to are actually only very rough estimates of average concentrations: “Each participant’s exposure to air pollution each year was defined by that year’s concentrations of PM2.5 in that participant’s city. Concentrations of PM2.5 were measured at a centrally located air-monitoring station in each community starting in 1979 and ending in 1986–1988 depending on the city. … We calculated city-specific annual mean PM2.5 concentrations as the average of four quarterly means of daily data for each available year. For years before sampling, PM2.5 values were assumed equal to the earliest sampling year.” In light of our results, such imputation of PM2.5 concentrations based on average values can lead to non-threshold, linear-looking estimated C-R curves even if the true curve has a sharp threshold; thus, such analyses should not be interpreted as revealing the shape of the true C-R function. Statements such as “the concentration–response curve is linear, clearly continuing below the current U.S. standard” should be clearly understood to refer only to the estimated C-R function, which maybe very different from the true C-R function.

These examples can be multiplied many times over, as the literature that treats estimated exposure concentrations as if they were error-free measurements is voluminous (Cox Jr. 2017). The key methodological points are the same for each: estimated C-R functions may be increasing at relatively low doses and lack thresholds even if the true C-R function has neither of these properties.

Our examples and illustrations have used simple step-functions as counter-examples, since these are the most extreme cases for testing whether estimation errors can obscure the shape of a true C-R relation, making even a step function look smooth, non-threshold, and approximately linear over the relevant range of concentrations, as cautioned by Rhomberg et al. (2011). Figures 16.6, 16.7, 16.8, and 16.9 support the conclusion that realistic exposure estimation errors do indeed create such distortions. Whether strongly nonlinear, threshold-like C-R functions are biologically plausible is a separate question from the methodological one of whether ignoring exposure estimation errors can conceal even such strong nonlinearities. However, the following considerations suggest that strong nonlinearities or thresholds in PM2.5 dose-response functions at or below current ambient levels are a realistic possibility that deserves to be considered carefully.

• Epidemiological data on the true shape of the low-dose concentration-response relation for PM2.5 are ambiguous, in part because true exposures are uncertain. Thus, while some previous expert commentators on the possible existence of a threshold concluded that “There also appears to be a monotonic (e.g., linear or log-linear) concentration-response relationship between PM2.5 and mortality
risk observed in cohort studies that extends below present-day regulations of 15 \( \mu \text{g/m}^3 \) for mean annual levels, without a discernable ‘safe’ threshold,” others warned that “At the human population level, however, various sources of variability and uncertainty tend to smooth and ‘linearize’ the concentration-response function (such as the low data density in the lower concentration range, possible influence of measurement error, and individual differences in susceptibility to air pollution health effects)… even though likely mechanisms include nonlinear processes for some key events,…The results from [selected studies] support no-threshold log-linear models, but issues such as the possible influence of exposure error and heterogeneity of shapes across cities remain to be resolved.” Other experts concluded that “The available epidemiological database on daily mortality and morbidity does not establish either the presence or absence of threshold concentrations for adverse health effects. … For the purpose of estimating public health impacts, the Panel favored the primary use of an assumed threshold of 10 \( \mu \text{g/m}^3 \).” (United States Environmental Protection Agency (US EPA) 2010)

- The fact that estimated C-R functions are expected not to have thresholds, whether or not true (i.e., without estimation error) C-R functions do, implies that not finding a threshold in estimated C-R functions provides no useful evidence about whether the underlying true C-R functions have thresholds.
- Recent findings that pathological responses to PM2.5 exposures are mediated by chronic inflammation involving the NLRP3 inflammasome, which requires sufficiently large and sustained exposure concentrations and durations to trigger assembly and activation, suggest that careful attention to biological thresholds for PM2.5 health effects is warranted (Wang et al. 2017; Xu et al. 2018).

Our finding that estimated and true C-R relations may be very different when realistic exposure error estimates are considered implies that frequent previous epidemiological findings of estimated C-R functions that appear to be approximately low-dose linear and no-threshold (e.g., Schwartz et al. 2008; Shi et al. 2016; Di et al. 2017) do not address or resolve the question of whether the true C-R function describing response probabilities caused by different exposure concentrations has a threshold, or perhaps a population distribution of thresholds. The question appears to be well worth pursuing further. In addition, although this chapter has focused exclusively on effects of exposure estimation errors in obscuring the true shape of the low-dose concentration-response function for PM2.5, this does not imply that resulting uncertainty about effect thresholds is the only reason to question whether ambient levels of PM2.5 cause the adverse effects often attributed to them. Additional uncertainties about causality arise from epidemiological studies that rigorously distinguish between association and causation (Chap. 17), as well as from animal data and biological mechanistic data on thresholds for inflammation-mediated diseases (Chaps. 3, 4, 5, and 6). Finally, even if outdoor ambient PM2.5 concentrations were to be quantified with little error, personal exposures to PM2.5 still depend largely—often predominantly—on indoor concentrations of PM2.5 and on occupational exposures, which can differ widely even for neighboring homes and among members of the same household.
The methodological points here are not intended to be new. Statisticians have frequently warned against treating averages as if they were actual known values, and this warning has been widely popularized, e.g., in work on the “flaw of averages” (Savage 2009). As previously acknowledged, Rhomberg et al. (2011) warned more specifically that ignoring exposure estimation uncertainty in quantitative estimation and regression modeling of C-R functions can yield distorted estimates that appear to be smooth and non-threshold, and possibly linear, even if the true function being estimated has clear thresholds. Our findings confirm these warnings for PM2.5 concentration estimates and estimation of C-R functions. We found that the differences between the true daily average PM2.5 values recorded for 10 AQS monitoring sites and the estimated values imputed from measurements at nearby sites (either the average over all 10 sites, as in Figs. 16.7 and 16.9; or the value at individual sites, such as site 5 in Fig. 16.8) were large enough to smooth out and to make sigmoid-appearing (Figs. 16.7 and 16.8) or approximately linear-looking (Fig. 16.9) estimates even of step-function C-R functions with well-defined concentration thresholds. The practical implication of these findings for PM2.5 in the LA area examined is that finding an estimated C-R function that appears to be linear no-threshold down to the lowest concentrations considered is not inconsistent with the possibility that the true-but-unknown C-R function has a response threshold well above these low levels. The key question of what the true C-R function looks like remains to be addressed, but addressing it usefully will probably require distinguishing between true and estimated exposure concentrations.

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