Eur Respir J 2000; 16: 723–728
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European Respiratory Journal
ISSN 0903-1936

Do respiratory epidemics confound the association between air pollution and daily deaths?

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Do respiratory epidemics confound the association between air pollution and daily deaths? A.L.F. Braga, A. Zanobetti, J. Schwartz. ©ERS Journals Ltd 2000.

ABSTRACT: Daily deaths are associated with air pollution. This association might be con*hhy;founded by uncontrolled risk factors. In order to estimate the potential confounding caused by respiratory epidemics of the association between air pollution and health effects, a time series study of air pollution and daily deaths was carried out.

Daily records of deaths for all ages were obtained from five US cities: Chicago, IL; Detroit, MI; Minneapolis, MN; Pittsburgh, PA; and Seattle, WA. Daily levels of particles with a 50% cut-off aerodynamic diameter of 10 μm (PM_{10}) and weather measurements were obtained. City-specific analysis was carried out using Poisson regression, adjusting for time trend, ambient temperature, dew point, barometric pressure and day of the week. A cubic polynomial was used for each epidemic period (≥10 days of excessive pneumonia hospital admissions), and a dummy variable was used to control for isolated epidemic days.

A 10-$\mu g \cdot m^{-3}$ increase in PM_{10} concentration (lag 0–1) was associated with increased daily deaths in Chicago (0.81%, 95% confidence internal (CI) 0.54–1.09); Detroit (0.87%, 95% CI 0.60–1.15), Minneapolis (1.34%, 95% CI 0.78–1.90), Pittsburgh (0.84%, 95% CI 0.51–1.18) and Seattle (0.52%, 95% CI 0.11–0.94). When controlling for respiratory epidemics, small decreases in the PM_{10} effect were observed (Chicago 9%, Detroit 11%, Minneapolis 3%, Pittsburgh 5%, and Seattle 15%). The overall effect of PM_{10} concentration was 0.85% (95% CI 0.60–1.10) per 10 $\mu g \cdot m^{-3}$ before controlling for epidemics and 0.78% (95% CI 0.51–1.05) after.

This study showed that the association between air pollution and daily deaths is not due to failure to control for influenza or pneumonia epidemics.

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Keywords: Air pollution, meta-analysis, respiratory epidemics, time series, total mortality

Received: March 15 2000
Accepted after revision June 14 2000

This work was supported, in part, by National Institutes of Environmental Health Sciences grant ES 0002 and Environmental Protection Agency Research Center Award R 827353. A. Braga is in receipt of personal grants from the Sào Paulo State Research Support Foundation, (FAPESP), Brazil (98/130214) and the University of Santo Amaro (UNISA).

Over recent decades, many studies have been published associating air pollution with daily deaths [1–5]. These studies have led some to conclude that air pollution remains a serious public health problem and tighter standards are justified [6, 7]. Others have expressed concern that these associations may be confounded by other uncontrolled risk factors [8, 9].

One important factor that varies over time, possibly in correlation with air pollution, is respiratory epidemics. Most published studies have not controlled for epidemics. A few have controlled for influenza epidemics, usually with an indicator variable for epidemic periods [6, 10–18]. This raises several issues. First, there has been no systematic analysis to assess whether control for epidemics changes the air pollution/mortality associations in a meaningful way. Secondly, the approach used to date may not adequately control for respiratory epidemics. Influenza is not the only pathogen that can produce pneumonia, so control for influenza outbreaks alone may miss some episodes.

Most studies have controlled for influenza epidemics using surveillance data to identify influenza cases. In general, these data do not distinguish between influenza B outbreaks, which produce few deaths, and influenza A, which can produce substantial increases in number of deaths. Moreover, even within strains of influenza, different outbreaks have different impacts. This suggests that a simple dummy variable for outbreak periods, which fits a single "epidemic effect" to each outbreak in studies that often span 10 yrs, is inadequate. Also a dummy variable for each outbreak assumes the effect turns on full on the first day of the outbreak, remains constant throughout the period and then falls to zero. A more plausible approach would be to fit the rise and fall of each respiratory epidemic separately, also including those not due to influenza, and see if this changes the associations between air pollution and daily deaths. This approach was applied to five US cities already analysed in a study of particles with a 50% cut-off aerodynamic diameter of 10 μm (PM_{10}) and daily deaths that has been reported previously [19].

