Men must endure their going hence, even as their coming hither. Ripeness is all.

—King Lear, Act 5, Sc 11a

An association between air pollution and hospital admission for heart failure was first noted in the literature in 1995 (1). The association was confirmed in subsequent studies (2, 3), along with many studies showing an association with a more general increase in cardiovascular admissions (4–6). The most consistent associations have been with carbon monoxide and particulate matter, and both Poisson time series (1, 2) and case-crossover analyses (3) have been used. Some of these studies have been quite large—for example, Wellenius et al. (3) examined seven cities and 293,000 emergency admissions.

More recently, studies of the health effects of air pollution have improved exposure assessment through better resolution in space within cities, differentiation among particle species indicative of different sources of pollution, and better resolution in time. A key limiting factor for all of these approaches is the need to collect more detailed data, whether on time, on place, or on exposure. This is particularly true for event data, as such information is difficult and expensive to obtain.

Better spatial resolution reduces exposure error, which is important for the study of pollutants that are not spatially homogeneous, such as traffic exhaust. For example, Kinney et al. (7) reported large differences in exposure to carbon particles from traffic between streets with bus routes and side streets in a Manhattan neighborhood. Making use of such variation, Kunzli et al. (8) used estimates of particulate matter with a diameter less than 2.5 μm (PM2.5) based on geographic information systems to identify an association between particulate exposure and atherosclerosis in Los Angeles, California. Jerrett et al. (9) recently reported a much larger association between within-city variation in particles and survival in the American Cancer Society cohort than had previously been reported for between-city variation in particles, demonstrating the importance of reducing this type of exposure error.

By differentiating particles into components that are tracers for specific sources, we help to identify the relative toxicity of emissions from those sources. Since, in the end, pollution control is done at sources, this can provide valuable information for public health policy. Investigators have begun to differentiate exposure in this as well. For example, O’Neill et al. (10) reported that both sulfate particles from coal-burning power plants and black carbon particles from traffic were associated with approximately 12 percent reductions in flow-mediated dilation of the brachial artery, a noninvasive measure of endothelial function with proven prognostication for cardiovascular endpoints (11).

This brings us to time. Previous studies of the association between fluctuations in air pollution and serious events have often been limited because the timing of the events was no better than calendar day. This has also limited studies of nonenvironmental risk factors. The case-crossover design is ideally suited for examining short-term influences on an event, while controlling by design for most potential confounders. Identification of the timing of events has been recognized as crucial for determining the roles of short-term potential triggers, such as anger. The design was first developed to identify triggers of myocardial infarction (12), and it has shown its continued usefulness for this purpose, including when examining effects of short-term exposure to particles (13). It requires data from hospital interviews to establish the time of onset of the myocardial infarction. In case-crossover studies, subjects who experienced an event at a given time are matched with themselves as controls, using another time in which they did not experience an event. This is a powerful approach, since in addition to controlling for personal risk factors by matching, controls can also be
matched on other factors, such as temperature (14). It has also been applied to emergency admissions for heart failure using conventionally available daily data (3).

In their study, Symons et al. (15) addressed this limitation by interviewing subjects admitted to a hospital through the emergency room for heart failure decompensation. In interviews with patients, they sought to identify the time of onset of symptoms, as well as other information. Marginally significant associations (in one case significant) were found with traffic-related pollutants and ozone, despite the small sample size, and associations were stronger when time of onset was known with a finer temporal resolution than 24 hours. This fits well with investigators’ experience with other cardiovascular outcomes; for example, Peters et al. (16) reported that exposure to traffic was associated with an increased risk of myocardial infarction in the next hour (odds ratio \(= 2.92, 95\) percent confidence interval: 2.22, 3.83).

The use of hourly exposure data to construct exposure using intervals appropriate to the time of onset also deserves some mention. This was done in the study by Symons et al. (15), and it highlights an important issue. Even if the appropriate averaging time for exposure triggering an event is 24 hours or longer, the choice of the correct 24-hour period matters.

For example, Gold et al. (17) reported that both previous-hour average pollution and previous-24-hour average pollution were associated with reductions in heart rate variability in a panel study in which participants were repeatedly seen for 12 weeks. Different participants had heart rate variability measurements taken at different times of day, and it was the 24-hour averages preceding each measurement, not midnight-to-midnight averages, that were associated with the health event. Similarly, if longer averaging times are appropriate for heart failure decompensation, they should be measured from the time of onset. Obviously, this is less well defined than in the case of a scheduled heart rate variability study, but it still reduces exposure error in comparison with calendar day.

At this point, a substantial body of literature has developed using hourly pollution data to construct exposures for specific time periods preceding health measurements. However, most of these have been panel studies, similar to the above studies, which have examined biomarkers of health rather than important health events themselves. The exception has been studies of myocardial infarction, as noted above, and now heart failure joins this list.

The study by Symons et al. (15) had some important limitations. Through no fault of the investigators, the air pollution monitor failed for a period in which 17 percent of the recruited participants had their onset and hospitalization. While the investigators filled in the missing period with data from other monitors, those monitoring locations used tapered element oscillating microbalances, which are known to have problems with loss of semivolatile particles (18). In addition, 38 of the 135 cases did not have an identified time of onset and were randomly assigned a time, resulting in considerable misclassification. Finally, because the study was a pilot study, the number of events was small. Not surprisingly, most of the reported associations had wide confidence intervals. However, the effect sizes, which were probably biased downward by these difficulties, were nontrivial.

The value of this study is not that by reducing exposure error through better resolution of timing, it allows the identification of a health effect not previously suspected. As noted above, there is considerable evidence associating heart failure exacerbation with air pollution. Rather, by providing us with the ability to detect latency and averaging times before events, it at least allows us to speculate about mechanisms, which may generate further targeted research. In addition, many pollutants that are correlated when averaged over calendar days are less correlated at shorter averaging times. For example, levels of traffic particles and sulfate particles are highly correlated during the summer in the eastern United States, when daily averages are used. However, traffic particles tend to have peak hourly concentrations around 6:00 a.m., whereas sulfate particles have peak hourly concentrations around 4:00 p.m. Hence, better resolution of timing may allow us to separate the effects of these two constituents.

Better attention to time is not merely a concern in evaluating acute effects of exposure to air pollution. Cohort studies have examined the effects of long-term average pollution in cities on the risk of death. However, pollution changes over time, and differently in different cities. In extended follow-up of the Harvard Six Cities Study, change in pollution between the two follow-up periods was associated with change in mortality risk (19). In air pollution research, the time has come to get serious about time. Ripeness is all.

ACKNOWLEDGMENTS

Conflict of interest: none declared.

REFERENCES