Data and methods

Five US cities with daily PM10 monitoring were selected to provide a reasonable number of locations for a combined analysis. The cities were Chicago, IL; Detroit, MI; Minneapolis/St Paul, MN (combined and treated as one city); Pittsburgh, PA and Seattle, WA. Daily deaths in the metropolitan county containing each city were extracted from the National Center for Health Statistics mortality tapes for the years 1986–1993. Deaths due to external causes (International Classification of Diseases, ninth revision 800–999) were excluded. In the present study, total mortality was considered the end point. The nearest airport weather station provided daily weather data (EarthInfo CD National Climatic Data Center (NCDC) Surface Airways, EarthInfo Inc., Boulder, CO, USA), and the US Environmental Protection Agency's Aerometric Retrieval System (AIRS) monitoring network provided daily concentrations of PM10. PM10 data was available daily in all of the cities except Chicago, for which it was available from 1988.

The assignment of PM10 exposure raised a number of issues. Many of the cities have more than one monitoring location. Some of them operate on a daily basis, with the others operating every third or sixth day. If the monitors were simply averaged, the daily mean would jump on days when new monitors were included merely because their annual mean differs from the monitoring stations that operate on a daily basis. The variance of PM10 measurements can also differ between monitoring locations. Hence day-to-day changes in which monitors are in the daily mean would also result in changes in day-to-day variations in the exposure measure that do not represent true changes in ambient concentrations, but only changes in the sampling of monitors. To remove these influences, the following algorithm was used. The annual mean for each monitor for each year, was subtracted from the daily values of that monitor. These daily deviances from each monitor's annual mean were then standardized by dividing by the SD for that monitor. The daily/standardized deviances for each monitor on each day were averaged, producing a daily mean standardized deviances. This was multiplied by the SD of all the monitor readings for the entire year and added to the annual mean of all the monitors. This approach has been described and used previously for these locations [19, 20].

Analytical approach

For each city, a generalized additive Poisson regression was fitted modelling the logarithm of the expected number of daily deaths as a sum of the smooth functions of the predictor variables [21]. The generalized additive model allows regressions to include nonparametric smooth functions to model the potential nonlinear dependence of daily admissions on weather and season. It assumes that:

$$\log Y_e = \beta 0 + S_1X_1 + \ldots + S_pX_p$$

where Y is the daily number of deaths, Y_e is the expected value of that number, X_i are the covariates and Si are the smooth (*i.e.* continuously differentiable) functions. Loess, a moving regression smoother was used [22]. For each covariate, it is necessary to choose a smoothing parameter that determines how smooth the function of that covariate should be.

The purpose of the smooth function of time is to remove the underlying long-term pattern from the data. Seasonal patterns can vary greatly between cities, and a separate smoothing parameter was chosen in each city to remove seasonality and to minimize the autocorrelation of the residuals. This approach was used because each death is an independent event, and autocorrelation of residuals indicates that there are omitted time-dependent covariates whose variation may confound air pollution. If autocorrelation is removed, the remaining variation in omitted covariates has no systematic temporal pattern, and hence confounding is less likely. Autoregressive terms were incorporated to eliminate serial correlation from the residuals as necessary.

The other covariates were ambient temperature, dew point and barometric pressure on the same day, the previous day's ambient temperature and the day of the week. The smoothing parameters for these covariates were chosen separately in each location, choosing the parameter for each variable that minimized the information criterion of AKAIKE [23]. PM10 concentration was treated as a linear term in this analysis to allow the use of meta-analytical techniques for the combination of results across cities. This approach has been described previously [19, 20, 24]. The two-day mean (lags 0 and 1) was adopted in the models.

In order to reduce sensitivity to outliers in the dependent variable, robust regression was used. These regressions were carried out using the generalized additive model function in Splus (Mathsoft Inc., Wash. USA), and M-estimation was the robust regression method. In order to reduce sensitivity to outliers in the pollution variable, and also study the association at common concentrations, analysis was restricted to days when PM10 levels were $<150\ \mu g \cdot m^{-3}$, the currently enforced ambient standard. This also ensures that the results would be unambiguously relevant to questions of revision of standards.

Definition of epidemic periods

It is possible to identify epidemic periods by looking at respiratory mortality [25] but this raises the uncomfortable question of whether it is proper to put mortality on both the left- and right-hand sides of the regression equations. A better approach is to use independent data. Pneumonia hospital admissions were chosen for use in defining outbreaks. This includes pneumonia caused by pathogens other than influenza, and omits influenza outbreaks that do not produce much life-threatening illness. Data on all hospital admissions for pneumonia of persons aged $\geq$65 yrs for each city were obtained from the US Health Care Financing Administration, for the same years as the mortality data. An epidemic period was defined as follows. All days on which the 3-day moving average of pneumonia hospital admissions was above its 90th percentile were defined as "epidemic days". If there were isolated days, an indicator variable was created for each day. Real outbreaks resulted in elevations for more extended periods. Periods with $\geq$10 consecutive "epidemic days" were adopted as epidemic. If, in the middle of each

epidemic period there were up to 3 days with low admissions, according to the criteria used, these days were assumed to be part of a single epidemic. This procedure avoided possible interruptions in the definition of an epidemic, which could be caused, for example, by the substantial decrease in admissions at weekends. For each of these epidemics, a variable was created that was the day number of the episode. In the mortality regressions, cubic polynomials were fitted to each of these day-of-episode variables, allowing the data to determine the steepness of the rise and fall in daily numbers of deaths resulting from the outbreak, as well as the height of each peak. Because the effects of respiratory epidemics on mortality may persist for some days after the end of the epidemic, the possibility of extending the epidemic period was considered and the precise choice for each epidemic was based on when the fitted epidemic curve returned to baseline.

A previous study has analysed this mortality data, without the use of such epidemic variables [8]. These models were taken as the starting point for those in the present study. The epidemic variables were added and the models re-estimated. Inverse variance weighting was used to summarize the results, with and without control for epidemics.

Results

Table 1 shows, for each city, the mean number of daily deaths, the 90th percentile of pneumonia admissions, the study period and mean levels of PM10, ambient temperature, barometric pressure and dew point. It also shows the number of epidemic periods for each city. As shown in figure 1, the duration of epidemics varied throughout the period of study and, according to the criteria used, were absent in some winters. In Seattle, the presence of two distinct epidemic periods in the same winter could be seen in 1989, 1990 and 1991. Two epidemics in the same winter were also seen in Chicago (1991) and Detroit (1993). However, It is interesting to note that the seventh epidemic period in Seattle (February 28–May 15, 1991) occurred after the influenza season, which generally continues until the 15th week of the year [26]. The same was seen in Chicago (fifth epidemic period (February 18–April 23, 1993), Detroit (in both the fourth (March 21–April 10, 1991), and seventh epidemic periods (March 11–April 28, 1993)) and Pittsburgh (sixth epidemic period (February 11–April 23, 1993)).

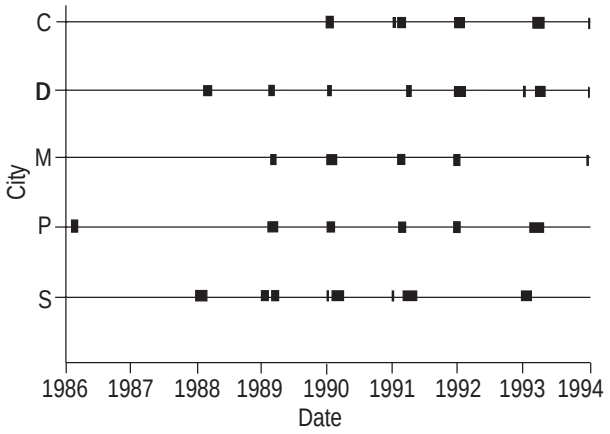

Fig. 1. – Respiratory epidemic periods (wide excerpt) occurring in the five US cities during the study (January 1, 1986—December 30, 1993).

The correlation between PM10 concentration and ambient temperature was positive in Chicago (0.36), Detroit (0.37), Minneapolis (0.31), and Pittsburgh (0.44), and negative in Seattle (-0.22). The correlation between PM10 concentration and barometric pressure was positive in Pittsburgh and Seattle, whereas, in the other three cities, it was small and negative. The estimated correlation between PM10 concentration and dew point followed the same pattern presented for ambient temperature, with positive values in Chicago (0.27), Detroit (0.33), Minneapolis (0.20) and Pittsburgh (0.36), and negative in Seattle (-0.31).

Figure 2 shows, in Chicago, the profile of the epidemics as determined by the cubic polynomial functions. In general, a quadratic shape can be seen, although some periods show a cubic shape. It should be noted that the impact of the epidemics on mortality varied substantially. In some cases, the numbers of deaths only increased by ~6% at the peak of the epidemic, whereas, in one case, the increase in mortality from all causes was 25%. The length of the epidemics also varied from 10 days for epidemic 2 to 60 days for epidemic 6.

Table 2 presents the percentage increase in daily deaths and 95% confidence interval for an increase of 10 $\mu g \cdot m^{-3}$ in the 2-day mean of PM10 level in models with and without controlling for respiratory outbreaks. In general, the results were quite comparable, with a slight tendency for a reduction in the effect size estimate for PM10. Overall, the estimated effect of PM10 concentration was reduced by 8% after control for respiratory epidemics.

Table 1. – Mean numbers of daily deaths, levels of particles with a 50% cut-off aerodynamic diameter of 10 μm (PM10) and meteorological variables, 90th percentile for pneumonia hospital admissions and number of epidemic periods

	Deaths n	PM10 $\mu g \cdot m^{-3}$	Ambient temperature °C	Dew point °C	Barometric pressure mmHg	Pneumonia admissions 90th percentile	Epidemic periods n
Chicago	133.4	36.3	10.1	4.3	29.3	36	6
Detroit	59.7	36.4	10.5	4.4	29.3	15	8
Minneapolis	32.3	28.0	7.9	1.8	29.1	8	5
Pittsburgh	42.4	36.1	11.2	5.1	28.8	16	6
Seattle	29.3	32.2	11.4	6.6	29.6	7	8

(1 mmHg=0.133 kPa.)

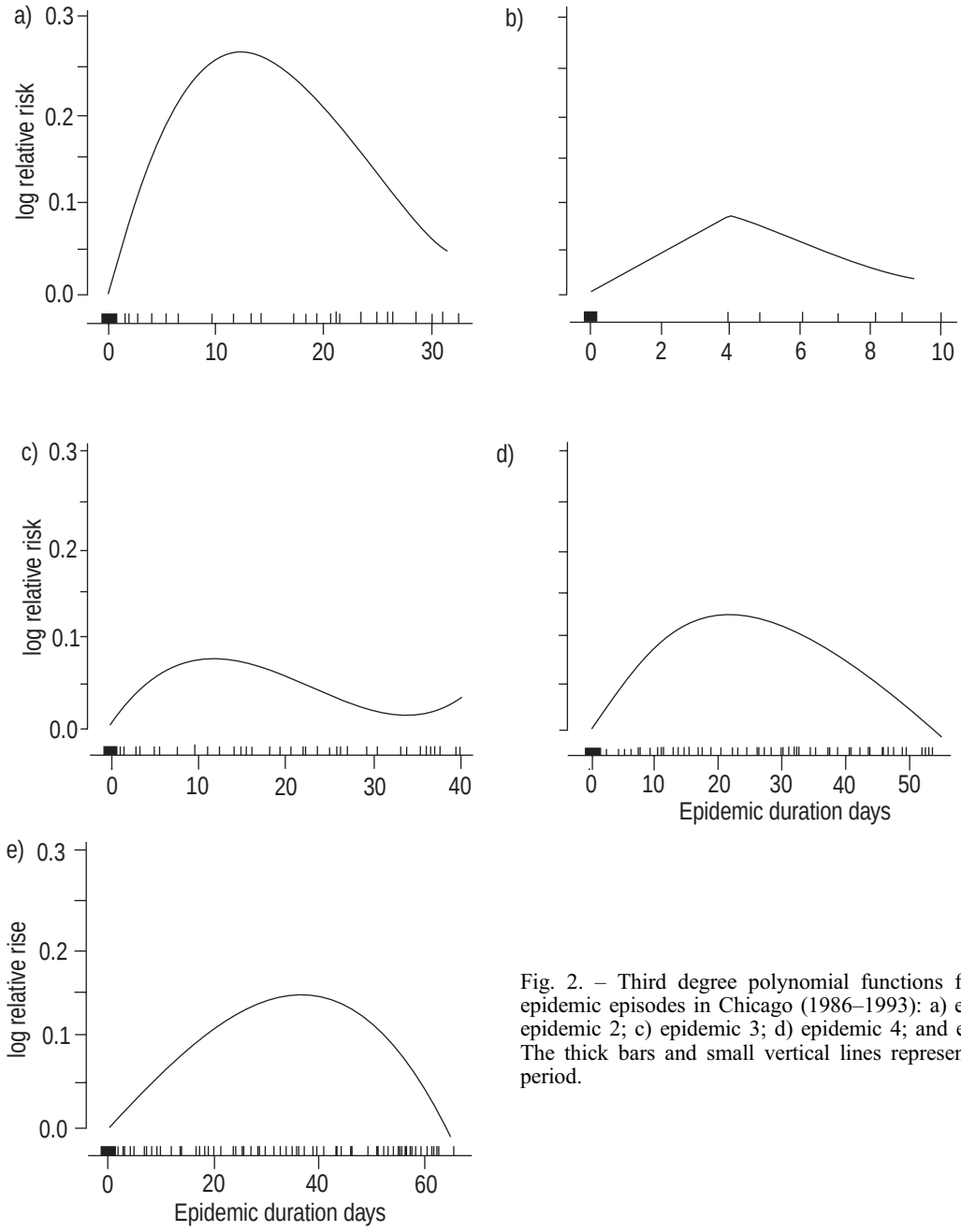

Fig. 2. – Third degree polynomial functions for respiratory epidemic episodes in Chicago (1986–1993): a) epidemic 1; b) epidemic 2; c) epidemic 3; d) epidemic 4; and e) epidemic 5. The thick bars and small vertical lines represent days of the period.

Discussion

The present work focused on determining whether respiratory disease epidemics are confounders of the association between the total number of daily deaths and daily air pollution fluctuations in five US cities. PM_{10} levels were positively associated with the total number of daily deaths in all cities encompassed by the study. It is fundamental to point out that the adverse effect was observed on days with particulate matter levels below the current standard (150 $\mu g \cdot m^{-3}$). As shown, controlling for epidemics, besides weather and seasonality, resulted in a small decrease in the PM_{10} effect in the cities. The decrease varied from 3% in Minneapolis to 15% in Seattle. The overall decrease in PM_{10} effect was 8%. However, these decreases did not modify significantly the association previously observed, confirming the strength of the association and supporting causality in the relationship between PM_{10} exposure and deaths.

The search for possible unknown confounders in the association between air pollutants and health effects has attracted increasing attention as more studies report significant associations. As previously mentioned, control for respiratory epidemics has been a concern for many authors. However, when carried out previously, this has generally involved dummy variables for influenza epidemics. A more flexible approach than a dummy indicator, piecewise harmonic waves, has been used to fit influenza epidemic

Table 2. – Estimates of percentage increase in daily deaths for a 10-μg·m^{-3} increase in the 2-day mean of concentration of particles with a 50% cut-off aerodynamic diameter of 10 μm, in models with and without controlling for respiratory epidemics

City	Increase in Daily Deaths % (95% CI)	
	Original model	Epidemics control
Chicago	0.81 (0.54–1.09)	0.74 (0.49–1.00)
Detroit	0.87 (0.60–1.15)	0.77 (0.50–1.05)
Minneapolis	1.34 (0.78–1.90)	1.30 (0.76–1.84)
Pittsburgh	0.84 (0.51–1.18)	0.80 (0.47–1.14)
Seattle	0.52 (0.11–0.94)	0.44 (0.03–0.86)
Overall effect	0.85 (0.60–1.10)	0.78 (0.51–1.05)

periods [18]. Despite the importance of influenza epidemics in morbidity and mortality rates, other pathogens can be identified as contributors to the overall number of both deaths and hospital admissions due to respiratory diseases. The presence of other agents promoting epidemics of respiratory diseases is indirectly supported by the present observation of epidemics that occurred outside the expected influenza periods (first 10–15 weeks of the year).

Indicators were constructed in order to identify true respiratory epidemic periods in a conservative way. In this study, using mortality data to identify respiratory epidemics could lead to biased estimates due to the high correlation between the epidemic indicator and the dependent variable. Conversely, use of morbidity data (pneumonia hospital admissions) allowed definition of an epidemic indicator less correlated with total number of deaths. The 3-day moving average of pneumonia admissions, defined to avoid sporadic days with unusual records, and the 90th percentile cut-off point for each specific city, allowed better identification of excessive pneumonia admission days. A minimum period of 10 days of excessive admissions was required to define an epidemic period, as it avoided multiple short periods that, despite an excess of admissions, do not necessarily characterize real outbreaks. This allowed separate analysis of the behaviour of each epidemic period, including its characteristic rise and fall, as well as its impact on the number of deaths.

Dummy variables have usually been employed on the assumption that isolated days [27] or periods [6] have the same impact on the dependent variable. However, as seen in figure 2, the contribution of epidemics to the total number of deaths in Chicago varies four-fold (6–25%). This could be explained, for example, by differences in the pathogens (or their virulence) that are mainly responsible for the outcomes in each specific period. The observed heterogeneity of epidemics behaviour reinforces the need to control epidemics separately.

Even a modest reduction in the PM10 effect after control for epidemics needs careful interpretation. Authors have reported a role of particles as facilitators and propagators of infectious diseases, specifically including the exacerbation of influenza and pneumonia [28, 29]. Therefore, control for influenza or pneumonia epidemics risks overcontrol in such a setting. Given this risk and the small reduction in effect size observed, the authors conclude that the effects of PM10 are not confounded by respiratory epidemics.

It is important to emphasize that peaks in PM10 concentration occurred during the winter in some cities and during the summer in others. If, in some of them, the correlation between epidemics and PM10 concentration was low, and no changes in PM10/mortality association were expected, the opposite might be expected in cities in which the correlation was high. This range of particles behaviour allows generalization of the results. The possibility of a more substantial effect on the PM10/mortality association in an isolated city cannot, however, be ruled out.

In summary, the present study has shown that the association between air pollution and the number of daily deaths is robust enough to support controlling for respiratory epidemics. The approach of modelling each epidemic used in this study allows clearer definition of the specific behaviour of each period and its relative contribution to the number of deaths. Finally, this study is concordant with previous results showing deleterious health effects of particles with a 50% cut-off aerodynamic diameter of 10 μm even at levels below the air quality standard, reinforcing the necessity of its revision.

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